

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208065Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 208065

SUPPL #

HFD # 107

Trade Name TAGRISSO

Generic Name Osimertinib

Applicant Name AstraZeneca Pharmaceuticals LP

Approval Date, If Known November 16, 2015

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference

to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2

YES

NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND #

YES

!
!

! NO

! Explain:

Investigation #2

IND #

YES

!
!

! NO

! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1
!
!
YES ! NO
Explain: ! Explain:

Investigation #2
!
!
YES ! NO
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

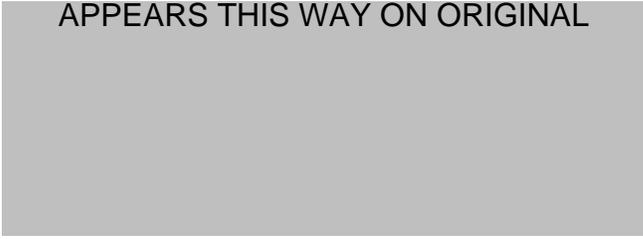
If yes, explain:

Name of person completing form: Ingrid Fan
Title: Regulatory Project Manager
Date: 10/5/2015

Name of Office/Division Director signing form: Patricia Keegan, M.D.
Title: Director, Division of Oncology Products 2

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

APPEARS THIS WAY ON ORIGINAL



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/s/

INGRID Y FAN
10/26/2015

PATRICIA KEEGAN
10/26/2015

Fan, Ingrid

Subject: FW: NDA 208065 TAGRISSO - Proposed labeling
Attachments: NDA 208065 - AZD9291 FINAL ANNOTATED USPI.DOC

From: Fan, Ingrid
Sent: Thursday, November 12, 2015 2:51 PM
To: 'Jazayeri, Jonathan'
Cc: Brown, Kelly R; Farias, Bianca (Regulatory)
Subject: RE: NDA 208065 TAGRISSO - Proposed labeling

Hello Jonathan,

Please find attached the TAGRISSO package insert and Patient Information. We accepted all your proposed changes and made one small change to a footnote in the table of section 14.

Please review, accept the edit if you are in agreement with, and provide a final draft label in both clean and tracked changes format as a formal submission to your NDA 208065 with an e-courtesy copy to me **today**.

Please confirm receipt.

Thank you,
Ingrid

Ingrid Fan
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone:301-796-5053

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/s/

INGRID Y FAN
11/12/2015

Fan, Ingrid

From: Fan, Ingrid
Sent: Tuesday, November 10, 2015 4:38 PM
To: Jazayeri, Jonathan (Jonathan.Jazayeri@astrazeneca.com)
Subject: NDA 208065 TAGRISSO - Proposed labeling
Attachments: NDA 208065 osimertinib PI-PPI_FDA edits_ 11_10_2015.doc

Hello Jonathan,

Attached is our proposed edits to the TAGRISSO package insert and Patient Information. Please review our proposed edits, accept all edits you are in agreement with, and update the dates where highlighted.

Please provide a final agreed upon draft label in both clean and tracked changes format as a formal submission to your NDA 208065 with an e-courtesy copy to me as soon as possible.

Please confirm receipt.

Thank you,
Ingrid

Ingrid Fan
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-5053

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/s/

INGRID Y FAN
11/10/2015

Fan, Ingrid

From: Fan, Ingrid
Sent: Monday, November 09, 2015 4:16 PM
To: Jazayeri, Jonathan (Jonathan.Jazayeri@astrazeneca.com)
Subject: NDA 208065 TAGRISSO -Proposed labeling
Attachments: NDA 208065 Osimertinib PI-PPI FDA edits 11_09_2015.docx

Hello Jonathan,

Attached is our proposed edits and comments to the TAGRISSO package insert and Patient Information. Please update relevant tables as needed and correct formatting where required.

In addition, please review our proposed edits and comments, accept all edits you are in agreement with, provide any requested supporting data, and make any additional edits in track-changes.

Please send me your updated labeling via email by **noon on Tuesday, November 10, 2015**.

Kindly confirm receipt and let me know should you have any questions.

Thank you,
Ingrid

Ingrid Fan
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-5053

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/s/

INGRID Y FAN
11/09/2015

Fan, Ingrid

From: Fan, Ingrid
Sent: Thursday, November 05, 2015 10:41 AM
To: Jazayeri, Jonathan (Jonathan.Jazayeri@astrazeneca.com)
Subject: NDA 208065 TAGRISSO - Proposed labeling
Attachments: NDA 208065 Osimertinib PI-FDA edits 11_05_2015.docx; NDA 208065 Osimertinib PPI_FDA Edits_ 11_5_2015.docx

Hello Jonathan,

Attached is our proposed edits and comments to the TAGRISSO package insert and Patient Information. Please update all table numbers as needed and correct formatting where required.

In addition, please review our proposed edits and comments, accept all edits you are in agreement with, provide any requested supporting data, and make any additional edits in track-changes.

We also have the following comment on your container labelling:

- 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.

Please send me your updated labeling via email by **noon on Monday, November 9, 2015**.

Kindly confirm receipt and let me know should you have any questions.

Thank you,
Ingrid

Ingrid Fan
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-5053

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/s/

INGRID Y FAN
11/05/2015

Fan, Ingrid

From: Fan, Ingrid
Sent: Tuesday, November 03, 2015 3:33 PM
To: Jazayeri, Jonathan (Jonathan.Jazayeri@astrazeneca.com)
Subject: NDA 208065 : FDA Information Request

Hello Jonathan,

Our Clinical Reviewer has the following information request that we wish you to address by **noon tomorrow, November 4th, 2015**. Please send your response to me via email and follow with a formal submission to your NDA 208065.

- Regarding the creatinine grade shifts that were reported in 94.4% of patients overall, can AZ please provide data on the percentage of patients who actually increased their creatinine above the upper limit of normal?

Please confirm receipt and let me know should you have any questions.

Thank you,
Ingrid

Ingrid Fan
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-5053

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/s/

INGRID Y FAN
11/03/2015

MEMORANDUM OF TELECONFERENCE

Teleconference Date: October 21, 2015

Application Number: NDA 208065

Product Name: osimertinib

Sponsor/Applicant Name: AstraZeneca Pharmaceuticals LP

Subject: Clarification of issues related to response to IR request submission S-0041 on Oct. 20, 2015.

FDA Participants

Olen Stephens, Ph.D., Branch Chief

William (Mike) Adams, Ph.D., Process Reviewer

Steven Kinsley, Ph.D., Regulatory Process Manager

Sponsor/Applicant Participants

Jonathan Jazayeri, PharmD, MS, RAC Regulatory Affairs Director

Eric Richards, MS, MPH Regulatory Affairs Senior Director

Silke Klick, PhD, Regulatory Affairs - CMC

Simon Collett, MS, Meng, Pharmaceutical Development Lead

Dawn Sievwright, PhD, Pharmaceutical Development Project Manager

Maria Eriksson, PhD, New Product Director

Kevin Day, PhD, Associate Principal Scientist

Ulrika Henningsson, PhD, Director QA and Qualified Person

Stefan Sandberg, PhD Global Supply Planner

1.0 BACKGROUND:

Reference is made to amendment S-0041 submitted 20-Oct-15 which responded email comments received 13-Oct-15; and to the teleconference between OPQ and AstraZeneca held on 21-Oct-15.

2.0 DISCUSSION:

1. The FDA and AstraZeneca confirmed the understanding that the five batches listed in Comment 1 of the amendment are allowed for commercial launch, but do not comply with the allowed (b) (4) bulk hold storage and 12 month shelf life described in Comment 4. These batches are being allowed for launch of this breakthrough designated product. The five batches for launch will be allowed to be marketed with a (b) (4) shelf life which includes a (b) (4) of bulk hold time. Subsequent commercial batches must comply with the bulk hold storage and shelf life described in Comment 4.

2. Shelf life is considered to be [REDACTED] (b) (4)
[REDACTED] Therefore, AstraZeneca's response to Comment 4 in bullet two is not consistent with FDA's designation of the start of shelf life. FDA and AstraZeneca confirmed the understanding that shelf life begins at [REDACTED] (b) (4)
[REDACTED] and that the 12 month shelf life encompasses any bulk hold time.
3. Regarding Comment 5, the protocol to study contiguous stability from [REDACTED] (b) (4)
[REDACTED] will be submitted to IND 117,879 as an amendment. This amendment will be prioritized on the part of AstraZeneca and FDA will provide feedback in a timely fashion. Additionally, AstraZeneca will include in the amendment updated stability data; a justification for method variability observed in the [REDACTED] (b) (4)
[REDACTED] addressed in Comment 1.

3.0 ACTION ITEMS:

See discussion Item #3.

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/s/

STEVEN A KINSLEY
10/26/2015

OLEN M STEPHENS
10/26/2015



**REQUEST FOR METHODS
VALIDATION MATERIALS**

NDA 208065

October 21, 2015

AstraZeneca Pharmaceuticals LP
Attention: Jonathan Jazayeri
One MidImmune Way
Gaithersburg, MD 20878

Dear Jonathan Jazayeri:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Osimertinib film coated tablet, 40 and 80 mg.

We will be performing methods validation studies on Osimertinib film coated tablet, 40 and 80 mg, as described in NDA 208065.

In order to perform the necessary testing, we request the following sample materials and equipments:

Method (current version)

- 1) Analytical Procedure for Organic Impurities by (b) (4)
[Redacted]
- 2) Analytical Procedure for (b) (4)
- 3) Analytical procedure for Assay by (b) (4)
- 4) Analytical procedure for Degradation Products by (b) (4)
[Redacted]

Samples and Reference Standards

- 2 x 500 mg of drug substance
 - 2 x 500 mg of AZD9291 mesylate reference standard
 - 2 x 50 tablets of 40 mg drug product
 - 2 x 50 tablets of 80 mg drug product
- [Redacted] (b) (4)

Equipment

[Redacted] (b) (4)

Please include the MSDSs and the Certificates of Analysis for the sample and reference materials.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: MVP Sample Custodian
645 S Newstead
St. Louis, MO 63110

Please notify me upon receipt of this email. You may contact me by telephone (314-539-2155), FAX (314-539-2113), or email (Laura.Pogue@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Laura C. Pogue, Ph.D.
MVP coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

LAURA POGUE
10/21/2015

Fan, Ingrid

From: Fan, Ingrid
Sent: Thursday, October 15, 2015 9:47 PM
To: Jazayeri, Jonathan (Jonathan.Jazayeri@astrazeneca.com)
Subject: NDA 208065 / TAGRISSO --- Proposed Labeling
Attachments: NDA 208065 Osimertiinib PI-PPI_ FDA Edits_10_15_2015.docx

Hello Jonathan,

Attached is our proposed edits and comments to the TAGRISSO package insert. Please update all table numbers as needed and correct formatting where required.

In addition, please review our proposed edits and comments, accept all edits you are in agreement with, provide any requested supporting data, and make any additional edits in track-changes.

We also have the following comments on your container labelling:

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.  (b) (4)

Please submit updated labeling to your NDA by COB on **Thursday, October 22, 2015**, with a courtesy copy to me via email.

Kindly confirm receipt and let me know should you have any questions.

Thank you,
Ingrid

Ingrid Fan
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-5053

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/s/

INGRID Y FAN
10/20/2015



NDA 208065

INFORMATION REQUEST

AstraZeneca Pharmaceuticals LP
Attention: Jonathan Jazayeri, Regulatory Affairs Director
One MedImmune Way
Gaithersburg, MD 20878

Dear Mr. Jazayeri,

Please refer to your original New Drug Application received June 5, 2015 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for osimertinib film-coated tablet, 40mg and 80mg strengths.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comment. We request a prompt written response in order to continue our evaluation of your NDA. Please submit your response prior to COB Thursday, October 15, 2015.

1. Pending approval of NDA 208-065, FDA has concluded that the following batches may be used for commercial launch: (CAAB, CAAC, AAAB, AAAC, AAAD).

2. The proposed release specification should be revised to specify that samples for release and stability testing will be taken from tablets in their finished package. Since you propose to (b) (4)

3. In the analytical method for Degradation Products by HPLC, the calculation for percent individual degradants and total degradants should be revised to (b) (4)



4. Pending approval of the NDA, we have concluded that based on the stability data and information submitted to the NDA, the data supports the following timeframes:

- a) (b) (4) storage of bulk tablets at 15-30°C in the proposed sealed laminate bag and
- b) A shelf life of 12 months with storage of finished product at USP controlled room temperature when packaged in the proposed HDPE bottle with (b) (4) closure and (b) (4)

The stability data and information submitted to the NDA does not include a study of (b) (4)

5. The proposed study to (b) (4) referenced in amendment 033 dated 08 Sep 2015 should be submitted as a formal proposal as an amendment to the NDA, which includes the following items:

- The study will include at least (b) (4) s approved in the NDA.
- The holding time for bulk tablets will apply to all commercial batches. Extrapolation beyond this time will not be acceptable without a formal study of contiguous manufacturing and holding and packaging of tablets.
- The long term stability study will continue through the proposed drug product shelf life. (b) (4)
- The date when the study is to be initiated and when it is expected to be submitted should be specified.
- The study results should be submitted to the NDA as a prior approval supplement since major changes are proposed for the drug product control strategy.



6. Regarding your response (8-Sep-15 and 11-Oct-15) to the information requests (20-Aug-15 and 8-Oct-15), please submit the following formal amendments to the NDA in the appropriate sections:

a) In the Master Batch Record,

- i. [Redacted] (b) (4)
- ii. [Redacted] (b) (4)
- iii. [Redacted] (b) (4)

b) In module 3.2.P.3.4, amend this section to reflect the [Redacted] (b) (4)

If you have any questions, please contact me, Steven Kinsley, Ph.D. Regulatory Business Process Manager, at (240) 402-2773.

Sincerely,

Olen
Stephens -S

Digitally signed by Olen Stephens -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Olen Stephens -
S,
0.9.2342.19200300.100.1.1=2000558826
Date: 2015.10.13 15:42:04 -04'00'

Olen Stephens, Ph.D.
Branch Chief, Branch II
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



NDA 208065

INFORMATION REQUEST

AstraZeneca Pharmaceuticals LP
Attention: Jonathan Jazayeri, Regulatory Affairs Director
One MedImmune Way
Gaithersburg, MD 20878

Dear Mr. Jazayeri,

Please refer to your original New Drug Application received June 5, 2015 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for osimertinib film-coated tablet, 40mg and 80mg strengths.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comment. We request a prompt written response in order to continue our evaluation of your NDA. Please submit your response prior to COB Wednesday, October 14, 2015.

We acknowledge your responses received October 2, 2015 to our information request dated September 29, 2015. The response to the information request does not provide sufficient assurance of [REDACTED] (b) (4) of drug product.

In order to resolve this issue, [REDACTED] (b) (4)

[REDACTED]



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

If you have any questions, please contact me, Steven Kinsley, Ph.D. Regulatory Business Process Manager, at (240) 402-2773.

Sincerely,

Olen
Stephens -S

Digitally signed by Olen Stephens -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Olen Stephens
-S,
0.9.2342.19200300.100.1.1=2000558826
Date: 2015.10.08 11:58:51 -04'00'

Olen Stephens, Ph.D.
Branch Chief, Branch II
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Fan, Ingrid

From: Fan, Ingrid
Sent: Wednesday, October 07, 2015 2:06 PM
To: Jazayeri, Jonathan (Jonathan.Jazayeri@astrazeneca.com)
Subject: NDA 208065: FDA Information Request

Hi Jonathan,

Our Clinical Reviewer has the following information request that we wish you to address by **COB tomorrow, Thursday, October 8th**. Please send your response to me via email and follow with a formal submission to your NDA 208065.

Please provide the following information to supplement and summarize the financial disclosure information submitted to the NDA.

- Total number of investigators in AURA phase 1/extension and AURA2
- Number of investigators who are Sponsor employees (including both full-time and part-time employees)
- Number of investigators with disclosable financial interests/arrangements (Form FDA 3455)
- If there are investigators with disclosable financial interests/arrangements, indicate the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f))
 - Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study
 - Significant payments of other sorts
 - Proprietary interest in the product tested held by investigator
 - Significant equity interest held by investigator in Sponsor of covered study
- Number of investigators with certification of due diligence (Form FDA 3454, box 3)

Please confirm receipt and let me know should you have any questions.

Thank you,
Ingrid

Ingrid Fan
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone:301-796-5053

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/s/

INGRID Y FAN
10/07/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: September 30, 2015
From: Ingrid Fan, RPM, DOP2/OHOP/CDER/FDA
Subject: NDA 208065 / AstraZeneca / AZD9291 /NSCLC

TELECONFERENCE

Sponsor Attendees:

Jonathan Jazayeri,	Regulatory Affairs Director
Eric Richards	Regulatory Affairs Senior Director
Hesham Abdullah	Regulatory Affairs VP - Oncology
Serban Ghiorghiu	Clinical Development Lead
Helen Mann	Biometrics & Informatics Lead
Renee Iacona	Biometrics & Informatics Head - Oncology
Antoine Yver	Global Head – Oncology

FDA Attendees:

Chana Weinstock – Clinical Reviewer, DOP 2
Sean Khozin – Clinical Reviewer, DOP2
Gideon Blumenthal – Clinical Team Leader, DOP2
Ingrid Fan – RPM, DOP2
Patricia Keegan – Division Director, DOP2
Richard Pazdur – Office Director, DOP2
Kun He – Statistical Team Leader, DBV
Lan Huang – Statistical Reviewer, DBV
Rajeshwari Sridhara – Division Director, DBV

Objectives:

Discuss AZ's proposed case control analysis for AZD9291.

Discussion:

During the teleconference, FDA stated that the case control analysis is an interesting approach, but we are not ready to comment on whether it's appropriate to use it. FDA encouraged AZ to formally submit the proposal to the IND for our comments and noted that randomized study data should also be submitted for our review.

AZ agreed that they will submit the case control analysis to the IND and will also provide the randomized study data.

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/s/

INGRID Y FAN
10/01/2015

Fan, Ingrid

From: Fan, Ingrid
Sent: Thursday, October 01, 2015 9:38 AM
To: Jazayeri, Jonathan (Jonathan.Jazayeri@astrazeneca.com)
Subject: NDA 208065 : FDA Information Request

Hi Jonathan,

Our Clinical Reviewer has the following information request that we wish you to address by **noon on Monday, October 5, 2015**. Please send your response to me via email and follow with a formal submission to your NDA 208065.

- In AURA extension and AURA 2, there were patients who were treated beyond RECIST progression. Please provide the number of patients in each trial that were treated beyond RECIST progression, the duration of treatment post progression (median, range), and reason(s) for eventual discontinuation. Include references to relevant datasets and programmatic data derivations.

Please confirm receipt and let me know should you have any questions.

Thank you,
Ingrid

Ingrid Fan
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-5053

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/s/

INGRID Y FAN
10/01/2015

Fan, Ingrid

From: Fan, Ingrid
Sent: Wednesday, September 30, 2015 1:41 PM
To: 'Jazayeri, Jonathan'
Cc: Brown, Kelly R; Farias, Bianca (Regulatory); Brown, Kelly R; Farias, Bianca (Regulatory)
Subject: RE: NDA 208065: FDA Clinical Information Request

Hi Jonathan,

Our Clinical Reviewer has the following information request that we wish you to address by **COB Monday, October 5th**. Please send your response to me via email and follow with a formal submission to your NDA 208065.

- Regarding section 6.1 of the Tagrisso label, please resubmit an updated Table 3 [REDACTED] (b) (4) [REDACTED] to include laboratory data though the 90-day safety update DCO date. Please submit updated data on **lymphocytes**.

Please confirm receipt and let me know should you have any questions.

Thank you,
Ingrid

Ingrid Fan
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-5053

From: Jazayeri, Jonathan [<mailto:Jonathan.Jazayeri@astrazeneca.com>]
Sent: Wednesday, September 30, 2015 3:28 AM
To: Fan, Ingrid
Cc: Brown, Kelly R; Farias, Bianca (Regulatory); Brown, Kelly R; Farias, Bianca (Regulatory)
Subject: RE: NDA 208065: FDA Clinical Information Request

Hi Ingrid,

Please kindly find the attached response to the information request referenced below. The response contains a formal Response Document with supportive tables for completeness. In addition, annotated and non-annotated versions of the updated FPI are included as WORD documents.

A formal submission to the NDA is forthcoming.

If you have any questions or comments, don't hesitate to let me know.

Kind Regards,
-Jonathan

From: Fan, Ingrid [<mailto:Ingrid.Fan@fda.hhs.gov>]
Sent: Wednesday, September 23, 2015 8:42 AM
To: Jazayeri, Jonathan

Cc: Brown, Kelly R; Farias, Bianca (Regulatory)
Subject: RE: NDA 208065: FDA Clinical Information Request

The team would like to have a response by COB Monday, September 28th.

Thank you,
Ingrid

From: Jazayeri, Jonathan [<mailto:Jonathan.Jazayeri@astrazeneca.com>]
Sent: Wednesday, September 23, 2015 5:10 AM
To: Fan, Ingrid
Cc: Brown, Kelly R; Farias, Bianca (Regulatory)
Subject: RE: NDA 208065: FDA Clinical Information Request

Hi Ingrid,

I am confirming receipt of the information request. I would like to note that the 29th of September is a Tuesday.

Best,
-Jonathan

From: Fan, Ingrid [<mailto:Ingrid.Fan@fda.hhs.gov>]
Sent: Tuesday, September 22, 2015 4:09 PM
To: Jazayeri, Jonathan
Subject: NDA 208065: FDA Clinical Information Request

Hello Jonathan,

Please find the following clinical comments and information request regarding NDA 208065. Please provide a response to these comments by **COB Monday, September 29, 2015**. Please send your response to me via email and follow with a formal submission to your NDA 208065.

1. Regarding section 6.1 of the Tagrisso label, please resubmit an updated Table 3 (b) (4) to include laboratory data through the 90-day safety update DCO date. Please submit updated data on platelets, hemoglobin, neutrophils, and lymphocytes.
2. When reviewing the safety database, incorporating the 90-day update data, we have noticed that White patients are much more likely than Asians to develop cerebrovascular accidents and venous thromboembolic events. This effect was seen both in the AURA extension/AURA II experience and to a lesser extent in the phase 1 cohorts. Does AstraZeneca have an explanation for this observation, such as increased use of brain and thoracic imaging in North American/European vs. Asian sites?

Please confirm receipt.

Thank you,
Ingrid

Ingrid Fan
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-5053

Confidentiality Notice: This message is private and may contain confidential and proprietary information. If you have received this message in error, please notify us and remove it from your system and note that you must not copy, distribute or take any action in reliance on it. Any unauthorized use or disclosure of the contents of this message is not permitted and may be unlawful.

Confidentiality Notice: This message is private and may contain confidential and proprietary information. If you have received this message in error, please notify us and remove it from your system and note that you must not copy, distribute or take any action in reliance on it. Any unauthorized use or disclosure of the contents of this message is not permitted and may be unlawful.

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/s/

INGRID Y FAN
09/30/2015



NDA 208065

INFORMATION REQUEST

AstraZeneca Pharmaceuticals LP
Attention: Jonathan Jazayeri, Regulatory Affairs Director
One MedImmune Way
Gaithersburg, MD 20878

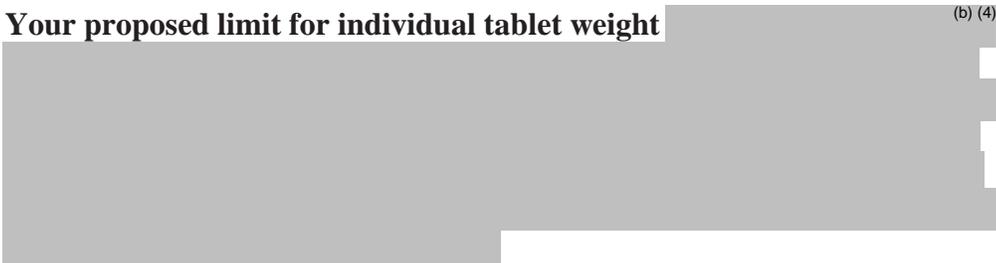
Dear Mr. Jazayeri,

Please refer to your original New Drug Application received June 5, 2015 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for osimertinib film-coated tablet, 40 mg and 80 mg strengths.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments. We request a prompt written response in order to continue our evaluation of your NDA. Please submit your response prior to COB Monday, October 5, 2015.

We acknowledge your responses to process question received on 09/08/2015. In order to proceed with timely review of your application the following remaining issues need to be resolved:

1. You propose to perform (b) (4)


2. Your proposed limit for individual tablet weight (b) (4)




DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

If you have any questions, please contact me, Steven Kinsley, Ph.D. Regulatory Business Process Manager, at (240) 402-2773.

Sincerely,

Olen Stephens -S

Digitally signed by Olen Stephens -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Olen Stephens -S,
0.9.2342.19200300.100.1.1=2000558826
Date: 2015.09.29 15:07:21 -04'00'

Olen Stephens, Ph.D.
Branch Chief, Branch II
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



NDA208065

MID-CYCLE COMMUNICATION

AstraZeneca Pharmaceuticals LP
Attention: Jonathan Jazayeri, Pharm.D., M.S., R.A.C.
Regulatory Affairs Director, Oncology
One MedImmune Way
Gaithersburg, MD 20878

Dear Dr. Jazayeri:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tagrisso (Osimertinib), 40 mg and 80 mg tablets.

We also refer to the teleconference between representatives of your firm and the FDA on September 11, 2015. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call me at (301) 796-5053.

Sincerely,

{See appended electronic signature page}

Ingrid Fan
Regulatory Project Manger
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: September 11, 2015 from 11:00 AM – 12:00 PM

Application Number: NDA 208065

Product Name: Tagrisso (Osimertinib)

Indication: (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.

Applicant Name: AstraZeneca Pharmaceuticals LP

Meeting Chair: Gideon Blumenthal, M.D.

Meeting Recorder: Ingrid Fan

FDA ATTENDEES

Patricia Keegan	Division Director
Gideon Blumenthal,	Medical Officer (TL and CDTL)
Sean Khozin,	Medical Officer (Efficacy)
Chana Weinstock,	Medical Officer (Safety)
Ingrid Fan,	Regulatory Project Manager
Joyce Cheng,	Statistics
Kun He,	Statistics Team Leader
Whitney Helms,	Non-Clinical Team Leader
Jun Yang,	Clinical Pharmacology
Hong Zhao,	Clinical Pharmacology Team Leader
Luning Zhuang,	Clinical Pharmacology/Pharmacometrics
Rosane Charlab Orbach,	Genomics (TL)
William Adams,	CMC ONDP
Latonia Ford ,	OSE PM
Carol McCloskey,	OSE DEPI
Tracy Salaam,	OSE DPV
Shaily Arora,	OSE DPV

Eastern Research Group

Christopher Sese

APPLICANT ATTENDEES

Jonathan Jazayeri,	Regulatory Affairs Director
Eric Richards,	Regulatory Affairs Senior Director
Hesham Abdullah,	Regulatory Affairs VP - Oncology
Marilyn Tsourounis,	Regulatory Affairs - Labeling
Silke Klick,	Regulatory Affairs - CMC
Simon Collett,	Pharmaceutical Development Lead
Maria Eriksson,	New Product Director
Mireille Cantarini,	Clinical Development
Serban Ghiorghiu,	Clinical Development Lead
Klaus Edvardsen,	Clinical Development VP - Oncology
Paul Howarth,	Patient Safety Physician
Andrew Walding,	Patient Safety Scientist
Jim Kotsanos,	Patient Safety Head - Oncology
Karthick Vishwanathan,	Clinical Pharmacology - Oncology
Kathryn Brown,	Clinical Pharmacometrics
Helen Mann,	Biometrics & Informatics Lead
Renee Iacona,	Biometrics & Informatics Head - Oncology
Mei Dey,	Programming Lead
Suzanne Jenkins,	Personalized Healthcare and Biomarkers
Antoine Yver,	Global Head - Oncology

1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

2.0 SIGNIFICANT ISSUES

Currently there are no significant issues regarding the following disciplines;

- Clinical
- Statistics
- Clinical Pharmacology
- Nonclinical

The following is the significant CMC issues:

1.  (b) (4)

Mid-Cycle Communication

2. [REDACTED] (b) (4)
3. [REDACTED] (b) (4)

Discussion during the meeting:

FDA stated that AZ's [REDACTED] (b) (4) is not acceptable. FDA will send comments/recommendations to AZ regarding this issue.

AZ also inquired about FDA's feedback regarding the following two topics:

1. The acceptance of 'clinical' drug substance (Campaign 4) to support initial commercial launch
2. Shelf life position for [REDACTED] (b) (4)

FDA noted that these topics will be evaluated and comments will be provided to AZ.

3.0 INFORMATION REQUESTS

At this time there are no outstanding information requests.

Discussion during the teleconference: AZ Acknowledged FDA's response and no discussion occurred.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

Currently there are no plans for a REMs

Discussion during the teleconference: AZ Acknowledged FDA's response and no discussion occurred.

5.0 ADVISORY COMMITTEE MEETING

Currently there are no plans to hold an Advisory Committee Meeting.

Discussion during the teleconference: AZ Acknowledged FDA's response and no discussion occurred.

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

The proposed date for the late cycle meeting is October 13, 2015.

Discussion during the teleconference: AZ asked if FDA could re-schedule the late cycle meeting. FDA stated that another date/time cannot be found that would fit the review team's schedule.

7.0 POSTMARKETING REQUIREMENTS (PMRs) AND POSTMARKETING COMMITMENTS (PMCs)

Clinical PMR

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

Clinical Pharmacology PMRs

2. Complete a pharmacokinetic study in patients (b) (4) AZD9291 with inhibitors of CYP3A4 in accordance with the FDA draft Guidance for Industry entitled “*Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations*” found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf>. Submit the final study report as PMR under the NDA.
3. Complete a pharmacokinetic study in patients to (b) (4) with inducers of CYP3A4 in accordance with the FDA draft Guidance for Industry entitled “*Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations*” found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf>. Submit the final study report as PMR under the NDA.
4. Complete a pharmacokinetic study to evaluate the effect of repeated doses of AZD9291 on the pharmacokinetics of a probe substrate of CYP3A4 (b) (4) in accordance with the FDA draft Guidance for Industry entitled “*Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations*” found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf>. Submit the final study report as PMR under the NDA.
5. Complete a pharmacokinetic study to evaluate the effect of repeated doses of AZD9291 on the pharmacokinetics of a probe substrate of BCRP (b) (4) in accordance with the FDA draft Guidance for Industry entitled “*Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations*” found at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf>. Submit the final study report as PMR under the NDA.

6. Conduct a pharmacokinetic trial to determine the appropriate dose of AZD9291 in patients with hepatic impairment in accordance with the FDA Guidance for Industry entitled “Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling” found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072123.pdf>. Submit the final study report as PMR under the NDA.

Discussion during the teleconference:

FDA requested AZ to provide milestone dates for the above PMRs by September 24, 2015 and AZ agreed.

FDA also noted that comments regarding the two ongoing clinical pharmacology studies will be provided to AZ.

ADDITIONAL COMMENT

[REDACTED] (b) (4)

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/s/

INGRID Y FAN
09/24/2015

Fan, Ingrid

From: Fan, Ingrid
Sent: Tuesday, September 22, 2015 4:09 PM
To: Jazayeri, Jonathan (Jonathan.Jazayeri@astrazeneca.com)
Subject: NDA 208065: FDA Clinical Information Request

Hello Jonathan,

Please find the following clinical comments and information request regarding NDA 208065. Please provide a response to these comments by **COB Monday, September 29, 2015**. Please send your response to me via email and follow with a formal submission to your NDA 208065.

1. Regarding section 6.1 of the Tagrisso label, please resubmit an updated Table 3 [REDACTED] (b) (4) [REDACTED] to include laboratory data though the 90-day safety update DCO date. Please submit updated data on platelets, hemoglobin, neutrophils, and lymphocytes.
2. When reviewing the safety database, incorporating the 90-day update data, we have noticed that White patients are much more likely than Asians to develop cerebrovascular accidents and venous thromboembolic events. This effect was seen both in the AURA extension/AURA II experience and to a lesser extent in the phase 1 cohorts. Does AstraZeneca have an explanation for this observation, such as increased use of brain and thoracic imaging in North American/European vs. Asian sites?

Please confirm receipt.

Thank you,
Ingrid

Ingrid Fan
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone:301-796-5053

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/s/

INGRID Y FAN
09/22/2015

Fan, Ingrid

From: Fan, Ingrid
Sent: Friday, September 18, 2015 6:42 PM
To: Jazayeri, Jonathan (Jonathan.Jazayeri@astrazeneca.com)
Subject: NDA 208065 / AZD9291/ FDA Information Request

Hello Jonathan,

Our Clinical Reviewer has the following information request that we wish you to address by **COB Thursday, September 24, 2015**. Please send your response to me via email and follow with a formal submission to your NDA 208065.

Please fill in the information in the following table for AURA extension and AURA2, with reference to the clinical study report and appropriate datasets.

	AURA extension (n=201) n, (%)	AURA2 (n=210)
Patients with following areas of disease at baseline: <ul style="list-style-type: none">• Bone• Liver		
Treated brain metastasis at baseline		
Untreated brain metastasis at baseline		
CNS ORR and DOR in patients with measurable CNS disease (per investigator and BICR assessment)		
Patients with CNS as the primary site of disease recurrence on AZD9291		
Patients on corticosteroids for brain metastasis at baseline <ul style="list-style-type: none">• Patients who discontinued corticosteroids due to symptom improvement while on AZD9291		

Please confirm receipt and let me know should you have any questions.

Thank you,
Ingrid

Ingrid Fan
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-5053

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/s/

INGRID Y FAN
09/18/2015



NDA 208065

INFORMATION REQUEST

AstraZeneca Pharmaceuticals LP
Attention: Jonathan Jazayeri, Regulatory Affairs Director
One MedImmune Way
Gaithersburg, MD 20878

Dear Mr. Jazayeri,

Please refer to your original New Drug Application received June 5, 2015 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for osimertinib film-coated tablet, 40mg and 80mg strengths.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments. We request a prompt written response in order to continue our evaluation of your NDA. Please submit your response prior to COB Thursday, September 03, 2015.

Facility

- 1. You propose to use clinical lots formulated with lots of API campaign 3 or 4 for commercial launch of your drug product. Confirm the drug substance and drug product batches intended to be used for launch, provide their dates and location of manufacture and packaging, and the manufacturing processes used. Include the manufacturing sites for these batches in the 356h form. Use of these batches will require a facilities evaluation and potentially inspection of their manufacturing sites before approval of the NDA.**

Biopharmaceutics

- 2.**  (b) (4)

Microbiology

You propose  (b) (4)

Address the following points.

3. Identify and justify critical control points in the manufacturing process that could affect (b) (4) of the drug product.
 - a. Establish the (b) (4)
 - b. Establish the (b) (4)
4. Describe microbiological monitoring and acceptance criteria for the critical control points that you have identified. Conformance to the acceptance criteria established for each critical control point should be documented in the batch record in accordance with 21 CFR 211.188.
5. Describe activities taken when microbiological acceptance criteria are not met at the critical control points.
6. You stated “A microbial mold challenge test study has also been conducted and demonstrated that AZD9291 does not support microbial growth.” Please describe this test and provide your test results.
7. You should minimally perform microbial limits testing at the initial stability time point. Provide an updated stability schedule to reflect this testing.

Drug Product

8. For the compatibility studies in NDA section 3.2.P.2.6, provide a description of the preparation of the proposed aqueous dispersion which details the pH, temperature, mixing time, mixing by (b) (4)
9. Section 2.2 of the package insert describes a method to prepare the tablet for patients who are unable to swallow the tablet. Include (b) (4) to support this route of dose preparation.
10. Provide a copy of the supplier’s certificate of analysis for each lot of each excipient used to manufacture of the NDA registration batches of 40 mg and 80 mg tablets.
11. Specify when and how samples for release and stability testing are selected.

12. Regarding the proposed HPLC and UV methods:

- a. **Revise the system suitability criteria to include** [REDACTED] (b) (4)

- b. **Provide copies of example chromatograms and UV spectra for the reference standard, test sample and blank.**

- c. **Describe how a** [REDACTED] (b) (4)

13. Regarding the HPLC method for identity, assay and impurities:

- a. **Explain why detection at** [REDACTED] (b) (4)

- b. **Specify whether testing for identity, assay and impurities are to be performed in the same analytical run.**

- c. **Provide a copy of the UV spectrum for each observed impurity** [REDACTED] (b) (4)

- d. **For the identity test, establish acceptable ranges for retention time on the HPLC chromatogram; and for maxima and minima in the UV spectrum. Visual comparison is not sufficient.**

- e. **Revise the method description to include a procedure for establishing system suitability across the analytical run.**

- f. **Provide a detailed description of the procedure for sample preparation which addresses the use of** [REDACTED] (b) (4)

- g. **Revise the description of the test sample and reference standard to include a statement of their stability.**

- h. **Specify whether purity of the reference standard includes a** [REDACTED] (b) (4)

i. Regarding the calculation for Percent Impurity:

1) Revise the equation to use [redacted] ^{(b) (4)}

2) Specify the [redacted] ^{(b) (4)} **for each observed impurity and incorporate this factor into the calculation.**

14. Using this corrected equation, re-calculate and submit the impurity test results reported in the batch analysis data (NDA section 3.2.P.5.4) and stability studies (NDA section 3.2.P.8.3).

15. Regarding the UV method for dissolution assay:

- a.** [redacted] ^{(b) (4)}
- b.** [redacted]
- c.** [redacted]

16. Regarding the submitted method validation studies:

- a. Specify when and where the studies were performed.**
- b. Provide** [redacted] ^{(b) (4)} **for each method.**
- c. For the dissolution assay method study, provide copies of the example** [redacted] ^{(b) (4)}
- d. For the HPLC impurities method, identify the source of the** [redacted] ^{(b) (4)}

17. For the batch analysis data (NDA section 3.2.P.5.4.), provide the [redacted] ^{(b) (4)} **for each observed impurity.**

18. Regarding the submitted container/closure system information:

- a. For the closure specification,** [redacted] ^{(b) (4)}
- b. Provide a description of the rigid container for the** [redacted] ^{(b) (4)}

19. Specify whether multiple batches of [REDACTED] (b) (4) [REDACTED] If yes, then the following additional information is needed:

- a. [REDACTED] (b) (4)
- b. [REDACTED]
- c. [REDACTED]

20. Establish a specification for the [REDACTED] (b) (4) [REDACTED]

21. Revise the post approval protocol (NDA section 3.2.P.8.2) to include the following:

- a. [REDACTED] (b) (4)
- b. [REDACTED] (b) (4)

22. Regarding the stability information in NDA sections 3.2.P.8.1 and 3.2.P.8.3:

- a. For tables 1 and 2 in NDA section 3.2.P.8.1, identify the site and date for packaging into bottles for each listed batch.
- b. The stress studies show increases in [REDACTED] (b) (4) over time and the formation of new degradation products under light stress, therefore the label storage statement should be revised to include a “protect from light [REDACTED] (b) (4) statement.

23. The submitted stability studies are not adequate to support the proposed shelf-life in that they do not address [REDACTED] (b) (4)

[REDACTED] (b) (4) In addition, only part of the studies [REDACTED] (b) (4) Until acceptable studies have been completed and submitted, we recommend the following:

a. [REDACTED] (b) (4)

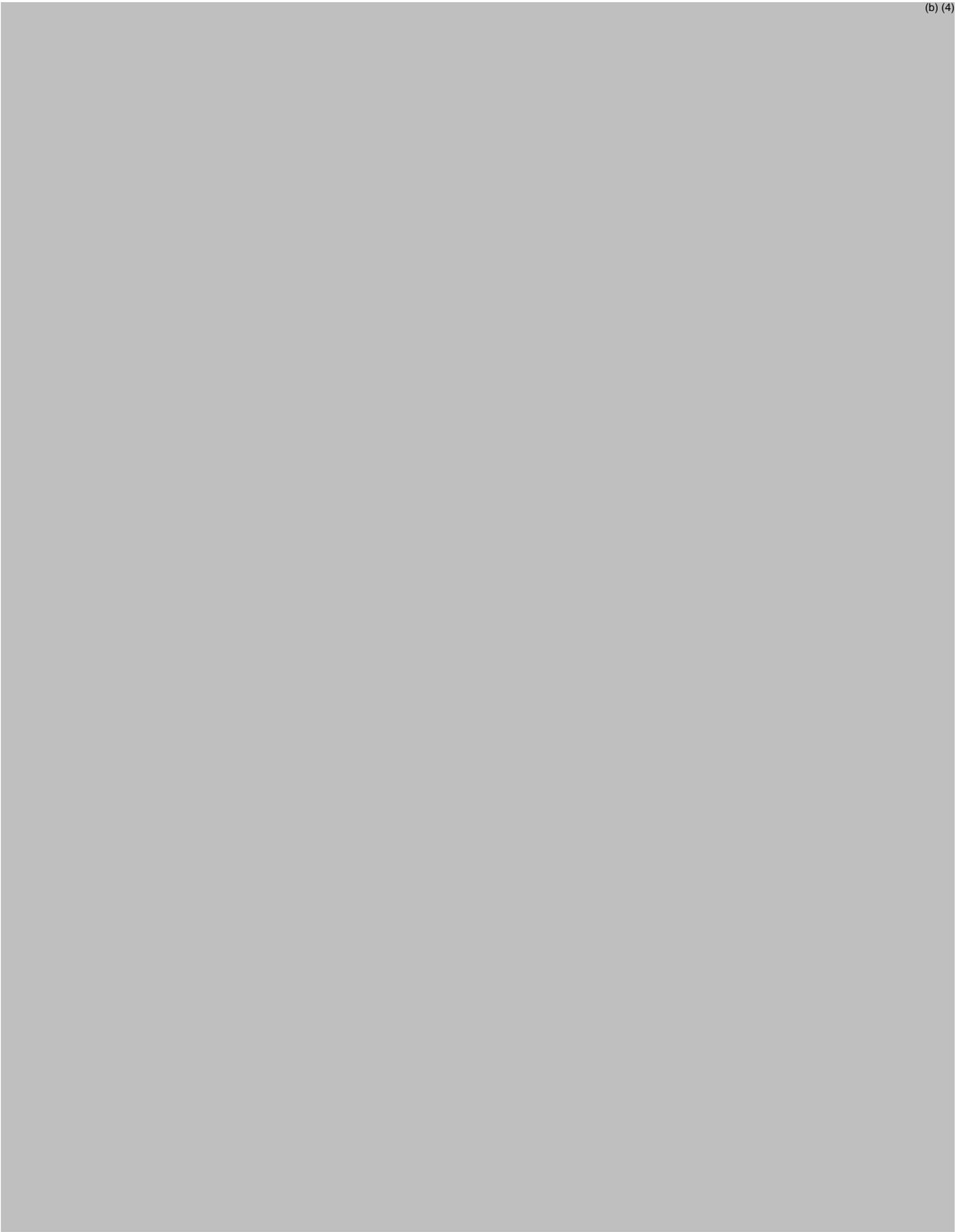
b. **The initial shelf-life for tablets in bottles should be revised to 12 months.**

24. [REDACTED] (b) (4)

Since the NDA submission date was June 5, 2015, the submission of additional stability study data will result in either the extension of the review clock or the submitted data will not be reviewed.

Process

[REDACTED] (b) (4)



Drug Substance

- 33. Include testing for elemental impurities in the drug substance consistent with the stage 4 ICH Q3D “Guideline for Elemental Impurities” or provide a risk assessment for the control strategy of elemental impurities and sufficient batch data to demonstrate testing of the drug substance batches is not necessary.**

If you have any questions, please contact me, Steven Kinsley, Ph.D. Regulatory Business Process Manager, at (240) 402-2773.

Sincerely,

Olen
Stephens -S

Digitally signed by Olen Stephens -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Olen Stephens -S,
0.9.2342.19200300.100.1.1=2000558826
Date: 2015.08.20 20:09:51 -0400

Olen Stephens, Ph.D.
Branch Chief, Branch II
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Fan, Ingrid

From: Fan, Ingrid
Sent: Wednesday, August 12, 2015 12:16 PM
To: Jazayeri, Jonathan (Jonathan.Jazayeri@astrazeneca.com)
Subject: NDA 208065: FDA Information Request

Hello Jonathan,

Our QT/IRT reviewer has the following information request that we wish you to address as soon as possible.

- Please submit all related ECG waveforms for study D516C002 to the ECG warehouse at www.ecgwarehouse.com

Please confirm receipt and let me know should you have any questions.

Thank you,
Ingrid

Ingrid Fan
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone:301-796-5053

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/s/

INGRID Y FAN
08/12/2015

Fan, Ingrid

From: Fan, Ingrid
Sent: Wednesday, August 12, 2015 5:16 PM
To: Jazayeri, Jonathan (Jonathan.Jazayeri@astrazeneca.com)
Subject: NDA 208065: FDA Clinical Comments and Information Request

Hello Jonathan,

Our clinical reviewer has the following clinical comment and information request that we wish you to address by **COB Friday, August 14, 2015**. Please send your response to me via email and follow with a formal submission to your NDA 208065.

- Please comment on patients in the combined AURA extension and AURA II studies who experienced increases in creatinine while on study. When analyzing grade shifts included in ADLB JMP datasets for AURA extension and AURA II, I only see 33 patients with grade shifts in creatinine. This is the same total you have provided in your pooled safety data, module 5.3.5.3, table 3.8.22. However, in table 42 of your summary of clinical safety you refer to 381 total patients (92.9%) as having creatinine grade shifts while on study, with the explanation of the discrepancy given in the footnote below-

“SOURCE: See Table 3.8.2.2 in Pooled Safety, Module 5.3.5.3. Note: Creatinine values included in this table are manually calculated from the individual study tables (see Table 34 of AURA extension and AURA2 CSRs in Module 5.3.5.2), due to **programmatic errors for this parameter** in the Ph II pooled safety output of Table 3.8.2.2 in Pooled Safety, Module 5.3.5.3”

- Please comment on which value for grade shifts in platelets is correct, 8% or 92.9%? If the correct value is 92.9%, please comment on how that number was obtained.

Kindly confirm receipt of this communication, and let me know should you have any questions.

Thank you,
Ingrid

Ingrid Fan
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone:301-796-5053

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/s/

INGRID Y FAN
08/12/2015

Fan, Ingrid

From: Fan, Ingrid
Sent: Friday, August 07, 2015 12:00 PM
To: Jazayeri, Jonathan (Jonathan.Jazayeri@astrazeneca.com)
Subject: NDA 208065: FDA Clinical Comment and Information Request

Hello Jonathan,

Our clinical reviewer has the following clinical comment and information request that we wish you to address by **COB Tuesday, August 11, 2015**. Please send your response to me via email and follow with a formal submission to your NDA 208065.

- When looking at the ISS-ISE dataset rslb and trying to recreate the sponsor's calculated shifts in laboratory values, the dataset seems to be problematic. There are many subjects missing baseline flags for various laboratory values. Additionally, when looking at the sponsor's calculated baseline shifts (in the "shift1" column) on the rslb datasets, these do not add up to the numbers provided, for example, in the proposed labelling (b) (4) [REDACTED] Please explain the discrepancy or, alternatively, please provide an updated rslb dataset that has updated baseline flags and "shift1" columns that correspond with the calculated totals.

Kindly confirm receipt of this communication, and let me know should you have any questions.

Thank you,
Ingrid

Ingrid Fan
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-5053

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/s/

INGRID Y FAN
08/07/2015

Fan, Ingrid

From: Fan, Ingrid
Sent: Thursday, August 06, 2015 12:59 PM
To: Jazayeri, Jonathan (Jonathan.Jazayeri@astrazeneca.com)
Subject: NDA 208065: FDA Information Request

Hello Jonathan,

Our clinical reviewer has the following clinical comments and information request that we wish you to address by **COB Monday, August 10, 2015**. Please send your response to me via email and follow with a formal submission to your NDA 208065.

1. The following three patients on AURA extension all died within the first two weeks of being dosed with study drug. They were listed as dying from “progressive disease”. Is there imaging confirmation available in any of these cases immediately prior to their deaths, or any other confirmation, that their disease had objectively worsened?
D5160C0001C/E4314702
D5160C0001C/E7800718
D5160C0001C/E7800741
2. On page 101 of the Summary of Clinical Safety, you mention regarding the later data cut-off for analysis of ILD cases,
“Please note: with this updated DCO date an additional 11 patients with ILD have been identified since the DCO of the Phase II studies (9th January, 2015). Because of the proximity of these events to the submission of the marketing application, patient narratives have not been completed in time for the initial submission. AstraZeneca is actively working to gather the information on these additional 10 patients and construct patient narratives for them. These additional narratives can be provided, once completed, upon request.”
Please provide those narratives, if available.
3. Please provide the Agency with any databases relating to PROs (patient-reported outcomes), which will be used for exploratory analyses.

Kindly confirm receipt of this communication, and let me know should you have any questions.

Thank you,
Ingrid

Ingrid Fan
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone:301-796-5053

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/s/

INGRID Y FAN
08/06/2015



NDA 208065

**FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED**

AstraZeneca Pharmaceuticals LP
Attention: Jonathan Jazayeri, Pharm.D., M.S., R.A.C.
Regulatory Affairs Director, Oncology
One MedImmune Way
Gaithersburg, MD 20878

Dear Dr. Jazayeri:

Please refer to your New Drug Application (NDA) dated June 5, 2015, received June 5, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for osimertinib tablets, 40 mg and 80 mg.

We also refer to your amendments dated June 10, 16, 24, and 26, 2015; and July 1, 2, 10 (2), 15, 16, 22, and 23, 2015.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is **February 5, 2016**. This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to: <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>).

However, we plan to act early on this application under an expedited review, provided that no significant application deficiencies or unexpected shifts in work priorities or team staffing prevent an early action.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by November 6, 2015. This date conforms to the 21st Century Review timeline for your application. If our review

continues on an expedited timeline, we may communicate revised dates for labeling and postmarketing requirement/commitment requests. In addition, the planned date for our internal mid-cycle review meeting is September 2, 2015. We are not currently planning to hold an advisory committee meeting to discuss this application.

During our filing review of your application, we identified the following potential review issue:

1. The analytical method descriptions do not demonstrate sufficient understanding to support the proposed (b) (4) regarding changes to be managed through your Quality Management System. Due to the accelerated time frame for this break-through product and the deficiencies in the method descriptions (an information request will be forthcoming), there will not be sufficient time to resolve the issues raised by this strategy. Therefore, (b) (4) in each analytical method that describes a (b) (4). We would like to discuss these (b) (4) to make agreements regarding the scope of the proposals and the data necessary to support the approach. We recommend that you request a CMC-only meeting to discuss these (b) (4) and ask that a representation from the Office of Policy for Pharmaceutical Quality be present for these discussions.

We are providing the above comment to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We request that you submit the following information:

2. 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).

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances, and

- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments or questions:

3. The product title and established pharmacologic class are missing in the full package Insert (FPI). Insert the approved proprietary name, if available, and established pharmacologic class.

We have also identified several labeling content issues. These issues are described in track changes and using the track changes "comment" function within the text of your PI, and are included as an attachment to this letter. Please review all content issues and revise your PI accordingly.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by August 14, 2015. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), and patient PI (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and patient PI (as applicable), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the drug for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, please call Ms. Ingrid Fan, Regulatory Health Project Manager, at (301) 796-5053.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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

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/s/

PATRICIA KEEGAN
08/04/2015



NDA 208065

GENERAL ADVICE

AstraZeneca Pharmaceuticals LP
Attention: Jonathan Jazayeri, Pharm.D., M.S., R.A.C.
Regulatory Affairs Director, Oncology
One MedImmune Way
Gaithersburg, MD 20878

Dear Dr. Jazayeri:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AZD9291.

We also refer to your May 20, 2015 electronic mail (e-mail) communication, formally submitted to your NDA on your June 10, 2015 submission, containing your request for comments and advice on clinical drug-drug interaction studies using Simcyp® PBPK simulations.

We have completed the review of your submission, and have the following comments and recommendations in response to your proposed questions.

1. Agency's interest in receiving [REDACTED] (b) (4) files for further evaluation by the Clinical Pharmacology reviewers.

FDA Response: No. These files can be [REDACTED] (b) (4)

2. If the Agency would like these files to be sent to them, please advise on the preferred mechanism of transfer

FDA Response: See FDA Response to Question 1, above.

If you have any questions, call Ingrid Fan, Regulatory Project Manager, at (301) 796-5053.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

PATRICIA KEEGAN
07/29/2015

From: Biable, Missiratch (Mimi)
To: jonathan.jazayeri@astrazeneca.com
Cc: paul.howarth@astrazeneca.com
Subject: NDA- 208065: Clinical Information Request -- Response Required
Date: Wednesday, July 08, 2015 3:41:00 PM
Importance: High

Dear Jonathan,

My Clinical reviewer has the following information request that we wish you to address by **COB, Friday, July 10, 2015.**

While reviewing the dataset included in your NDA, there is death that occurred on Study AURA2 by the data cut-off-date (DCO), but the investigator did not complete the death form in time so this does not appear anywhere in the spreadsheets. The only place this death is alluded to is in the disposition table (Table 11.1.1 AURA2 CSR, module 5.3.5.2). This makes the total number of AURA2 deaths 10 rather than 9.

Please provide additional information about the death, including date USUBJID, narrative, and CRF.

Please provide your response via email to me and follow that with a formal submission to your NDA. Confirm receipt of this communication and let me know if you have any questions.

Regards,

Missiratch (Mimi) Biable, M.S., R.A.C (US)
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Email: Missiratch.biable@fda.hhs.gov
Phone: 301-796-0154

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/s/

MISSIRATCH BIABLE
07/08/2015

From: Biable, Missiratch (Mimi)
To: "jonathan.jazayeri@astrazeneca.com"; "paul.howarth@astrazeneca.com"
Cc: [Fan, Ingrid](#)
Subject: NDA- 208065: Clinical Information Request -- Response Required
Date: Tuesday, July 07, 2015 2:43:00 PM
Importance: High

Dear Jonathan,

This is in follow-up to the email below from Dr. Blumenthal. Please provide the requested information via email to me by **COB, tomorrow, Wednesday, July 8, 2015** and follow that with a formal submission to your NDA.

In addition, please note that I will be covering this NDA for Ms. Ingrid Fan as she is out of the office unexpectedly.

Confirm receipt of this communication and let me know if you have any questions.

Regards,

Missiratch (Mimi) Biable, M.S., R.A.C (US)
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Email: Missiratch.biable@fda.hhs.gov
Phone: 301-796-0154

From: Blumenthal, Gideon
Sent: Tuesday, July 07, 2015 1:47 PM
To: paul.howarth@astrazeneca.com
Cc: Khozin, Sean (FDA); Weinstock, Chana; jonathan.jazayeri@astrazeneca.com; Biable, Missiratch (Mimi)
Subject: Dataset query

Dear Paul,

When querying the ISS-ISE ae and ISS-ISE adae, we excluded the screening by EPOCH and pre-treatment APHASE patients and came up with 395 patients rather than the expected 411 patients.

Please advise.

Thanks,
Gideon

Gideon Blumenthal, M.D.

Clinical Team Leader, Thoracic and Head and Neck Oncology

Division of Oncology Products- 2, OHOP, OND, CDER

U.S. Food and Drug Administration

10903 New Hampshire Avenue

Silver Spring, MD 20903

301.796.5369 (office)

(b) (6) (blackberry)

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/s/

MISSIRATCH BIABLE
07/07/2015

Fan, Ingrid

From: Fan, Ingrid
Sent: Wednesday, June 24, 2015 2:51 PM
To: Jazayeri, Jonathan (Jonathan.Jazayeri@astrazeneca.com)
Subject: NDA 208065 - FDA Nonclinical Information Request

Hi Jonathan,

Our Nonclinical Reviewer has the following information request that we wish you to address by **COB on Friday, June 26, 2015**. Please send your response to me via email and follow with a formal submission to your NDA 208065.

The report for (b) (4) Study 526253, entitled “AZD9291: Three month oral (gavage) toxicity study in the dog” states that the dogs used in this study were supplied by AstraZeneca.

Please provide additional information about the source of these animals (e.g. whether purchased from a supplier or, if purpose-bred by AstraZeneca, please provide information about the source of the founder animals), and indicate whether the animals were treatment-naïve at the time of study initiation.

Kindly confirm receipt of this communication, and let me know should you have any questions.

Thank you,
Ingrid

Ingrid Fan
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-5053

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/s/

INGRID Y FAN
06/24/2015



NDA 208065

INFORMATION REQUEST

AstraZeneca Pharmaceuticals LP
Attention: Jonathan Jazayeri
Director of Regulatory Affairs
One MedImmune Way
Gaithersburg, MD 20878

Dear Mr. Jazayeri:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AZD9291.

We also refer to your June 5, 2015 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. To facilitate our review of the dissolution data in the NDA, provide tables summarizing the amount (%) of drug released at each sampling time point per individual vessel (similar to Tables 13, 14 and 19 in 3.2.P.2.2. Pharmaceutical Development), in addition to the mean, RSD and range at 30 minutes. Provide the requested information for all clinical and stability batches included in 3.2.P.5.4 [Batch Analyses] and 3.2.P.8.3 [Stability Data]. For our convenience, provide (in the table or as part of the title or footnotes) information regarding the tablet strength, whether the tablet is debossed or plain, the number of tablets tested, the dissolution method details, and the clinical trial(s) where the specific batch or lot was used.
2. FDA refers you to the briefing document submitted 20-Feb-15 and the written feedback sent 24-Oct-15. As a follow-up to your questions 1 in the briefing document, specify the drug substance batches from the Establishment campaign you propose to use in AZD9291 drug product manufacture for initial commercial distribution. As a follow-up to your question 2 in the briefing document, specify the investigational AZD9291 film-coated tablet batches you request to use for initial commercial distribution.

If you have any questions, please contact me, Rabiya Laiq, Pharm.D., Regulatory Business Process Manager, at (240) 402-6153. Please respond by July 7, 2015.

Sincerely,

Rabiya Laiq, Pharm.D.
Regulatory Business Process Manager
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Rabiya Laiq

-S

Digitally signed by Rabiya Laiq -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Rabiya Laiq -S,
0.9.2342.19200300.100.1.1=2001555007
Date: 2015.06.23 11:31:00 -0400'



NDA 208065

NDA ACKNOWLEDGMENT

AstraZeneca Pharmaceuticals LP
Attention: Jonathan Jazayeri, Pharm.D., M.S., R.A.C.
Regulatory Affairs Director, Oncology
One MedImmune Way
Gaithersburg, MD 20878

Dear Dr. Jazayeri:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Osimertinib tablets, 40 mg and 80 mg

Date of Application: June 5, 2015

Date of Receipt: June 5, 2015

Our Reference Number: NDA 208065

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 4, 2015, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Products 2
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call Ingrid Fan, Regulatory Project Manager, at (301) 796-5053.

Sincerely,

{See appended electronic signature page}

Melanie Pierce
Acting Chief, Project Management Staff
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

MELANIE B PIERCE
06/19/2015

Fan, Ingrid

From: Fan, Ingrid
Sent: Friday, June 12, 2015 3:11 PM
To: Jazayeri, Jonathan (Jonathan.Jazayeri@astrazeneca.com)
Subject: NDA 208065 : FDA Information Request

Hello Jonathan,

Regarding NDA 208065, please provide or direct us to the location of following:

- 1) Name, address and contact information for all CROs used in the conduct of the clinical trials D5160C0001 and D5160C0002. This information was requested by OSI during the pre-application phase, and the sponsor indicated that these items would be found in the following location in the CSR under Appendix 12.1.4.4.

Reference: bimo-office-of-scientific-investigations-osi-part-1.pdf (page 21)

Section 3. Physical location of Documents (Table 3) Indicated the following under the request for physical location of Documents for [the studies]: Located in Appendix 12.1.4.4 of the respective Clinical Study Reports D5160C00001 and D5160C00002

- 2) *Provide the blinded ICR charter(s) used to support studies D5160C00001 and D5160C00002 or direct us to the location(s) in the application.*

Please confirm receipt and let me know should you have any questions.

Thank you,
Ingrid

Ingrid Fan
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-5053

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/s/

INGRID Y FAN
06/12/2015

Fan, Ingrid

From: Fan, Ingrid
Sent: Thursday, June 11, 2015 11:36 AM
To: Jazayeri, Jonathan (Jonathan.Jazayeri@astrazeneca.com)
Subject: NDA 208065 : FDA Information Request

Hi Jonathan,

Our Clinical Reviewer has the following information request that we wish you to address by **COB Thursday June 18, 2015**. Please send your response to me via email and follow with a formal submission to your NDA 208065.

1. Please clarify Table 1 in CTD 5.3.5.4 Office of Scientific Investigation Information, Part I document. Specifically, the difference between columns number of patients screened and number of patients randomized.
2. Please provide a tabular summary of individual tumor responses per IRC and investigator assessment (including tumor measurements) for sites 7800 (STUDY D5160C0001C) and 7401 (STUDY D5160C00002)

Please confirm receipt and let me know should you have any questions.

Thank you,
Ingrid

Ingrid Fan
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-5053

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/s/

INGRID Y FAN
06/11/2015

Fan, Ingrid

From: Fan, Ingrid
Sent: Wednesday, June 10, 2015 11:10 AM
To: Jazayeri, Jonathan (Jonathan.Jazayeri@astrazeneca.com)
Subject: NDA 208065 : FDA Information Request

Hello Jonathan,

Our Statistical Reviewer has the following information request that we wish you to address. Please provide your response as soon as possible, as we would like to have this information prior to the application orientation meeting scheduled on June 19, 2015.

1. Please provide executable SAS program(s) with adequate document(s) to duplicate the analysis datasets derivation from raw datasets.
2. Please provide the SAS programs as well as format library files used for efficacy and safety data analysis. If the SAS programs use any SAS macro, please provide all necessary macro programs.
3. Please provide SAS programs with adequate document(s) for the derived datasets and the analyses associated with the results presented in the proposed package insert.

Please confirm receipt and let me know should you have any questions.

Thank you,
Ingrid

Ingrid Fan
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-5053

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/s/

INGRID Y FAN
06/10/2015

Fan, Ingrid

From: Jazayeri, Jonathan <Jonathan.Jazayeri@astrazeneca.com>
Sent: Wednesday, May 20, 2015 3:41 PM
To: Fan, Ingrid
Subject: NDA 208065 - AZD9291 - Simcyp and Application Orientation Meeting

Dear Ingrid,

Due to the accelerated development of AZD9291, clinical drug-drug interaction (DDI) studies are ongoing and are not available to characterize the magnitude of the impact of co-dosed compounds. PBPK simulations using Simcyp® have been conducted by the sponsor [REDACTED] (b) (4)

If it will be helpful for the review, AstraZeneca would like to offer provision of the following files (see below) to the agency. However, since the submission structure does not allow transmission of these files through the normal electronic submission process, AstraZeneca would like inquire

- (1) Agency's interest in receiving all of these non-standard files for further evaluation by the Clinical Pharmacology reviewers
- (2) If the Agency would like these files to be sent to them, please advise on the preferred mechanism of transfer

The following files are available and AstraZeneca will be happy to submit them when requested by the Agency. AstraZeneca has utilized Simcyp® version 14.0 for these DDI evaluations.

1. The Simcyp workspace file, which has a .wksx extension (This can be opened in Simcyp software)
2. The AZD9291 compound file, which has a .cmpx extension (can be opened in Simcyp software)
3. The clinical invivo data file, which has a .xml extension
4. The results/output file from the simulations are excel files (4 excel files, each approximately 0.2 gb in size)

In addition, as we get closer to our planned submission date of June 5th, our team is looking forward to the opportunity to conduct an application orientation meeting with the Office. As a number of our team members are located globally, I would like to kindly request, if at all possible, to provide us with a proposed date(s) for this meeting. Given the anticipation of an expedited review under the breakthrough therapy designation process, we would like to ensure our team is prepared and available for the soonest possible date.

Kind Regards,
-Jonathan

Jonathan Jazayeri, PharmD, MS, RAC
Regulatory Affairs Director, Oncology

AstraZeneca | Global Medicines Development | GRAPSQA
200 Orchard Ridge Drive, Gaithersburg, MD 20878
T: (301) 398-0403 M: [REDACTED] (b) (6)
jonathan.jazayeri@astrazeneca.com

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/s/

INGRID Y FAN
06/08/2015



NDA 208065

MEETING REQUEST GRANTED

AstraZeneca Pharmaceuticals LP
Attention: Jonathan Jazayeri, Pharm.D., M.S., R.A.C.
Regulatory Affairs Director, Oncology
One MedImmune Way
Gaithersburg, MD 20878

Dear Mr. Jazayeri:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AZD9291.

We also refer to your May 20, 2015, email communication requesting an application orientation meeting.

The meeting is scheduled as follows:

Date: Friday, June 19, 2015
Time: 2:30 PM – 3:30 PM
Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1313
Silver Spring, Maryland 20903

Invited CDER Participants:

Patricia Keegan, Director, DOP2
Ingrid Fan, RPM
Sean Khozin, Medical Officer
Gideon Blumenthal, Medical officer Team Leader
Joyce Cheng, Statistics
Kun He, Statistics Team Leader
Jun Yang, Clinical Pharmacology
Hong Zhao, Clinical Pharmacology Team Leader
Shawna Weis, Non-Clinical
Whitney Helms, Non-Clinical Team Leader
Charles Jewell, CMC
William Adams, CMC
Liang Zhou, CMC Team Leader
Olen Stephens, CMC ONDP Branch Chief
Kasturi Srinivasachar, CMC OLDP Branch Chief

Teicher Agosto, CMC RBPM

Please e-mail me your attendee list at least one week prior to the meeting. For each foreign visitor, complete and email me the enclosed Foreign Visitor Data Request Form, at least two weeks prior to the meeting. A foreign visitor is any non-U.S. citizen who does not have Permanent Resident Status or a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

A few days before the meeting, you may receive an email with a barcode generated by FDA's Lobbyguard system. If you receive this email, bring it with you to expedite your group's admission to the building. Ensure that the barcode is printed at 100% resolution to avoid potential barcode reading errors.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Upon arrival at FDA, provide the guards with either of the following numbers to request an escort to the conference room: Ingrid Fan, 301796-5053.

If you have any questions, call me at (301) 796-5053.

Sincerely,

{See appended electronic signature page}

Ingrid Fan
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Foreign Visitor Data Request Form

FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH (MM/DD/YYYY)	
PLACE OF BIRTH (city and country)	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	
MEETING ENDING DATE AND TIME	
PURPOSE OF MEETING	
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	
HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number)	
ESCORT INFORMATION (If different from Hosting Official)	

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/s/

INGRID Y FAN
06/08/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 208065

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

AstraZeneca Pharmaceuticals LP
One Med Immune Way
Gaithersburg, MD 20878

ATTENTION: Jonathan Jazayeri
Regulatory Affairs Director

Dear Mr. Jazayeri:

Please refer to your presubmission New Drug Application (NDA) dated and received January 26, 2015, submitted under section 506 of the Federal Food, Drug, and Cosmetic Act for Osimertinib Tablets, 40mg and 80mg.

We also refer to:

- your correspondence, dated and received March 31, 2015, requesting review of your proposed proprietary name, Tagrisso
- your amendment, dated and received April 13, 2015, to your request for name review
- your amendment, dated and received May 29, 2015, to your request for name review

We have completed our review of the proposed proprietary name, Tagrisso and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your above submissions are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Latonia Ford, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4901. For any other information regarding this application, contact Ingrid Fan, Regulatory Project Manager in the Office of New Drugs, at 301-796-5053.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Deputy Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

LATONIA M FORD
06/02/2015

TODD D BRIDGES
06/02/2015

Fan, Ingrid

From: Fan, Ingrid
Sent: Tuesday, April 21, 2015 3:24 PM
To: 'Jazayeri, Jonathan'
Subject: RE: NDA 208065 - AZD9291 - Request For Feedback - PK Modeling

Hi Jonathan,

I forwarded your below email to the review team and we conclude that your proposals are acceptable.

Thank you,
Ingrid

Ingrid Fan

Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-5053

From: Jazayeri, Jonathan [<mailto:Jonathan.Jazayeri@astrazeneca.com>]
Sent: Monday, April 13, 2015 4:18 PM
To: Fan, Ingrid
Subject: NDA 208065 - AZD9291 - Request For Feedback - PK Modeling

Dear Ingrid,

AstraZeneca is the final stages of preparing the clinical portion of a New Drug Application for AZD9291 for the treatment of patients with (b) (4) metastatic EGFR T790M mutation-positive non-small cell lung cancer (NSCLC) who have progressed on or after EGFR TKI therapy. A rolling NDA submission was initiated by submitting the nonclinical portion of the NDA on January 27th, 2015, with the final, clinical and CMC, components of the submission being planned for June 5th 2015.

The following 3 reports will be included in the NDA submission:

- 1) Population PK Modeling & Simulation Report for AZD9291 incorporating clinical data from D5160C00001 (AURA), D5160C00005 and D5160C00002 (AURA2)
- 2) PK/PD Modeling & Simulation Report for AZD9291 incorporating clinical data from D5160C00001 (AURA) and D5160C00002 (AURA2)
- 3) Modeling & Simulation Report to Explore the Relationship Between the QT/QTc Interval and Plasma Concentrations for AZD9291 with ECG Data Collected from D5160C00002 (AURA2)

The analysis described in these 3 reports is based upon data files extracted from the clinical study databases according to predefined data specifications. Subsequent to the initiation of the analysis and reporting there have been minor updates to the clinical databases as follows:

1. There is 1 subject in AURA extension who missed 2 doses during Cycle 1. In the data files used in the analysis this patient is recorded as having had continuous dosing throughout Cycle 1. This has been corrected in the update to the AURA extension clinical database. In AURA extension a PK profile is collected on Cycle 2 Day 1. Since AZD9291 has a relatively long half-life (approximately 50 hours) this minor dose update to Cycle 1 would not be expected to significantly impact the Cycle 2 Day 1 PK profile. This will be confirmed by rerunning the final PK

model outputs using datasets that include the updates to the clinical databases and demonstrating that the model outputs are in agreement. These outputs will be included as an Appendix to the Population PK Modelling and Simulation Report.

2. The flag used to indicate patients with brain metastases at entry was not derived correctly for all patients in the data files used in the analysis. This has been corrected in the update to the AURA extension and AURA2 clinical databases. As per the data analysis plan submitted to the FDA (AZD9291 Population PK and PKPD Modelling & Simulation Analysis Plan, dated 15 January 2015), brain metastases at entry was only to be included in the analyses if a positive efficacy exposure response relationship was observed (as part of an assessment of the impact of potential confounding risks). The brain metastases at entry variable is not currently used in any of the analyses therefore this update has no impact on the reported analysis.

AstraZeneca has determined that these differences would therefore not be expected to impact the analyses or results presented in the 3 reports detailed above. As such, the proposed approach to provide the NONMEM datasets with the original predefined data specifications as .xpt files should be sufficient to support the NDA for AZD9291, but would greatly appreciate the Agency's feedback to confirm. AstraZeneca would welcome a teleconference if the Agency believes this would be helpful or necessary.

A formal submission to the IND with this request for Agency Feedback will be forthcoming.

Kind Regards,
-Jonathan

Jonathan Jazayeri, PharmD, MS, RAC
Regulatory Affairs Director, Oncology

AstraZeneca | Global Medicines Development | GRAPSQA
200 Orchard Ridge Drive, Gaithersburg, MD 20878
T: (301) 398-0403 M: (b) (6)
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/s/

INGRID Y FAN
04/30/2015

Fan, Ingrid

From: Fan, Ingrid
Sent: Wednesday, February 04, 2015 8:46 AM
To: Jazayeri, Jonathan (Jonathan.Jazayeri@astrazeneca.com)
Subject: NDA 208065: FDA Memorandum - Nonclinical Comment and Information Request - Response Required!

Hello Jonathan,

Our Non-clinical Reviewer has the following comment and information request that we wish you to address by **COB Friday, February 20, 2015**. Please send your response to me via email and follow with a formal submission to your NDA 208065.

FDA notes that a number of nonclinical reports submitted to NDA 208065 have undergone revision since they were originally submitted to IND 117,879. For each report that has been revised, provide a complete summary of changes as well as a statement of impact regarding the overall study interpretation.

Kindly confirm receipt of this communication, and let me know should you have any questions.

Thank you,
Ingrid

Ingrid Fan
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-5053

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INGRID Y FAN
02/04/2015



NDA 208065

ACKNOWLEDGE NDA PRESUBMISSION

AstraZeneca Pharmaceuticals LP
Attention: Jonathan Jazayeri, Pharm.D., M.S., R.A.C.
Regulatory Affairs Director, Oncology
One MedImmune Way
Gaithersburg, MD 20878

Dear Mr. Jazayeri:

We have received the first section of your New Drug Application (NDA) under the program for step-wise submission of sections of an NDA (section 506 of the Federal Food, Drug, and Cosmetic Act) for the following:

Name of Drug Product: AZD9291

Date of Submission: January 26, 2015

Date of Receipt: January 26, 2015

Our Reference Number: NDA 208065

We will review this presubmission as resources permit. Presubmissions are not subject to a review clock or to a filing decision by FDA until the application is complete.

Please cite the NDA listed above at the top of the first page of any communications concerning this supplemental application. Unless you are using the FDA Electronic Submissions Gateway (ESG), send all submissions by overnight mail or courier to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Products 2
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (301) 796-5053.

Sincerely,

{See appended electronic signature page}

Ingrid Fan
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

INGRID Y FAN
01/29/2015



IND 117879

MEETING MINUTES

AstraZeneca Pharmaceuticals LP
Attention: Jonathan Jazayeri
Regulatory Affairs Director
One MedImmune Way
Gaithersburg, MD 20878

Dear Mr. Jazayeri:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for AZD9291.

We also refer to the meeting between representatives of your firm and the FDA on December 9, 2014. The purpose of the meeting was to discuss and reach agreement on the potential data package required to support an accelerated approval of AZD9291 in patients with [REDACTED]^{(b) (4)} [REDACTED] /metastatic EGFR T790M mutation-positive non-small cell lung cancer (NSCLC) who have received prior EGFR TKI therapy.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-5053.

Sincerely,

{See appended electronic signature page}

Ingrid Fan
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: Tuesday, December 9, 3:30 PM - 4:30 PM
Meeting Location: White Oak Building 22, Conference Room: 1309

Application Number: IND 117879
Product Name: AZD9291
Indication: Treatment for patients with [REDACTED] ^{(b) (4)} metastatic, EGFR T790M mutation-positive, non-small cell lung cancer (NSCLC) who have received prior a EGFR tyrosine kinase inhibitor (TKI).

Sponsor/Applicant Name: AstraZeneca

Meeting Chair: Gideon Blumenthal
Meeting Recorder: Ingrid Fan

FDA ATTENDEES

Patricia Keegan Division Director, DOP2
Sean Khozin Clinical Reviewer, DOP2
Gideon Blumenthal Clinical Team Leader, DOP2
Ingrid Fan Regulatory Project Manager, DOP2
Laura Fernandes Statistical Reviewer, DBV
Shenghui Tang Statistical Team Leader, DBV
Ruby Leong Clinical Pharmacology Reviewer, DCPV
Stacy Shord Clinical Pharmacology Acting Team Leader, DCPV
Liang Zhao Pharmacometrics Team Leader, OCP/DPM
Whitney Helms Pharmacology/Toxicology Team Leader, DHOT
Ali Al Hakim Chemistry Branch Chief, ONDQA

EASTERN RESEARCH GROUP ATTENDEES

Patrick Zhou Independent Assessor

SPONSOR ATTENDEES

Eric Richards Senior Director, Regulatory Affairs, Oncology
Jonathan Jazayeri Director, Regulatory Affairs, Oncology
Hesham Abdullah VP, Regulatory Affairs, Oncology

Antoine Yver	Senior VP Head Oncology, Global Medicines Development
Paul Dickinson	Senior Clinical Pharmacology Scientist, Early Clinical Development
Andrew Walding	Safety Management Team Leader, Patient Safety
Michael Lahn	Global Patient Safety Physician, Oncology

On the Phone:

Serban Ghiorghiu	Global Clinical Lead
Nicola Schmitt	Global Product Statistician, Oncology
Flavia Borellini	VP, Global Product Development
Kathryn Brown	Senior Clinical Pharmacometrician, Oncology
Suzanne Jenkins	Diagnostics, Personalized Healthcare and Biomarkers
Simon Collett	Project Director, Pharmaceutical Development
Silke Klick	Director, Regulatory CMC
Mei Dey	Global Programming Lead
John Freeman	Director, Clinical Development
Marilyn Tsourounis	Associate Director, Regulatory Labeling
Lesley Farrington	Director, Regulatory Affairs (Roche Molecular Systems)
Elias Ketchum	Manager, Regulatory Affairs (Roche Molecular Systems)

1.0 BACKGROUND

Regulatory History:

AstraZeneca states that AZD9291 is a tyrosine kinase inhibitor (TKI) that selectively and irreversibly inhibits epidermal growth factor receptor (EGFR) mutations that are activating mutations considered “sensitive” to approved EGFR TKI and of the EGFR T790M mutation; AZD 9291 has limited inhibition of wild type EGFR.

The original IND was submitted on June 11, 2013. An application for Fast Track Designation was granted on November 6, 2013 for the investigation of AZD9291 for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) [REDACTED] (b) (4) and have progressed following prior EGFR TKI therapy, based on the development program designed to demonstrate a clinically important increase in progression free survival as compared to available therapy. A type C meeting was held on January 14, 2014 to discuss the overall clinical development program for AZD9291 to support approval for the treatment of patients with [REDACTED] (b) (4), EGFR T790M mutation-positive NSCLC.

An application for Breakthrough Therapy Designation was submitted on February 27, 2014 and granted on April 16, 2014 for the treatment of patients with metastatic, EGFR T790M mutation-positive, non-small cell lung cancer (NSCLC) whose NSCLC has progressed during treatment with an FDA-approved, EGFR tyrosine kinase inhibitor. AstraZeneca submitted an Initial Pediatric Study Plan (iPSP) on July 1, 2014 which described their intent to submit a waiver for the pediatric requirements in the NDA. AstraZeneca submitted an Orphan Drug Designation application to the Office of Orphan Product Development (OOPD) on July 2, 2014; orphan

designation was granted on September 4, 2014 for the treatment of epidermal growth factor receptor mutation-positive non-small cell lung cancer.

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

On October 2, 2014 and October 7, 2014, Type B meetings were held to discuss the proposed clinical, nonclinical, and CMC components of the NDA filing respectively. While FDA generally agreed with the proposed contents for a future NDA, FDA stated that AstraZeneca should request a formal Pre-NDA meeting to reach final agreement on the NDA content and format in advance of submitting the NDA.

On October 15, 2014, AstraZeneca submitted a Type B Pre-NDA Meeting request to discuss and reach agreement on the proposed content of the NDA and additional logistical issues to facilitate the review and submission of the NDA.

AstraZeneca intends to submit an NDA for the following proposed indication:

“TRADENAME is indicated for the treatment of patients with (b) (4) /metastatic EGFR T790M mutation-positive NSCLC (as determined by an FDA-approved test) who have received prior EGFR TKI therapy.”

NDA Submission in Support of the Proposed Indication:

AstraZeneca states that AZD9291 will be marketed as an 80 mg tablet for oral administration. A40 mg tablet strength will also be marketed for use in patients requiring dose reduction for adverse reactions.

According to AstraZeneca’s electronic mail (email) dated November 13, 2014, the most recent efficacy and safety data intended to support the proposed indication was provided as part of the Briefing Document for the Breakthrough Therapy Designation Type B Meeting, held on October 2, 2014 and the next planned data cut for efficacy will be in February 2015. The available data describing efficacy of AZD9291 as abstracted from these minutes are:

“AstraZeneca states that as of August 1, 2014, the confirmed ORR is 61%; 95% CI (52% to 70%), across 78 responding patients among 127 evaluable, EGFR T790M+ patients treated with AZD9291. In more than 80% of the confirmed responses observed, the response has been sustained for more than 24 weeks. The median duration of response (DOR) among approximately 50 patients with objective responses who were treated with the recommended Phase 2 dose of AZD9291 in the phase 1 portion of the AURA trial is estimated to be 8.2 months with a lower 95% CI of 6.9 months based on the Kaplan Meier method.”

AstraZeneca intends to submit a NDA in June 2015 which will include the final and interim results, respectively, of the AURA extension and AURA2 trials. Both trials are multicenter, single-arm, clinical trials of AZD9291, conducted in patients with advanced NSCLC patients whose tumors harbor the EGFR T790M mutation, with disease progression following treatment with an EGFR TKI, with or without prior chemotherapy (Table-1, and Figure 1). AstraZeneca proposes to initiate the NDA as a rolling review in January 2015 and will be requesting a priority review for the NDA submission.

Table 1. Summary of key single arm efficacy trials with AZD9291

Study	Design	Patient population
D5160C00001 (AURA)	Ongoing Phase I multi-center, open-label, dose-escalation, and dose-expansion study to determine safety and tolerability, MTD, biologically effective dose, PK, and preliminary anti-tumor activity of AZD9291	Advanced NSCLC patients who have progressed following prior therapy with an EGFR TKI agent ± chemotherapy (mostly ≥second-line patients, as well as 2 first-line cohorts).
D5160C00001 (AURA extension)	“Phase 2” expansion cohort portion of AURA.	Advanced NSCLC patients who have progressed following either one prior therapy with an EGFR TKI (second-line chemotherapy-naïve, n≈approximately 50) or following treatment with both EGFR TKI and at least one other prior line of therapy, such as cytotoxic doublet chemotherapy or immunotherapy (≥third-line, n≈ 125).
D5160C00002 AURA2	Ongoing Phase 2, single-arm, open label non-randomized study to replicate the efficacy and safety data observed in the AURA extension	Advanced NSCLC patients who have progressed following either one prior therapy with an EGFR TKI (second-line chemotherapy-naïve, n= approximately 50) or following treatment with both EGFR TKI and at least one prior platinum-based doublet chemotherapy (≥third-line, n≈ 125).

Prior to the October 2014 Type B meetings, AstraZeneca had planned to include efficacy data for the proposed NDA on

- an interim analysis of objective response rate (ORR) on all patients in AURA extension (n=175)
- An interim analysis of ORR in 175 evaluable patients from the AURA2 trial.

AstraZeneca proposed to assess ORR in the “evaluable for response” population defined as the subset of patients who received the first dose of AZD9291 at least 13 weeks prior to the date of data cut-off and for whom there were a baseline RECIST assessment and at least 2 follow-up RECIST scans to enable confirmation of response, or patients who had withdrawn or died before the second RECIST assessment.

Therefore, the assessment of efficacy in the proposed NDA would be based on approximately 350 subjects from AURA extension and AURA2, with all patients having at least 3-months of follow-up. Supplemental information to provide characterization of the durability of response will be provided from approximately 50 patients enrolled in the dose-escalating portion of AURA 1 who were treated at the 80 mg dose.

On October 28, 2014, AstraZeneca submitted a request for rolling review of the proposed NDA according to the following schedule:

Rolling Submission Part	Approximate Date	CTD Section	Comment
Part 1	12 Jan 2015	M4 (Non-clinical) M2 (Non-clinical) M5 (DMPK)	<ul style="list-style-type: none"> For non-clinical sections of Module 2, references to clinical PK and safety will use preliminary clinical data from the latest update used for the ESMO data cut (1 August 2014). Final conclusions on the safety profile in humans versus animals (where required) would be included in the clinical modules. Non-clinical DMPK reports will be submitted under Module 5, but will be summarized along with the Non-clinical sections in Module 2.
Part 2	27 March 2015	OSI Datasets	
Part 3	05 June 2015	M3 (Quality) M2 (Quality) M2 (Clinical) M5 (Clinical)	<ul style="list-style-type: none"> If deemed necessary, Module 3 of the NDA will provide final qualification specifications and safety characterization for potential impurities. Final data from the human metabolite ID study will read out in April 2015. Preliminary evaluation of the qualitative and quantitative metabolite profile in humans and confirmation of adequate non-clinical characterization of metabolites will be included in the clinical pharmacology sections in Module 5.

According to AstraZeneca's email communication dated November 10, 2014, AstraZeneca clarified their plan to have final specifications, including qualification data for organic impurities, in the M3 section at the time of submission of the last component of the rolling submission.

AstraZeneca also stated that if a separate nonclinical toxicology is required to qualify new impurities, there is a small chance that the study report may not be available until after the last component of the rolling submission, but would definitely be available within 30-days of the final component of the rolling submission. AstraZeneca intends to communicate with FDA within first quarter of next year following review of impurity profiles of drug substance batches manufactured at the proposed commercial site. If required, AstraZeneca will request an amendment of the rolling submission plan, allowing for the submission of this report within the 30-days allowed by PDUFA V.

According to AstraZeneca, the results of the following studies conducted to characterize the pharmacokinetic profile of AZD9291 are not planned for inclusion in the NDA:

- [REDACTED] (b) (4)
- [REDACTED] (b) (4) Assess the Effect of (b) (4) of (b) (4) AZD9291 (b) (4) (a CYP3A4 Inhibitor) on the Pharmacokinetics of (b) (4)
- [REDACTED] (b) (4) to Assess (b) (4) the Effect of AZD9291 on the Pharmacokinetics of (b) (4) CYP3A4 (b) (4) Substrate) (b) (4)
- [REDACTED] (b) (4) to Assess (b) (4) the Effect of (b) (4) (a CYP3A4 Inducer) on the Pharmacokinetics of AZD9291 (b) (4)
- [REDACTED] (b) (4) to Assess (b) (4) the Effect of AZD9291 on the Pharmacokinetics of (b) (4) BCRP (b) (4) Substrate) (b) (4)
- [REDACTED] (b) (4)

AstraZeneca states that the planned confirmatory trial is AURA3 [Study D5160C00003], a randomized study comparing AZD9291 to platinum-based doublet chemotherapy for the (b) (4) treatment of patients with EGFR T790M mutation-positive NSCLC. Milestones for submission of this trial are uncertain and will be determined closer to the NDA filing date.

DISCUSSION

Clinical:

1. a. At the Breakthrough Therapy Designation Type B Meeting on 02 October 2014, the Agency requested updated DoR data for those subjects with a confirmed response in the Phase II studies in the initial clinical NDA package to be submitted during the NDA review. Does the Agency agree with the proposed plan for the provision of these data?

FDA Response: AstraZeneca's proposal to submit updated DoR data no later than July 31, 2015, more than 30 days after the submission of the final component of the NDA on June 5, 2015 is acceptable with the understanding that FDA may not review such late submissions. It would be preferable to include this information as the final component of the rolling NDA application in order to include more mature data on the duration of response.

Sponsor Response (12/9/2014 Email):

Sponsor acknowledges, please see response to Question 1c

- b. In addition to the updated DoR on the Phase II Studies (as described above), does the Agency agree that updated DoR can also be provided on the 80 mg Phase I Expansion and Paired Biopsy cohorts (D5160C00001), should a median DoR not be reached in these cohorts of subjects by the initial NDA filing?

FDA Response: Please see FDA response to Question 1a.

Sponsor Response (12/9/2014 Email):

Sponsor acknowledges, please see response to Question 1c

- c. Does the Agency agree that the updated DoR data requested by the Agency (b) (4)

FDA Response: FDA will make a determination on the inclusion of the updated DoR data (b) (4)

(b) (4)

Sponsor Response (12/9/2014 Email):

Sponsor acknowledges the Agency's comments and would like to discuss if the provision of updated clinical information within 30 days of the NDA file will increase the likelihood of the Agency's review [REDACTED] (b) (4)
[REDACTED]

Discussion during Meeting of Questions 1a-1c:

FDA requested that the updated information characterizing duration of response be submitted within 30 days after the last modules of the rolling NDA submission as a late minor component under the PDUFA V Program. AstraZeneca will determine whether this is feasible.

2. a. Does the Agency agree with the proposed list of Preferred Terms for each Adverse Event Topic in Appendix A?

FDA Response: FDA cannot comment on the proposed list of Preferred Terms for each Adverse Event Topic given that no information on the MedDRA version used is provided. AstraZeneca should ensure that a single version of MedDRA is used for coding of all adverse events across all clinical trials. Standardized MedDRA Queries (SMQs) are generally acceptable for exploration of safety signals provided that the grouping of the Preferred Terms follow established SMQ standards.

Sponsor Response (12/9/2014 Email):

Sponsor has used MedDRA (version 17.1) and will be consistent with this version throughout the NDA

- b. Does the Agency agree with the analysis approach to present the nature, frequency and severity of Adverse Effects of Special Interest for submission in the NDA?

FDA Response: Yes, FDA generally agrees with AstraZeneca's approach for presentation of data on Adverse Effects of Special Interest. Please note that at the time of the NDA review and based on FDA's analysis of the safety database, FDA may consider characterization of adverse events (e.g. rash) in the label based on a composite of several related Preferred Terms that may be different than AstraZeneca's proposal presented in Appendix A of the meeting package.

Sponsor Response (12/9/2014 Email):

Sponsor acknowledges the Agency's response. If the Agency alters the grouping of preferred terms that are relevant for labeling during the review, the sponsor respectfully requests to be notified as soon as possible. This will

facilitate the alignment of the Sponsor's documents with that of the Agency's analyses.

Discussion during Meeting of Questions 2a-2b:

FDA acknowledged AstraZeneca's response. There was no discussion during the meeting.

3. Does the Agency agree with the list and approach for analyses of intrinsic and extrinsic factors relating to safety?

FDA Response: Yes, FDA generally agrees with AstraZeneca's approach for assessing the impact of intrinsic and extrinsic factors on the safety profile of AZD9291. Please note that FDA may conduct safety explorations that may differ from AstraZeneca's proposed analyses for inclusion in the label.

In addition to the safety analyses presented in the meeting package, please provide the following safety analyses:

- Adverse events leading to dose interruption
- Adverse events leading to dose reduction
- Time to first dose reduction (median, range)
- Time to first dose interruption (median, range)
- Duration of dose interruption (median, range)

Sponsor Response (12/9/2014 Email):

Tabulations and listings of the adverse events leading to dose interruption and reduction will be included for the individual studies and for the pooled datasets in the NDA.

Analyses for the time to dose reduction/interruption, as well as duration dose interruption will be provided for the pooled datasets.

Discussion during Meeting:

FDA acknowledged AstraZeneca's response. There was no discussion during the meeting.

Clinical Pharmacology:

4. Does the Agency agree to the proposed plan for population PK and exposure-response analyses?

FDA Response: In general, the proposed plan for population PK and exposure-response (E-R) analyses appears reasonable. FDA recommends evaluating the effect of confounding risk factors on E-R outcome in the event of a positive E-R relationship for adverse events or efficacy endpoints. Refer to Additional Comment #24.

Sponsor Response (12/9/2014 Email):

In the event of a positive E-R relationship following initial graphical exploration for adverse events (occurrence of rash or diarrhoea) or response rate efficacy endpoints, diagnostic plots that relate the (b) (4) will be used to assess the absence of confounding risk factors, in a similar manner to that described in the following reference: “Diagnostics for confounding in PK=PD models for oxcarbazepine”, J.R. Nedelman et al, Statist. Med. 2007; 26:290–308. Does the agency consider this acceptable?

Discussion during Meeting:

FDA stated that E-R analysis should account for any potential risk factors. AstraZeneca agreed to provide the recommended information requested in FDA’s response to Question 4 and FDA’s additional comment 24.

Regulatory:

5. Does the Agency agree with the contents of the proposed NDA as delineated in the attached Table of Contents (ToC)?

FDA Response: Except for the proposed stability update, the Table of Contents for the proposed NDA is acceptable and would be considered a complete application.

The proposal for submitting updated stability data not acceptable. Under PDUFA V, amendments should be submitted no later than 30 days after filing and should include at least 12 months of primary stability data.

Please refer to the meeting minutes of January 14, 2014, regarding the acceptability of conducting an embryo-fetal development study in only one species.

Sponsor Response (12/9/2014 Email):

With regards to the requirement for 12 months of primary stability data, the Sponsor respectfully refer to the TC held with the CMC review division on 12th August 2014 and the written summary provided by the Agency on September 11, 2014. AstraZeneca had identified that 12 month primary stability data would not be available for a submission in Q2 2015 and requested that the FDA consider acceptance of a package with supportive stability data and 6 month primary batch stability data.

FDA agreed with the proposal, subject to a number of requests to characterize the stability data package in the NDA submission. The Sponsor is committed to provide the information requested, as outlined in the FDA meeting minutes written summary dated 11th September, as part of the NDA submission.

Regarding the post-marketing commitments under Question 9, the Sponsor agrees not to submit 9-month and 12-month primary stability data until explicitly requested by the FDA.

The Sponsor would like to confirm that submission based on 6mo stability data in accordance with feedback received on 12 August, 2014 and 11 September, 2014 is still acceptable to the Agency.

Furthermore, effects of AZD9291 on embryo-fetal development and early postnatal survival/growth were assessed in a modified rat embryo-fetal development study, which included both a preimplantation administration phase plus a littering phase because both the preimplantation and perinatal time periods were predicted (based on other molecules in the same pharmacological class) to be the most sensitive periods. This study was designed to comply with ICHS5 regulatory guidelines where few animals are required to detect high frequency effects (n=6 dams per dose group were used in the different study phases; dose levels between 1 and 30 mg/kg/day were evaluated). Toxicokinetic assessment of exposure to AZD9291 in dams, fetuses and suckling pups was included in this study. Histopathological assessment of key target organs (tongue and cornea) was also included for dams to confirm a pharmacodynamic effect. In this study, AZD9291 showed unequivocal evidence of marked adverse effects on both embryonic survival plus early postnatal viability and growth in the rat at clinically relevant exposures (~1.4 times the exposure at the recommended human dose of 80 mg daily based on total AUC).

AstraZeneca therefore considers that a confirmatory embryo-fetal development study in the rabbit is not required to inform product labelling and no further studies are planned (in line with ICHS9 guidance and the referenced meeting on 14 January 2014).

Discussion during Meeting:

FDA acknowledged the prior discussion agreeing to submission of 6-month stability data plus supportive data of 12-month DP stability data from clinical batches and 24-month DS stability data from clinical batches. FDA confirmed that this is the minimum acceptable data to support an initial commercial expiry period. However, FDA expressed strong preference to receive 9-month DP stability data within 30 days of the final component of the NDA submission.

AstraZeneca will determine whether providing the above data within 30 days of the final component of the NDA submission is possible.

FDA stated that based on AstraZeneca's description of the rat embryo-fetal development study included in the response, this study appears sufficient to support filing without an additional confirmatory study in rats or rabbits.

AstraZeneca confirmed that they will submit any necessary impurity qualification studies within 30 days of the final component of the NDA submission.

6. Would the Agency be able to provide potential dates for a Day-45 Application Orientation Meeting?

FDA Response: This question is premature and should be revisited in May 2015 prior to the submission of the last reviewable unit of the NDA.

Sponsor Response (12/9/2014 Email):

Sponsor acknowledges and has no further comment.

Discussion during Meeting:

FDA acknowledged AstraZeneca's response. There was no discussion during the meeting.

7. Does the Agency agree that a separate 1-hour meeting may be scheduled with the FDA clinical and statistical reviewers, following the application orientation meeting (preferably on the same day), to orient the reviewers to the clinical research trial (CRT) package?

FDA Response: Yes.

Sponsor Response (12/9/2014 Email):

Sponsor acknowledges and has no further comment.

Discussion during Meeting:

FDA acknowledged AstraZeneca's response. There was no discussion during the meeting.

8. Does the Agency have any particular software that might be used during labeling negotiations so that both parties may view changes that the Agency makes to the label live, to facilitate collaborative resolution of the final label?

FDA Response: No.

Sponsor Response (12/9/2014 Email):

Sponsor acknowledges and has no further comment.

Discussion during Meeting:

FDA acknowledged AstraZeneca's response. There was no discussion during the meeting.

9. Does Agency agree with the proposed post-marketing commitments/requirements?

FDA Response: FDA generally agrees with the proposed post-marketing commitments/requirements for clinical pharmacology and clinical studies. Please note that the results of the confirmatory clinical trial to verify clinical benefit for

AZD9291 if accelerated approval is granted must be a post-marketing requirement under 21 CFR 314 Subpart H. In the NDA submission, provide a description of the goals of the studies, the study designs, and milestones for study completion and submission of the final study reports. Additional postmarketing requirements or commitments may be requested upon review of the NDA.

Sponsor Response (12/9/2014 Email):

Sponsor acknowledges and has no further comment.

Discussion during Meeting:

FDA acknowledged AstraZeneca's response. There was no discussion during the meeting.

10. Does the Agency agree with the proposal to include [REDACTED] (b) (4)

FDA Response: No, FDA does not agree with the proposal to [REDACTED] (b) (4)
[REDACTED] Please see FDA response to question 5.

Sponsor Response (12/9/2014 Email):

Sponsor acknowledges and will endeavor to include as part of the initial submission.

Discussion during Meeting:

FDA acknowledged AstraZeneca's response. There was no discussion during the meeting.

ADDITIONAL COMMENTS

Sponsor Response (12/9/2014 Email):

Sponsor acknowledges the advice for the NDA and will address the relevant components of the advice provided below as part of the NDA submission.

Clinical Pharmacology

Address the following clinical pharmacology related questions in the NDA submission:

11. What is the basis for selecting the dose(s) and dosing regimen used in the registration trial(s)?
12. What are the exposure-response relationships (dose-response, exposure-response) for activity/efficacy and for safety?
13. How was the QT prolongation potential of AZD9291 assessed? What are the conclusions and proposed labeling description?
14. What are the characteristics of absorption, distribution, metabolism and excretion of AZD9291 and its active metabolites?
15. What are the effects of food on the bioavailability of AZD9291? What are the dosing recommendations with regard to meals or meal types? Provide justification for recommendation with regard to meals or meal types.
16. What influence do intrinsic factors (such as those listed below) have on AZD9291 exposure, activity/efficacy and safety? What dose and administration modifications are recommended?
 - a. sex
 - b. race
 - c. weight
 - d. disease
 - e. genetic polymorphism
 - f. hepatic impairment
 - g. renal impairment
17. What influence do the extrinsic factors (such as those listed below) have on AZD9291 exposure, activity/efficacy and safety? What dose and administration modifications are recommended?
 - a. concomitant medications
 - b. CYP and/or transporter based drug-drug interactions
 - c. diet
 - d. smoking

Provide the following in preparing clinical pharmacology sections of the NDA submission:

18. Bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics studies.
19. Complete datasets for clinical pharmacology and biopharmaceutics studies. The subject's unique ID number in the pharmacokinetic (PK) datasets should be consistent with those in datasets submitted for clinical review.

20. All datasets for concentration-time profile, derived PK parameters, population PK analysis, and exposure-response analysis as SAS transport files (*.xpt). Provide a description of each data item in a Define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
21. Present the PK parameter data as geometric mean with coefficient of variation (and mean \pm standard deviation) and median with range as appropriate in the study reports.
22. Identify individual subjects with dose modifications (such as dose reduction, interruption or discontinuation); the time to the first dose modification and the reasons for dose modifications within the population PK and exposure-response datasets. Provide the relevant descriptive statistics for each of these variables in support of the proposed dose and administration.
23. Submit the following data and information to support the population PK analysis:
 - a. All datasets used for model development and validation.
 - b. Model codes or control streams and output listings for all major model building steps (e.g., base structural model, covariate models, final model, and validation model). Submit these files as ASCII text files with *.txt extension (e.g., myfile_ctl.txt, myfile_out.txt).
 - c. A model development decision tree or table which gives an overview of modeling steps.
 - d. Include the following in the population analysis reports:
 - Standard model diagnostic plots
 - Individual plots for a representative number of subjects including observed concentrations, the individual prediction line and the population prediction line
 - Model parameter names and units in tables. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1)
 - Summary of the report describing the clinical application of modeling results

Refer to the following pharmacometric data and models submission guidelines <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm> for more information.

24. Submit the following items to support the exploratory exposure-response analysis for measures of effectiveness, biomarkers and toxicity relationships for AZD9291 and its major active metabolites in the targeted patient population.
- a. Consider including the following when submitting the exposure-response analyses:
- Analyses may include but not be limited to exploratory analyses such as Kaplan-Meier analyses stratified by subgroups of drug exposure, univariate and multivariate logistic and/or Cox regression analyses, whichever are deemed appropriate to support the dose selection or adjustment.
 - Drug exposure to be used in the analyses may include but not be limited to trough concentration at steady state, maximum concentration at steady state, or average concentration at steady state. A justification should be provided for the exposure metric that is used for the analysis.
 - Response should at least include primary and key secondary endpoints for efficacy, overall safety events, or adverse events of interest.
 - A model development flow chart, decision tree, or table that gives an overview of model development steps. Model codes and output listings for all major model building steps (e.g., base structural model, covariate models, final model, and validation model).
 - All datasets, NONMEM control streams, and scripts used for model development, validation, and simulation. Data files should be submitted as SAS transport files and other files be submitted as ASCII text files (e.g., myfile_ctl.txt, myfile_out.txt).
- b. Include the following in the exposure-response analysis reports:
- A summary of baseline characteristics, including but not limited to demographics, disease features, and lab measurements, for all patients used in the analysis and subgroups based on drug exposure(s).
 - Distribution of drug exposure(s) for the full population used in analysis.
 - A summary table of final model parameters with their corresponding units.
 - Any plots deemed appropriate to support the clinical interpretation of modeling results.
 - A summary describing the clinical application of modeling results.

Refer to Guidance for Industry found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf> and <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf> for more information.

25. Submit the following items for QTc study/assessment:
- a. Copy of the QT/QTc study protocol
 - b. Copy of the Investigator's Brochure
 - c. Annotated CRF
 - d. Define file which describes the contents of the electronic data sets
 - e. Electronic data sets as SAS transport files (in CDISC SDTM format – if possible) and all the SAS codes for the analyses
 - f. ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)
 - g. Completed Highlights of Clinical Pharmacology Table

Additional Discussion During the Meeting:

- AstraZeneca informed FDA of their plans to open an expanded access program in April 2015. AstraZeneca confirmed that this access program will not interfere with the accrual to the ongoing confirmatory trials.
- AstraZeneca intends to submit a marketing application for AZD9291 to the EMA and to the PMDA around the time of submission of the final module of the rolling NDA to the FDA.
- AstraZeneca will submit the updated results of AURA 2 and AURA Extension studies to the IND by mid-January, approximately a week prior to the revised schedule for the first component of the rolling submission.
- AstraZeneca inquired about FDA's response to the QT-IRT submission dated July 28, 2014. In response to the briefing document for QT-IRT (eCTD Sequence No. 0080 submitted on July 28, 2014) and Question 2b of the briefing document for the Type B Breakthrough Therapy meeting held on October 2, 2014 (eCTD Sequence No. 0096 submitted on September 2, 2014), QT-IRT found the ECG monitoring and analysis plan to be adequate as stated in the meeting minutes dated October 17, 2014.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.

All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion on the need for a REMS was held it was concluded that a REMS will not be required for filing of the NDA based on the available data. A final decision will be made during the review of the application.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. FDA agreed that the following minor components of the NDA may be submitted within 30 calendar days after the submission of the original application:
 1. Updated clinical information on durability of based on the data cut-off date of May 1, 2015.
 2. 9-month stability data on the commercial DP and DS batches.
 3. Necessary impurity qualification studies.

AstraZeneca must prominently identify each submission containing late component(s) with the following wording in bold capital letters at the top of the first page of the submission:

NDA NUMBER: LATE COMPONENT - CLINICAL
NDA NUMBER: LATE COMPONENT - NONCLINICAL
NDA NUMBER: LATE COMPONENT - QUALITY

ATTACHMENTS AND HANDOUTS

AstraZeneca presented the following data during the meeting:

Table 1: Clinical Database to support assessment of AZD9291 80mg T790M mutation positive patients

Study	Follow-up		
D5160C00001 (AURA): Ongoing Phase I multi-center, open-label, dose-escalation, and dose-expansion study to determine safety and tolerability, MTD, biologically effective dose, PK, and preliminary anti-tumor activity of AZD9291	Projected follow-up at time of submission	Data to be provided by end of January 15	Final data for NDA
	Data cut-off	DBL: 22nd Dec 2014	DBL: 22nd Dec 2014
	Number of subjects	65	65
	Subjects with ≥3months follow-up	62	62
	Subjects with ≥6 months follow-up	49	49
	Subjects with ≥12 months follow-up	25	25
	Discontinued prior to 3 months	3 (1 day, 6 wks and 9wks)	3 (1 day, 6 wks and 9wks)
Maximum Duration of Follow-up	15 months	15 months	
D5160C00001 (AURA extension): Ongoing Phase II single-arm, open label non-randomized study extension to AURA	Projected follow-up at time of submission	Draft data to be provided by end of December 2014	Final data for NDA
	Data cut-off	11th November 2014	DBL: February 2015
	Number of subjects	200	201
	Subjects with ≥3months follow-up	116	201
	Subjects with ≥6 months follow-up	0	59
	Maximum duration of follow-up	6 months	8 months
D5160C00002 AURA2: Ongoing Phase II, single-arm, open label non-randomized study to replicate the efficacy and safety data observed in the AURA extension.	Projected follow-up at time of submission	Draft data to be provided by end of January 2014	Final data for NDA
	Data cut-off	1st December 2014	DBL: February 2015
	Number of subjects	202	210
	Subjects with ≥3months follow-up	102	210
	Subjects with ≥6 months follow-up	0	22
	Maximum duration of follow-up	5.5 months	7 months

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation for this indication, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidance.

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e. phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

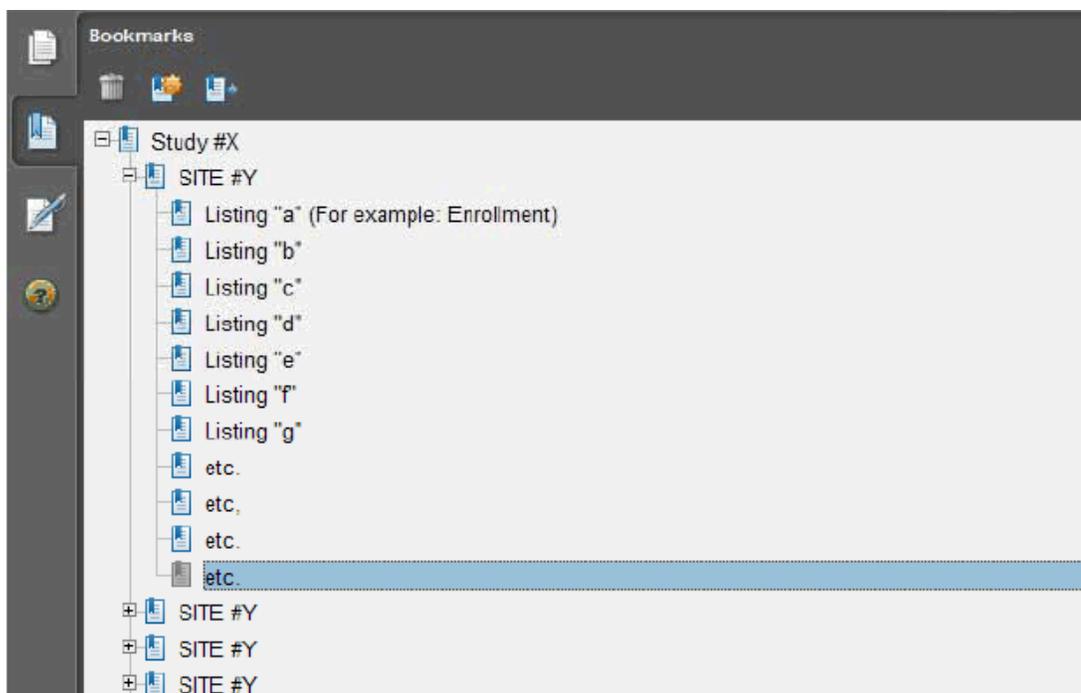
1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:

- a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g. Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
 3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g. as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
 4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
 5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated

- b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft “Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection

Planning” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

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

/s/

INGRID Y FAN
12/30/2014



IND 117879

MEETING MINUTES

AstraZeneca Pharmaceuticals LP
Attention: Jonathan Jazayeri
Regulatory Affairs Director
1800 Concord Pike, P.O. Box 8355
Wilmington, DE 19803-8355

Dear Mr. Jazayeri:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for AZD9291

We also refer to your August 8, 2014, correspondence, received August 8, 2014, requesting a meeting to seek the Agency's agreement on a number of topics regarding the CMC data package required to support an accelerated approval of AZD9291.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Teicher Agosto, Regulatory Project Manager at (240) 402-3777.

Sincerely,

{See appended electronic signature page}

Ali H. Al Hakim, PhD
Branch Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: October 7, 2014, 11:30 – 12:30 pm EST
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1311
Silver Spring, Maryland 20903

Application Number: 117879
Product Name: AZD9291
Indication: Treatment for patients with [REDACTED] ^{(b) (4)}/metastatic EGFR
T790M mutation-positive non-small cell lung cancer (NSCLC)
who have received prior EGFR TKI therapy.

Sponsor/Applicant Name: AstraZeneca Pharmaceuticals

Meeting Chair: Ali Al Hakim, Branch Chief
Meeting Recorder: Teicher Agosto, Regulatory Project Manager

FDA ATTENDEES

Ali Al Hakim, Ph.D., Branch Chief, ONDQA
Liang Zhou PhD, CMC Lead, ONDQA
Elsbeth Chikhale, Ph.D., Biopharmaceutics Reviewer, ONDQA
Whitney Helms, Ph.D., Pharmacology/Toxicology, Supervisor OHOP/DHOT
Shawna Weis, Pharmacology/Toxicology Reviewer, OHOP/DHOT
Teicher Agosto, PharmD, Regulatory Project Manager, ONDQA

SPONSOR ATTENDEES

Eric Richards
Silke Klick
Simon Collett
Dawn Sievwright
Gwydion Churchill
Julie Cahill
Stephen Smith
Paul Dickinson

1.0 BACKGROUND

AstraZeneca Pharmaceuticals submitted a Type B, CMC meeting request to the FDA on August 8, 2014, requesting a CMC Type B meeting to seek the Agency's agreement on a number of topics regarding the CMC data package required to support an accelerated approval of AZD9291. A meeting requested granted letter was mailed on August 25, 2014 to AstraZeneca Pharmaceuticals. AstraZeneca Pharmaceuticals sent meeting briefing packages on September 9, 2014. Meeting preliminary comments were sent to AstraZeneca Pharmaceuticals on October 3, 2014. On October 6, 2014, after reviewing the agency preliminary responses, the sponsor stated that they would like to seek further clarification and discuss questions 2a, 3, 5, 6 and 8. The sponsor sent additional information to be discussed during the meeting on October 6, 2014.

2.0 DISCUSSION

Question #1:

AstraZeneca proposes to select [REDACTED] (b) (4) in the manufacture of the drug substance.

Does the Agency agree with AstraZeneca's classification of these materials?

FDA response to Question #1

According to the limited information provided in the briefing document, the [REDACTED] (b) (4) [REDACTED] s of the manufacture of AZD9291 mesylate could be acceptable. The following information is needed to complete the evaluation; [REDACTED] (b) (4) for the related impurities of the proposed starting materials and a complete discussion on the carry-forward impurities (including test results). Therefore, the final determination on the suitability of the starting materials will be assessed at the time of NDA review taking into consideration the overall assessment of CMC information provided in the NDA submission.

In your NDA submission, provide the following information for the proposed starting materials:

- a. Impurity profiles***
- b. In-house acceptance criteria and vendor's COA***
- c. Brief description of synthetic strategies and methods of manufacture***
- d. Detailed discussion on carry-forward impurities***
- e. Controls and analytical methods to separate and measure appropriate impurities.***
- f. Supplier information for the starting materials used to manufacture***

- g. Detailed discussion on [REDACTED] ^{(b) (4)} using impurities to demonstrate the ability of the manufacturing process to remove and control the impurities to the desired levels*
- h. Change of control strategies for any potential revisions to the manufacture of proposed starting materials including the vendor's reporting of any changes in starting material specification or control.*
- i. Supportive literature data, if available.*

Meeting Discussion

With respect to impurities, please note that your proposed NDA should include specification (tests and limits) for impurities profile, characterization of impurities, specified and unspecified impurities, etc. for the drug substance and drug product. The NDA specification should meet the regulatory requirements including FDA and ICH guidelines.

Question #2:

AstraZeneca have conducted a program of work to identify a suitable dissolution method to control the quality of AZD9291 tablets at release and throughout the shelf life of the product. AstraZeneca proposes the use of a dissolution procedure using a simple aqueous medium of [REDACTED] ^{(b) (4)}. Details of the available evidence supporting this proposal are provided within this briefing document. To ensure that an appropriate dissolution control strategy is presented in the NDA, AstraZeneca would appreciate the Agency's view on the proposed method conditions.

Does the agency agree with the proposal to use a simple aqueous [REDACTED] ^{(b) (4)} dissolution media during the routine testing of AZD9291 tablets?

FDA response to Question #2a

On face your approach appears reasonable. However, note that the overall results of your experiments investigating the optimal conditions, including the complete data supporting the discriminating capability of the selected method should be incorporated into a dissolution method development report for submission within the NDA. Note that, based on the dissolution method development report, the final determination on the acceptability of the dissolution method is a review issue that can be determined during the IND or NDA.

Sponsor Response:

Sponsor acknowledges the response and would like to clarify:

1) The information required within the dissolution method development report.

Sponsor proposes to include the following details in the dissolution method development report:

- The development data provided in the briefing document which includes variants with changes in formulation composition, manufacturing variables and stability supporting the discriminating capability of the method.*
- Complete dissolution profile data from the bio-batches.*

- *Complete dissolution profile data from both primary and supportive stability batches (initial time-point).*
- *Complete dissolution profile data from batches manufactured at the clinical and commercial manufacturing sites.*
- *Complete dissolution profile data with plain and debossed tablets.*

In addition to the above, would the Agency anticipate any further information to be provided in the dissolution method development report?

2) The sponsor would like to discuss the process by which the acceptability of the dissolution method can be determined during the IND.

Meeting Discussion

- 1) The Agency clarified that in addition to the bullet points mentioned under 1) above, all relevant information from the meeting package (drug solubility data, sink conditions, etc.) should be submitted in the Dissolution Method Development Report. In addition, the Agency recommended that the Sponsor explores the possibility of (b) (4) and recommended that the Sponsor explores the use of a dissolution medium with a pH around (b) (4) to obtain a dissolution method with better discriminating capability. The relevance of the dissolution method with regards to the in vivo behavior of the drug product was discussed. The Sponsor stated that observed changes in the dissolution profile (e.g. between capsules and tablets) did not translate in changes to the in vivo drug exposure, and that therefore, a more discriminating dissolution method may detect changes that are not relevant in vivo. The Agency discussed the importance of the dissolution method as a quality control method.
- 2) The Agency stated that the Dissolution Method Development Report can be submitted as an amendment to the IND. The Sponsor should clearly indicate in the cover letter that they are expecting a response. In addition, the Agency advised the Sponsor to alert the project manager when the amendment is submitted. Review of the Dissolution Method Development Report should in general take approximately 2 months, depending on the workload of the Reviewer.

2b. Does the Agency agree with the proposal to use a (b) (4) dissolution acceptance criterion with a lower limit?

FDA response to Question #2b

In general, a (b) (4) acceptance criterion is set for the dissolution test of IR drug products. However, it is noted that the evaluation of the proposed dissolution acceptance

criterion will be based on the overall data and will be determined during the NDA review.

For the setting of the drug dissolution acceptance criterion, the following points should be considered:

- Complete dissolution profile data (i.e., multiple time points at 10, 15, 20, 30, etc. minutes, n=12) from the bio-batches and primary (registration) stability batches of your product. These data would be used for the setting of the dissolution acceptance criterion of your product (i.e., acceptance criterion-sampling time point and acceptance criterion value).*
- The dissolution profile should encompass the timeframe over which at least (b) (4) % of the drug is dissolved or where the plateau of drug dissolved is reached if incomplete dissolution is occurring.*
- The specification-time point should be set when $Q = (b) (4) \%$ of dissolution occurs.*

Any difference (e.g., debossing, coating, over-encapsulation, manufacturing site, etc.) between the drug product that you will use in the Phase 3 clinical trial and the to-be-marketed drug product needs to be appropriately bridged.

Additionally, based on the provided information you may consider using disintegration in lieu of dissolution. If you decide to use disintegration, the following supportive information should be provided in the NDA.

- Solubility profiles of the drug substance throughout the physiological pH range (1.2 to 6.8).*
- Dissolution profiles of the proposed drug product at pHs 1.2, 4.0 and 6.8.*
- Data showing a relationship between dissolution and disintegration.*
- Information on the formulation and process factors that may impact dissolution/disintegration (e.g., amount of disintegrant, surfactant, and lubricant, harness, etc.).*
- Data showing that disintegration is more sensitive than dissolution to meaningful changes on the critical manufacturing process parameters and the product's quality attributes.*
- Data showing that the disintegration test will be able to detect those changes affecting the quality of the product throughout its life cycle.*

- *Disintegration data for the bio-batches (PK and clinical) and the primary registration stability batches.*

It is noted that the FDA's recommendation for using disintegration in lieu of dissolution is a review issue under the NDA; therefore, dissolution profile data using an adequate dissolution test should be collected for the biobatches and primary stability batches and provided under the NDA. Also note that the SUPAC changes under post-approval supplements are supported with dissolution profile and similarity f_2 data.

Meeting Discussion

No further discussion is required.

Question #3:

AstraZeneca have conducted a program of work to develop a suitable specification for the particle size of AZD9291 mesylate to assure the quality and performance of AZD9291 beige film-coated tablets at release and throughout the shelf life. AstraZeneca will provide the data and conclusions to support the proposed specification clause for the particle size of AZD9291 mesylate.

Does the Agency agree with the proposed specification limit for D_{(b) (4)} of not more than (b) (4) μm ?

FDA response to Question #3:

The proposed specification limit for D_{(b) (4)} of not more than (b) (4) μm for the particle size control strategy as presented in the briefing package appears reasonable. The final determination on the proposed strategy will be assessed at the time of NDA review taking into consideration the information provided in the NDA submission. Provide data to demonstrate the absence of any polymorphic form in the drug product.

Sponsor Response:

Sponsor acknowledges the response and would like to seek clarity on the information requested regarding (b) (4) form in the drug product. AZD9291 mesylate exists as a (b) (4) which has been consistently produced by the drug substance manufacturing process. (b) (4)

under long-term, accelerated or stressed storage conditions.

Meeting Discussion

The sponsor agreed to propose a USAN chemical name and to provide additional CMC information regarding the absence of any (b) (4) in the NDA.

Question #4:

AstraZeneca is currently developing the control strategy for synthetic mutagenic impurities and is currently proposing to work towards limits of (b) (4) µg/day based on the seriousness of the disease in the proposed patient population. This approach is supported by principles defined in ICH M7 and ICH S9.

Does the Agency agree with the proposed limits for mutagenic impurities in this patient setting?

FDA response to Question #4

The approach of limiting mutagenic impurities to no more than (b) (4) µg/day may be acceptable; however, whether this limit is acceptable for individual mutagenic impurities may depend in part on the number of these impurities present in the product.

Meeting Discussion

No further discussion is required.

Question #5:

AstraZeneca would like to discuss with the Agency its approach to the justification of specification limits for non-mutagenic impurities in the marketed product. As a result of the accelerated development plan for AZD9291 and in the absence of further toxicology studies at the time of the submission, unqualified non-mutagenic impurities may be present in the drug substance at levels (b) (4). AstraZeneca propose to justify the control of these impurities as appropriate to a level of NMT (b) (4) % based on the following:

- (b) (4)

Does the agency agree with AstraZeneca's approach?

FDA response to Question #5

No, FDA does not agree. Either (b) (4) or provide (b) (4) qualification in animal studies or other scientific (b) (4)

Sponsor Response:

Sponsor acknowledges the FDA response and would welcome the Agency's perspective regarding what would constitute an acceptable scientific (b) (4)

(b) (4) in the drug substance specification in an (b) (4) cancer population.

AstraZeneca is completing establishment of the drug substance processes at the commercial site by end of 2014 and believes (b) (4) of toxicologically unqualified impurities could be present (b) (4) AstraZeneca's interpretation of (b) (4) and would like to explore with the Agency how this could be applied.

Meeting Discussion

Consistent with the principles described in the ICH S9 guidance, (b) (4) for use in patients with (b) (4) cancer. From a pharmacology/toxicology perspective it may be acceptable in this case for levels of a given impurity to (b) (4) in the drug substance/product, if adequate justification is provided, as discussed in the guideline. If the drug product qualification threshold (b) (4) µg/ day for the proposed AZD9291 dose level of 80 mg) (b) (4), then a 14-day toxicology study in the rodent may be needed to demonstrate the biological safety of the impurity in the drug substance/product, unless the safety of the impurity can be otherwise justified (e.g., the impurity is also a metabolite of the API in animals or humans, published data are available that describe the safety profile of the impurity, etc.).

Question #6:

AstraZeneca is currently developing the intended control strategy that will ensure appropriate and consistent quality of AZD9291 drug substance. AstraZeneca has outlined both the proposed control strategy and the data that will be provided to support it in the briefing document.

Does the agency agree that the intended approach is appropriate?

FDA response to Question #6

Insufficient information was provided in the briefing document to allow the Agency to make a meaningful assessment on the control strategy of AZD9291 drug substance.

Sponsor Response:

Sponsor acknowledges the response. AstraZeneca has outlined the general strategy and approach for transparency. AstraZeneca would like to discuss whether the approach is broadly in line with FDA's expectations and any further items which could strengthen the package at the time of NDA filing.

Meeting Discussion

The agency requested that the applicant should provide details description and related CMC information for the control strategy in the NDA submission.

Question #7:

AstraZeneca is currently developing the control strategy that will ensure appropriate and consistent quality of AZD9291 drug product.

Does the agency agree that the intended approach is appropriate?

FDA response to Question #7

According to the limited information provided in the briefing document, the proposed approach for the control strategy of AZD9291 drug product appears reasonable. Regarding the dissolution method, refer to our response to Question 2.

Meeting Discussion

No further discussion is required.

Question #8:

AstraZeneca would like the ability to further optimize drug substance and / or drug product manufacturing processes while the NDA is under review and post marketing approval by making use of Comparability Protocols.

Would the Agency be willing to review and comment on the acceptability of one or more comparability protocols prior to NDA submission to enable AstraZeneca to provide appropriate content?

FDA response to Question #8

Since you submitted only very limited information in the briefing document about future manufacturing changes and you are still developing your control strategy, it is premature to address your question at this time. Also, we do not recommend that you submit manufacturing changes during the NDA review.

Sponsor Response:

The sponsor acknowledges that this question might be unclear and would like to clarify that there is no intention to submit any manufacturing changes during the NDA review.

The intention of this question is to get clarity on whether;

- a. Comparability protocols could be an appropriate mechanism to facilitate and accelerate implementation of post-approval changes;*
- b. The Agency would be willing to review draft comparability protocols to the IND and prior to inclusion in the NDA, in order to review and comment on appropriateness.*

Meeting Discussion

Since the comparability protocol deals with the post approval changes, the agency recommended that the sponsor submits the proposed comparability protocols in the original NDA.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There are no specific issues requiring further discussion at this time.

4.0 ACTION ITEMS

There are no specific due dates or time lines for submission of information or other action items.

5.0 ATTACHMENTS AND HANDOUTS

Handout provided by AstraZeneca Pharmaceuticals on October 6, 2014, see attached.

Responses to FDA Preliminary Comments

In reference to the preliminary comments received via email (dated, 03-OCT-2014), AstraZeneca (sponsor), hereby submits the following responses to facilitate the face-to-face Type B Meeting on Tuesday, October 7th.

The sponsor acknowledges the Agency's responses to Questions 1, 2b, 4 and 7 and no further discussion is required on these topics. However, the sponsor would like to interact with the Agency to discuss the comments provided to Questions 5, 2a, 3, 6 and 8 and would propose to discuss in this order.

The sponsor also acknowledges verbal comments made regarding proposed commercial supply sites in the Type B meeting which was held on Thursday October 2nd & provides below a tabulation of proposed commercial supply sites & recent inspection history.

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/s/

ALI H AL HAKIM
11/10/2014



IND117879

MEETING MINUTES

AstraZeneca Pharmaceuticals LP
Attention: Jonathan Jazayeri
Regulatory Affairs Director
1800 Concord Pike, P.O. Box 8355
Wilmington, DE 19803-8355

Dear Mr. Jazayeri:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for AZD9291.

We also refer to the meeting between representatives of your firm and the FDA on October 2, 2014. The purpose of the meeting was to discuss and reach agreement on the potential data package required to support an accelerated approval of AZD9291 in patients with ^{(b) (4)} metastatic non-small cell lung cancer (NSCLC) whose disease has progressed with previous epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) therapy ^{(b) (4)}

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-5053.

Sincerely,

{See appended electronic signature page}

Ingrid Fan
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Breakthrough Therapy-Initial Comprehensive
Meeting Date and Time: Thursday, October 2, 2014, 1:00 PM
Meeting Location: White Oak Building 22, Conference Room: 1311
Application Number: IND 117879
Product Name: AZD9291
Indication: The treatment of patients with (b) (4) metastatic non-small cell lung cancer (NSCLC) whose disease has progressed with previous epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) therapy (b) (4)
Sponsor/Applicant Name: AstraZeneca
Meeting Chair: Patria Keegan
Meeting Recorder: Ingrid Fan

FDA ATTENDEES

Patricia Keegan, Division Director, DOP2
Paul Kleutz Deputy Office Director, OHOP
Sean Khozin, Clinical Reviewer, DOP2
Gideon Blumenthal, Clinical Team Leader, DOP2
Ingrid Fan, Regulatory Project Manager, DOP2
Laura Fernandes, Statistical Reviewer, DBV
Shenghui Tang, Statistical Team Leader, DBV
Runyan Jin, Clinical Pharmacology Reviewer, DCPV
Liang Zhou, Chemistry Team Leader, ONDQA
Ali Al Hakim, Chemistry Branch Chief, ONDQA
Frances Fahnbulleh Project Manager, Office of Surveillance and Epidemiology (OSE)
Timothy Schaefer Reviewer, OIR/Center for Devices and Radiologic Health
Karen Bijwaard Reviewer, OIR/Center for Devices and Radiologic Health
Robert Becker Chief Medical Officer, OIR/Center for Devices and Radiologic Health
Liang Zhao Clinical Pharmaceutical Team Leader
Deanne Varney Regulatory Project Manager, DOP2
Dow-Chung Chi Clinical Reviewer, DOP2

SPONSOR ATTENDEES

Eric Richards, Senior Director, Regulatory Affairs, Oncology
Jonathan Jazayeri, Director, Regulatory Affairs, Oncology
Hesham Abdullah VP, Regulatory Affairs, Oncology

Antoine Yver	Senior VP Head Oncology, Global Medicines Development
Serban Ghiorghiu	Global Clinical Lead
Nicola Schmitt	Global Product Statistician, Oncology
Mei Dey	Global Programming Lead
Paul Dickinson	Senior Clinical Pharmacology Scientist, Early Clinical Development
Peter Ballard	DMPK Project Leader, Oncology
Paul Howarth	Global Patient Safety Physician, Oncology
Simon Collett	Project Director, Pharmaceutical Development
Suzanne Jenkins	Diagnostics, Personalized Healthcare and Biomarkers
Abha Sharma	Director, Biostatistics (Roche Molecular Systems)
Elias Ketchum	Manager, Regulatory Affairs (Roche Molecular Systems)

SPONSOR ATTENDEES VIA TELEPHONE

John Freeman	Director, Clinical Development
Andrew Walding	Safety Management Team Leader, Patient Safety
Michelle Coulson	Associate Director, Toxicology Project Leader, Drug Safety and Metabolism
Darren Cross	Principle Scientist, Bioscience, Oncology
Silke Klick	Director, Regulatory CMC
Flavia Borellini	VP, Global Product Development

BACKGROUND

On July 28, 2014, DOP2 received a Type B Meeting request from AstraZeneca for IND 117879 for AZD9291, designated as a breakthrough therapy for the proposed indication of the treatment of patients with (b) (4) metastatic NSCLC whose disease has progressed with previous EGFR TKI therapy (b) (4).

The primary purpose of the meeting is to discuss and reach agreement on the development program to provide an adequate data package to support an NDA submitted under the provisions of 21 CFR 314 Subpart H (accelerated approval) for AZD9291 for the treatment of patients with (b) (4) /metastatic NSCLC whose disease has progressed with previous EGFR TKI therapy (b) (4).

AstraZeneca states that AZD9291 is an EGFR TKI and is a selective, irreversible inhibitor of various EGFR activating mutations, including T790M, but was designed to have limited activity against tumors bearing wild type EGFR.

Nonclinical

Non-clinical studies proposed to support a proposed NDA for AZD 9291 for the treatment of patients with (b) (4) metastatic NSCLC whose disease has progressed with previous EGFR TKI therapy (b) (4) were listed in Table 5, Section 3.1 of the meeting briefing document. The details of the non-clinical finding, including the toxicology package were provided in the briefing documents submitted on October 8, 2013 and December 12, 2013. During the Type C meeting held on January 14, 2013, FDA stated that the proposed nonclinical toxicology program appears sufficient to support the submission of an NDA for this patient population.

Chemistry, Manufacturing, and Controls (CMC)

According to AstraZeneca, the AZD9291 drug product is a film-coated tablet formulation and minor changes will be made to processes used for manufacture of clinical and commercial material. The synthetic route of manufacture of the AZD9291 mesylate drug substance has remained unchanged during development. AstraZeneca notes that only minor changes have been made to the processes used in the manufacture of material for clinical studies as compared to proposed commercial manufacture. AstraZeneca states that the NDA submission will include a comparison of all changes in the manufacturing processes and in the formulation for clinical material used in supportive and primary stability studies and the proposed commercial processes.

AstraZeneca notes that 6-month stability data for both drug substance and drug product will be available for inclusion in the planned final NDA component of the proposed rolling submission in April 2015. In addition, supportive stability data from development batches will also be provided in the NDA.

AstraZeneca has requested a separate CMC-specific meeting scheduled for October 7, 2014, to obtain FDA’s advice on CMC information to support an NDA submission of AZD9291.

Clinical

AstraZeneca intends to submit an NDA in April 2015 based on the results of two ongoing clinical studies of AZD9291 in EGFR TKI pre-treated (b) (4) NSCLC patients (b) (4) (Table-1, and Figure 1). AstraZeneca proposes to initiate the NDA as a rolling review in January 2015 and will be requesting a priority review for the NDA submission.

Table 1. Summary of key single arm efficacy trials with AZD9291

Study	Design	Patient population
D5160C00001 (AURA)	Ongoing Phase I multi-center, open-label, dose-escalation, and dose-expansion study to determine safety and tolerability, MTD, biologically effective dose, PK, and preliminary anti-tumor activity of AZD9291	Advanced NSCLC patients who have progressed following prior therapy with an EGFR TKI agent ± chemotherapy (mostly ≥second-line patients, as well as 2 first-line cohorts).
D5160C00001 (AURA extension)	“Phase 2” expansion cohort portion of AURA.	Advanced NSCLC patients who have progressed following either one prior therapy with an EGFR TKI (second-line chemotherapy-naïve, n≈approximately 50) or following treatment with both EGFR TKI and at least one other prior line of therapy, such as cytotoxic doublet chemotherapy or immunotherapy (≥third-line, n≈ 125).
D5160C00002 AURA2	Ongoing Phase 2, single-arm, open label non-randomized study to replicate the efficacy and safety data observed in the AURA extension	Advanced NSCLC patients who have progressed following either one prior therapy with an EGFR TKI (second-line chemotherapy-naïve, n= approximately 50) or following treatment with both EGFR TKI and at least one prior platinum-based doublet chemotherapy (≥third-line, n≈ 125).

In the meeting package submission, AstraZeneca states their intent to provide the primary efficacy data intended to support the proposed NDA from two studies: these will be:

- 1) an interim analysis of objective response rate (ORR) on all patients in AURA extension trial (n=175) and
- 2) an analysis of ORR in the subgroup of 100 patients from the AURA2 trial who have 13 weeks of follow up (including 1 week window for the RECIST scan).

AstraZeneca proposed to

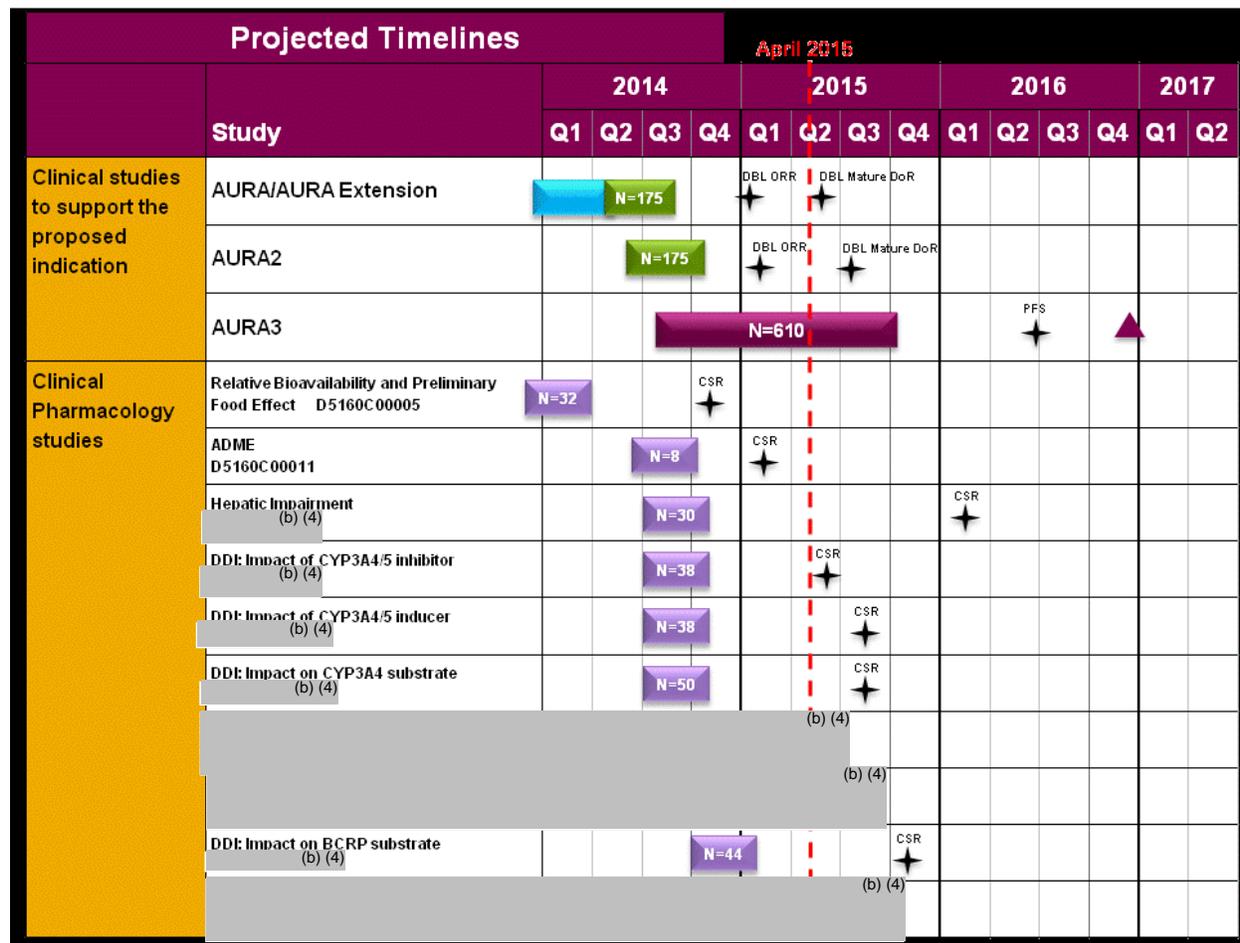
(b) (4)

On September 25, 2014, AstraZeneca communicated to FDA via email that they will be able to send the data from all the 175 patients in AURA2 trial, a change which they stated will delay the NDA submission by about a month but will lead to simpler analyses of the efficacy data and simpler labeling. Based on the September 25, 2014 e-mail, the assessment of efficacy in the proposed NDA would be based on approximately 350 subjects enrolled in the AURA extension and AURA2 trials, with all patients having at least 3-months of follow-up. Furthermore, efficacy information obtained in approximately 50 patients enrolled in the Phase I portion of AURA 1 who were treated at the recommend Phase 2 dose with exposures up to approximately 20 months will also be submitted in the NDA to provide additional data on durability of response.

AstraZeneca states that as of August 1, 2014, the confirmed ORR is 61%; 95% CI (52% to 70%), across 78 responding patients among 127 evaluable, EGFR T790M+ patients treated with AZD9291.¹ In more than 80% of the confirmed responses observed, the response has been sustained for more than 24 weeks. The median duration of response (DOR) among approximately 50 patients with objective responses who were treated with the recommended Phase 2 dose of AZD9291 in the phase 1 portion of the AURA trial is estimated to be 8.2 months with a lower 95% CI of 6.9 months based on the Kaplan Meier method.

¹ Evaluable patients defined as those with a baseline RECIST assessment and at least 2 follow-up RECIST scans to enable confirmation of response, or patients who had withdrawn or died before the second RECIST assessment.

Figure 1 Projected clinical data delivery



According to AstraZeneca, the following studies may be delivered as post-marketing commitments:

- (b) (4)
- (b) (4) (b) (4) (a CYP3A4 Inducer) on the Pharmacokinetics of AZD9291 (b) (4)
- (b) (4) (b) (4) Assess the Effect of AZD9291 on the Pharmacokinetics of CYP3A4 Substrate (b) (4)
- (b) (4) (b) (4)

Assess the Effect of AZD9291 on the Pharmacokinetics of (b) (4) (a
BCRP Substrate) (b) (4)

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The meeting package also includes a synopsis of the proposed confirmatory trial, Study D5160C00007 (FLAURA), a double-blind, randomized study in patients with locally advanced or metastatic EGFR mutation-positive (EGFRm+) NSCLC who are treatment-naïve and eligible for first-line treatment with an EGFR TKI. The trial will assess the safety and efficacy of AZD9291 (80 mg orally, once daily) compared to a standard of care (SoC) EGFR TKI (either gefitinib (250 mg orally, once daily or erlotinib 150 mg orally, once daily). Approximately, 650 patients will be randomized in a 1:1 ratio, stratified according to racial origin (Asian/Non-Asian) and type of sensitizing mutation (L858R/Ex19del). The primary endpoint will be progression-free survival (PFS). For patients randomized to SoC, cross-over to AZD9291 following disease progression will not be permitted.

Regulatory History:

The original IND was submitted on June 11, 2013. An application for Fast Track Designation for the use of AZD9291 as a treatment for patients with (b) (4) NSCLC (b) (4) was submitted on October 8, 2013 and granted on November 6, 2013. A type C meeting was held on January 14, 2014 to discuss the overall non-small cell lung cancer clinical development program for AZD9291 to support approval for the treatment of patients with (b) (4) EGFR T790M-positive NSCLC.

An application for Breakthrough Therapy Designation was submitted on February 27, 2014 and granted on April 16, 2014 for the treatment of patients with metastatic, EGFR T790M mutation-positive, non-small cell lung cancer (NSCLC) whose NSCLC has progressed during treatment with an FDA-approved, EGFR tyrosine kinase inhibitor. AstraZeneca submitted an Initial Pediatric Study Plan (iPSP) on July 1, 2014 which describes their intent to submit a waiver for the pediatric requirements in the NDA. On July 2, 2014, AstraZeneca submitted an Orphan Drug Designation application to the Office of Orphan Product Development (OOPD).

AstraZeneca is currently using a tissue-based diagnostic test to identify patients with EGFR T790M mutation-positive NSCLC eligible for clinical studies. On July 8, 2014, AstraZeneca and Roche Molecular Systems (RMS) met with CDRH to discuss RMS' plans to develop (b) (4) the tissue-based (b) (4) diagnostic for AZD9291. It is intended that the PMA submission for the tissue-based EGFR mutation test would coincide with the NDA submission for AZD9291.

DISCUSSION

Clinical:

Refer to background information for Questions 1 from page 23 to 25 in AstraZeneca Briefing Document.

1. Does the Agency agree that data demonstrating durable responses in approximately 50 \geq second-line patients dosed with 80 mg once daily from the D5160C00001 AURA Phase I component could provide an adequate assessment of the durability of the confirmed objective response [REDACTED] (b) (4)

FDA Response: Yes, FDA generally agrees that demonstration of blinded independent central review (BICR) confirmed durable responses in a substantial proportion of the second-line patients treated with AZD9291 80 mg once daily in the Phase 1 portion of D5160C00001 AURA (n~50) could potentially enable an adequate assessment of the durability of the confirmed objective responses for the purpose of making a regulatory decision; [REDACTED] (b) (4)

[REDACTED] Please note the clinical significance of the magnitude and duration of responses will be assessed by reviewing the totality of the evidence, including the data on the approximately 350 patients from AURA extension and AURA2 trials.

Sponsor Response (10/2/2014 Email):

AstraZeneca acknowledges the Agency's response. In addition, the sponsor would like to provide the tables below to further delineate the proposed clinical package for the planned NDA. As both of these Phase II studies have now fully enrolled, it is possible to project with a reasonable amount of precision, the subject numbers and approximate follow-up of the clinical database for the planned NDA. AstraZeneca hopes these tables are helpful in further understanding the proposed clinical database, and would be happy to review them with the Agency during the meeting if desired.

Please note: Table 1 and 2 shows the projected follow-up (i.e. number of months since first dose) at the time of submission, assuming a data cut-off in December 2014 for AURA (the phase I study) and January 2015 for AURA Extension and AURA2 (the two Phase II studies). The final numbers and actual exposure times may be influenced by discontinuations, which cannot be predicted at this time.

Discussion During Meeting:

AstraZeneca stated their intent to provide efficacy data from 431 patients with at least 3 months of follow-up with a maximum duration of follow-up of 7-8 months in the Phase 2 studies. AstraZeneca also stated that they plan to provide safety data of 511 patients treated at the proposed dose. AstraZeneca will provide the STD datasets for all patients in AURA studies regardless of mutation status or dose levels.

FDA found that the proposal for the number of patients in the safety and efficacy populations and for the selection of patients for inclusion in the efficacy population, as described above to be acceptable to support the proposed NDA filing.

AstraZeneca will provide a proposal at the pre-NDA meeting to further characterize the durability of response during the review, e.g. in the 90 day safety update. The pre-NDA meeting will occur prior to the start of the rolling submission.

AstraZeneca plans to submit clinical data in May, 2015 for AZD9291 NDA submission.

Refer to background information for Questions 2 from page 25 to 29 in AstraZeneca Briefing Document.

2. Currently the Sponsor is conducting a comprehensive monitoring and analysis of cardiac function within Study D5160C00001 (AURA extension) and Study D5160C00002 (AURA2).
 - a. Does the Agency agree that the cardiac monitoring and proposed analysis are sufficient to quantify a significant effect, or lack of effect, of AZD9291 on Left Ventricular Ejection Fraction (LVEF) for labeling purposes?

FDA Response: FDA finds the proposed cardiac monitoring and analysis plan to be adequate to characterize cardiac toxicity, however whether the information to be provided in the NDA is sufficient to identify and quantify a significant adverse effect on cardiac function will be determined during NDA review. It may be necessary to conduct post-marketing requirements to further assess the effect on LVEF.

Sponsor Response (10/2/2014 Email):

Sponsor acknowledges and has no further comment.

- b. Does the Agency agree that the electrocardiogram (ECG) monitoring and analysis is sufficient to quantify a significant effect, or lack of effect, of AZD9291 on QTcF prolongation for labeling purposes?

FDA Response: Yes, FDA finds your ECG monitoring and analysis plan to be adequate to support an NDA filing; FDA cannot comment on product labeling at this time.

Sponsor Response (10/2/2014 Email):

Sponsor acknowledges and has no further comment.

Refer to background information for Questions 3 from page 29 to 31 in AstraZeneca Briefing Document.

3. a. Given the almost identical study design and eligibility criteria utilized in studies D5160C00001 (AURA extension) and D5160C00002 (AURA2), does the Agency agree with the Sponsor's proposal to pool the data from the Phase II studies in the summaries of safety and efficacy (Module 2)?

FDA Response: FDA generally agrees with the proposed pooling strategy for Studies D5160C00001 (AURA extension) and D5160C00002 (AURA2) in the summaries of safety and efficacy. However, at the time of NDA submission, provide a detailed justification for combining the two studies and include tabulated summaries of key variables such as drug exposure and patients' baseline characteristics for each individual study. In addition, summarize and compare the major differences between the design and conduct of the studies, including the eligibility criteria. Provide the demographic and baseline tumor characteristics, and drug exposure for the pooled safety and efficacy populations.

Sponsor Response (10/2/2014 Email):

Sponsor acknowledges and has no further comment.

- b. Does the Agency agree that it may be possible to present pooled safety data, as well as the pooled efficacy data (ORR) in the label, as outlined in Table 2 and Table 3 respectively?

FDA Response: Yes, FDA finds the presentation of safety and efficacy data in the proposed tables acceptable.

Sponsor Response (10/2/2014 Email):

Sponsor acknowledges and has no further comment.

Refer to background information for Questions 4 on page 32 in AstraZeneca Briefing Document.

4. Does the Agency agree with the proposal to [REDACTED] (b) (4) [REDACTED] submitted to FDA on 17 July 2014 (Serial No:0077)?

FDA Response: No, FDA does not agree with the proposal in the July 17, 2014 submission. However, FDA agrees with the proposal in AstraZeneca's email communication to FDA on September 25, 2014, that the primary analysis of ORR per

BIRC assessment will be calculated based on all 350 patients in AURA extension AURA2 trials.

Sponsor Response (10/2/2014 Email):

Sponsor acknowledges and has no further comment.

Refer to background information for Questions 5 on page 33 in AstraZeneca Briefing Document.

5. AstraZeneca believes that efficacy data produced in patients with progressing EGFR T790M mutation-positive NSCLC who have received a prior EGFR inhibitor will be clinically relevant regardless of the specific EGFR inhibitor used. Does the Agency agree?

FDA Response: Yes, FDA agrees, given that the indication will be based on the presence of a specific acquired EGFR mutation (T790M).

Sponsor Response (10/2/2014 Email):

Sponsor acknowledges and has no further comment.

Statistics:

Refer to background information for Questions 6 on page 34 in AstraZeneca Briefing Document.

6. Does the Agency agree with the Sponsor's proposal to provide CDISC SDTM datasets and analysis datasets for the individual studies and to provide analysis datasets only for the pooled Phase II efficacy and safety data?

FDA Response: Yes, FDA finds the proposed format of datasets acceptable. FDA encourages AstraZeneca to provide CDISC SDTM datasets for the pooled efficacy and safety data. Additionally, please include a study identifier in the pooled datasets.

Sponsor Response(10/2/2014 Email):

Sponsor acknowledges and has no further comment.

Regulatory:

7. Does the Agency agree with the proposed approach for a rolling submission?

FDA Response: Yes, FDA generally agrees with AstraZeneca's approach for a rolling submission as outlined in the meeting package. However, all CMC information should be submitted at the same time in module 2 and module 3. Additionally, include all the required OSI elements as outlined in the Attachment to the preliminary responses.

Sponsor Response(10/2/2014 Email):

Sponsor acknowledges and has no further comment.

8. AstraZeneca would value the Agency's thoughts regarding the wording of the indication statement provided below. AstraZeneca acknowledges that the final indication will be a review issue.

As such, AstraZeneca believes the following indication statement is reflective of the population studied:

TRADENAME is indicated for the treatment of patients with [REDACTED] (b) (4) [REDACTED] /metastatic EGFR T790M mutation-positive NSCLC who have received prior EGFR TKI therapy

FDA Response: Yes, FDA generally agrees with the proposed indication; however, the exact indication will be determined at the time of review based on the analysis of the data submitted. Additionally, the indication must specify that an FDA-approved test for T790M mutational status should be used for patient selection. In addition, the proposed indication should include language denoting that this is an accelerated approval.

Sponsor Response(10/2/2014 Email):

Sponsor acknowledges and has no further comment.

Clinical Pharmacology:

Refer to background information for Questions 9 and 10 from page 36 to 37 in AstraZeneca Briefing Document.

9. Does the Agency agree that the proposed clinical pharmacology data package is sufficient to support an accelerated approval of AZD9291 in [REDACTED] (b) (4) NSCLC?

FDA Response: The proposed clinical pharmacology package appears generally acceptable to support the proposed NDA for AZD9291; however, the adequacy of the clinical pharmacology data will be evaluated at the time of NDA submission. The NDA should also include population pharmacokinetic and exposure-response analyses.

In the NDA submission, provide a description of the hepatic impairment, drug-drug interaction, and absolute bioavailability studies as postmarketing requirements (PMRs), including major milestones (e.g., study completion date, submission of final study report). Under the PDUFA V Program, FDA cannot agree to accept a major component (e.g., clinical pharmacology study reports) as a late submission. AstraZeneca will need to provide adequate justification as to why the original NDA submission is complete without these study reports. If AstraZeneca does not plan to submit the study reports for [REDACTED] (b) (4) drug-drug interaction studies with the original NDA

submission, AstraZeneca should propose PMRs or postmarketing commitments (PMCs) to submit these study reports, including milestones, to the FDA for review in the original NDA submission.

Sponsor Response(10/2/2014 Email):

Sponsor acknowledges and has no further comment.

10. Does the Agency agree with the proposed methodology for assessing drug-drug interaction potential?

FDA Response: FDA does not object to the proposed methodology for assessing drug-drug interaction potential.

Sponsor Response(10/2/2014 Email):

Sponsor acknowledges and has no further comment.

First-line EGFRm+ NSCLC Development Question:

Refer to background information for Question 11 from page 38 to 42 in AstraZeneca Briefing Document.

11. Does the Agency agree with the proposed study design for the randomized, Phase III, first-line study in EGFRm+ NSCLC (D5160C00007 [FLAURA])?
- a. Does the Agency agree with the use of gefitinib and erlotinib as acceptable standard of care (SoC) comparators in the proposed study?

FDA Response: Yes, FDA agrees with the use of gefitinib and erlotinib as acceptable standard therapies. However, FDA recommends including afatinib as a standard of care option in the trial.

Sponsor Response(10/2/2014 Email):

Sponsor acknowledges the comment and recognizes that afatinib is an approved agent in this setting in the US. As such, the sponsor had considered inclusion of afatinib as a comparator in the proposed Phase 3 study. However, based on usage data and discussions with KOLs, afatinib is not commonly used. Erlotinib and gefitinib are the most commonly used agents globally and should be sufficient comparators to address the objective of the study. In addition, the inclusion of afatinib to the standard of care options introduced substantial technical difficulties related to tablet masking, which would impact the ability to sufficiently keep the study blinded.

- b. Does the Agency agree that the observation of a 25% reduction in the risk of progression or death which is estimated to be associated with an approximate 3-month improvement in median PFS may be sufficient to demonstrate clinical benefit for a first-line indication?

FDA Response: Yes, FDA agrees that demonstration of a highly statistically significant improvement in PFS with an improvement in median PFS of at least 3 months in Study D5160C00007 (FLAURA) with a favorable benefit-risk profile can potentially support a first-line indication for AZD9291. It should be noted that a larger magnitude of PFS improvement may be needed in Study D5160C00007 (FLAURA) if emerging data suggest that progression on first-line AZD9291 may confer resistance to currently available EGFR TKI therapies.

Sponsor Response(10/2/2014 Email):

Sponsor acknowledges and has no further comment.

- c. Does the Agency agree that the planned [REDACTED] (b) (4) may serve as substantial evidence of clinical benefit for a marketing application, should the result cross the pre-specified efficacy boundary?

FDA Response: No, since the results of the [REDACTED] (b) (4)

Sponsor Response(10/2/2014 Email):

Sponsor acknowledges and has no further comment.

- d. Does the Agency agree that selecting patients for the FLAURA study based on the results of local EGFRm testing, is an acceptable method of enrolling patients and that the primary analysis may be conducted on this ITT population?

FDA Response: Yes, CDER generally agrees with the proposed EGFR mutation testing for Study D5160C00007 (FLAURA) via local or central laboratory with mandatory collection of samples for central confirmation of mutational status with the FDA-approved cobas® assay.

Sponsor Response(10/2/2014 Email):

Sponsor acknowledges the comment and would like to clarify that the primary analysis will be based on the ITT population, defined as all patients that are randomized regardless of the testing approach used for inclusion in the study (ie: local or central testing). As noted above, there will be mandatory collection of tissue that will be retrospectively analyzed at a central test lab using the currently FDA-approved cobas® EGFR Mutation Test). The sponsor plans to conduct

sensitivity analyses on the central assay and will discuss the analysis plan at a future meeting.

Discussion During Meeting:

AstraZeneca clarified that the ITT population will be based on all randomized population regardless of the test used to determine the eligibility. AstraZeneca confirmed that enrollment will be limited to patients with exon 19 deletions and L858R as determined by a central or local test. FDA acknowledged the clarification and finds the proposed definition for the ITT population acceptable.

Post-meeting note:

RMS contacted FDA to inform the Agency that the cobas[®] EGFR Mutation test used to identify patients' EGFR mutation status for the AURA and FLAURA studies is an investigational assay. The test is identical to the FDA-approved cobas[®] EGFR Mutation test except it identifies additional EGFR mutations (e.g., T790M) that are not described in the FDA-approved labeling for this test. RMS intends to submit a PMA supplement seeking approval to expand the Intended Use of the cobas[®] EGFR Mutation test to include identification of the EGFR T790M mutation.

ADDITIONAL COMMENTS

12. See Attachment to the preliminary responses, titled "OSI Pre-NDA/BLA Request".

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

FDA acknowledges receipt of AstraZeneca's Initial Pediatric Study Plan submitted on July 1, 2014. This fulfills AstraZeneca's requirements at this stage of development to reach an Agreed Initial Pediatric Study Plan with the Agency as required by FDASIA for products that would trigger PREA at the time of NDA submission.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order

to meet the needs of its reviewers. The web page may be found at:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see [CDER/CBER Position on Use of SI Units for Lab Tests \(http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm\)](http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm).

OSI Pre-NDA/BLA Request

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e. phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

Part I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

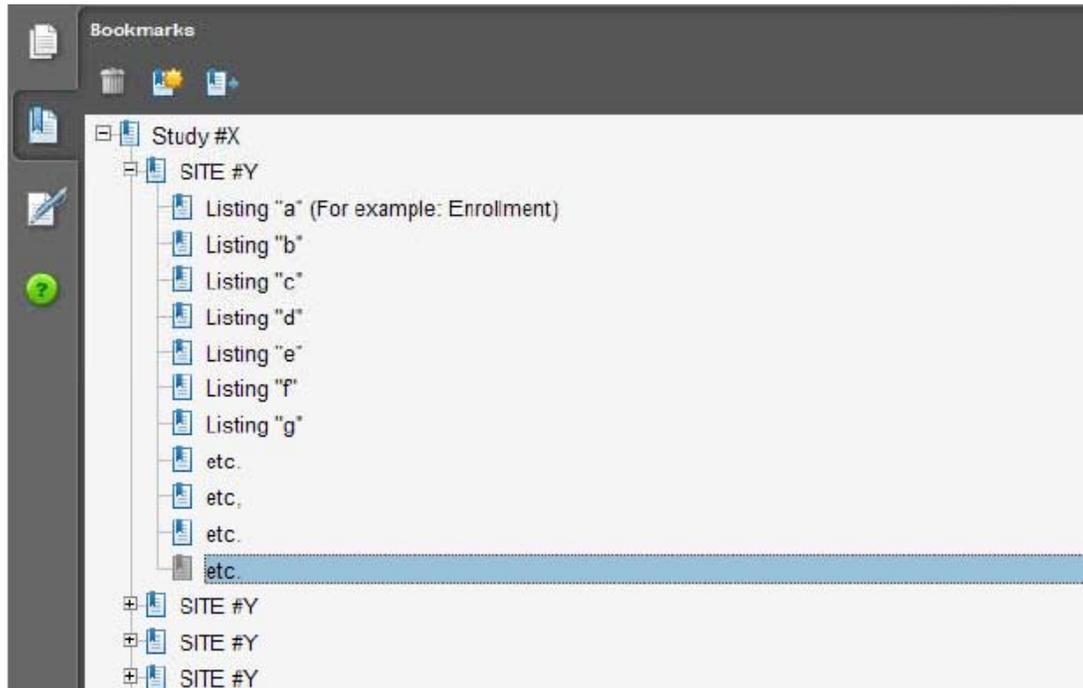
1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g. Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6,

- Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
- b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g. as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
 5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

Part II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



Part III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft “Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Attachment 1

Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item ¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

¹ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page

(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

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

/s/

INGRID Y FAN
10/17/2014

**PeRC BPCA/Pediatric Study Plan
Subcommittee Meeting Minutes
September 10, 2014**

PeRC Members Attending:

Wiley Chambers

George Greeley

Rosemary Addy

Julia Pinto Non Responsive

Tom Smith

Lily Mulugeta

Maura O'Leary Non Responsive

Hari Cheryl Sachs Non Responsive

Melissa Tassinari

Colleen Locicero Non Responsive

Kevin Krudys Non Responsive

Daiva Shetty

Michelle Roth-Cline

Nisha Jain Non Responsive

Barbara Buch Non Responsive

Adrienne Hornatko-Munoz Non Responsive

Agenda

BPCA/Initial Pediatric Study Plan

Non Responsive

IND

117879

AZD9291 iPSP (Full Waiver)

NSCLC

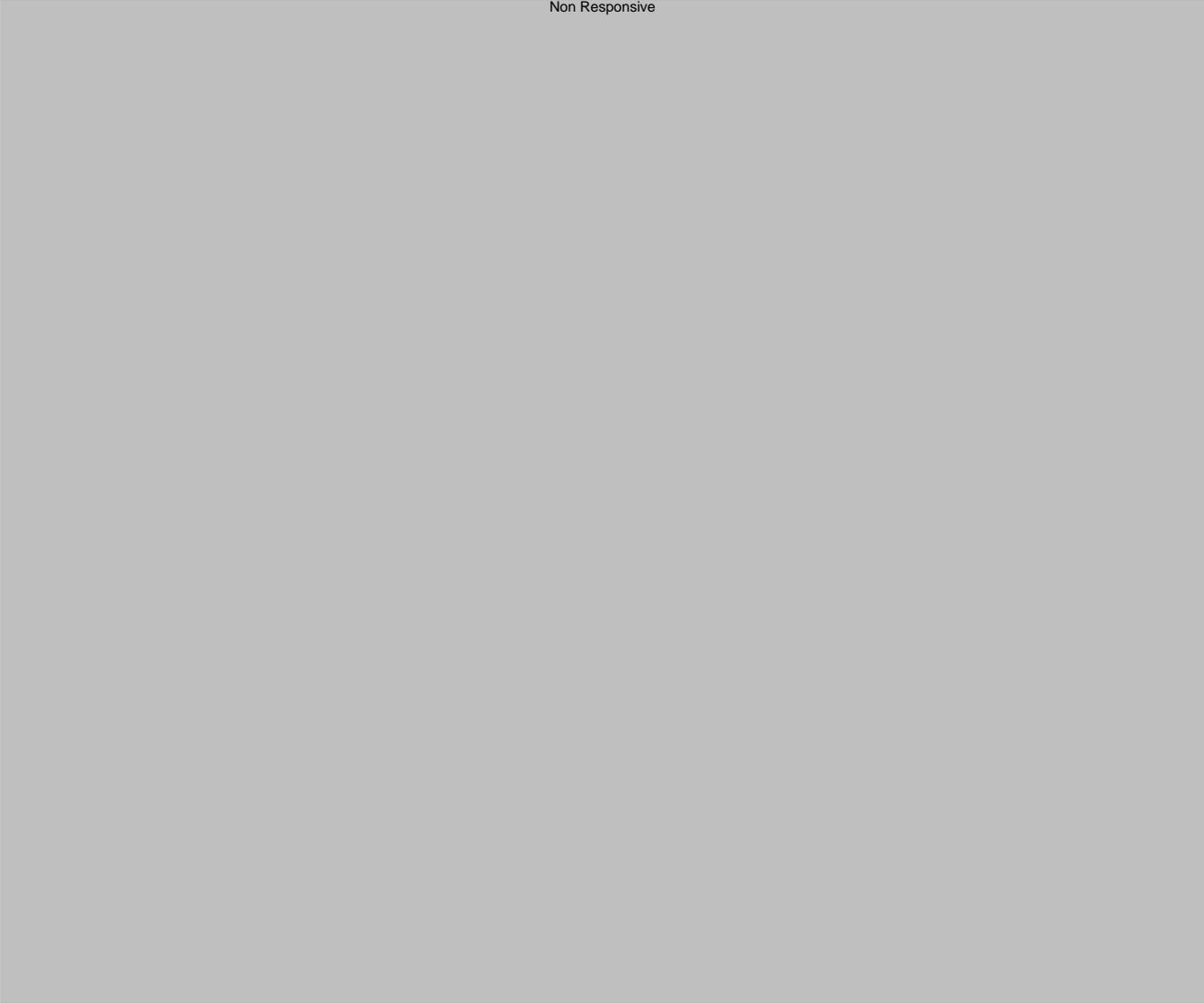
Non Responsive

Non Responsive

AZD9291 iPSP (Full Waiver)

- Proposed Indication: Non-small cell lung cancer (NSCLC)
- *PeRC Recommendations:*
 - The PeRC agreed with the plan for full waiver for this product.

Non Responsive



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

/s/

GEORGE E GREELEY
09/23/2014



IND 117879

**GRANT –
BREAKTHROUGH THERAPY DESIGNATION**

AstraZeneca Pharmaceuticals LP
Attention: Nicholas J. Troise
Regulatory Affairs Director
1800 Concord Pike; P.O. Box 8355
Wilmington, DE 19803-8355

Dear Mr. Troise:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for “AZD9291.”

We also refer to your February 27, 2014, request for Breakthrough Therapy designation. We have reviewed your request and have determined that AZD9291 for the treatment of patients with metastatic, EGFR T790M mutation-positive, non-small cell lung cancer (NSCLC) whose NSCLC has progressed during treatment with an FDA-approved, EGFR tyrosine kinase inhibitor meets the criteria for Breakthrough Therapy designation. Therefore, we are granting your request for Breakthrough Therapy designation. Please note that if the clinical development program does not continue to meet the criteria for Breakthrough Therapy designation, we may rescind the designation.

FDA will work closely with you to provide guidance on subsequent development of AZD9291 for this indication to help you design and conduct a development program as efficiently as possible. For further information regarding Breakthrough Therapy designation and FDA actions to expedite development of a designated product, please refer to section 902 of the Food and Drug Administration Safety and Innovation Act (FDASIA) and the draft *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics*.¹

In terms of next steps, please submit a Type B meeting request. This meeting will be for a multidisciplinary comprehensive discussion of your drug development program, including planned clinical trials and plans for expediting the manufacturing development strategy. Attachment 1 lists potential topics for discussion at this initial breakthrough therapy meeting. Please refer to the *Guidance for Industry: Formal Meetings between FDA or Sponsors and Applicants*² for procedures on requesting a meeting. If you feel that submitting a meeting request for such a meeting at this point is pre-mature or if you have recently held a major milestone meeting, please contact the Regulatory Health Project manager noted below to discuss the timing of this meeting.

¹ <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

² <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>

If the breakthrough therapy designation for AZD9291 for the treatment of patients with metastatic, EGFR T790M mutation-positive, NSCLC that has progressed during treatment with an FDA-approved, EGFR tyrosine kinase inhibitor is rescinded, submission of portions of the NDA will not be permitted under this program. However, if you have Fast Track designation you will be able to submit portions of your application under the Fast Track program.

If you have any questions, contact Norma Griffin, Senior Regulatory Project Manager, at (301) 796-4255.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Attachments:

Attachment 1: Breakthrough Designated Product, Initial Multidisciplinary Comprehensive Meeting between FDA/Sponsor, Potential Topics for Discussion

Attachment 1: Breakthrough Designated Product
Initial Multidisciplinary Comprehensive Meeting between FDA/Sponsor
Potential Topics for Discussion

General/Regulatory:

- Planned target date for NDA/BLA submission, including plans for rolling review
- Other indications in development
- Expanded access plans, including intent to communicate these plans publicly
- Plans to seek accelerated approval
- Regulatory status with non-U.S. regulatory agencies
- Plans to defer or waive studies or trials, including those to be conducted as postmarketing commitments/postmarketing requirements (PMC/PMRs)
- Rationale for proposed flexibility in study and trial design
- Plans for submission of a proprietary name request
- If a drug/device combination product, device development information and plan
- In-vitro diagnostic development plan with the Center for Device and Radiologic Health (CDRH)
- Target product profile for proposed indication
- Gantt chart of development timeline, including information on all areas noted below
- Proposed communication plan for periodic development program updates to the FDA, including timelines and content

Clinical Activity and Data Analysis:

- Existing and planned clinical sites and accrual data
- Efficacy
 - Status of all clinical studies and topline summary results
 - Preliminary evidence of proof of concept
 - Planned or completed clinical trials intended to support efficacy, including:
 - Overall study design, the population to be studied, trial size, proposed indications, endpoints, power, plans for interim analyses, plans for resizing of trials, Type I error control, and expected initiation/completion dates
 - Validity of the outcomes and endpoints. If using drug development tools, such as a patient reported outcomes or biomarkers, plans for the development and validation of the instrument, if appropriate.
- Safety
 - Potential safety issues from nonclinical studies/early clinical trials
 - Liver, kidney, cardiac, immune suppression, carcinogenicity, genotoxicity, and immunogenicity safety profile
 - Clinical trials safety monitoring plan for safety signals identified in nonclinical studies and early clinical trials, and for post-market drug safety and surveillance (pharmacovigilance)
 - Proposed size of safety population
 - Plan or need for long-term safety studies

- Pre-approval
- Post-approval
- Plans to mitigate/minimize risk, proposed Risk Evaluation and Mitigation Strategy (REMS)
- Specific Populations
 - Dose, study design, efficacy endpoints, size and composition of population, additional safety trials, for populations such as:
 - Geriatrics
 - Pediatrics
 - Hepatically/Renally Impaired
 - Proposed pediatric development plan with outlines/synopses of additional studies.

Clinical Pharmacology and Pharmacokinetics:

- Justification for all dose selections, including number of doses, dose intervals, etc
- Clinical pharmacology, pharmacodynamics, and pharmacokinetics studies: completed, ongoing, planned, and requests for deferral, such as:
- Immunogenicity
- Dosing
 - Single ascending dose
 - Multiple ascending dose
 - Dose response study
- Food-effect
- Drug-drug interactions (DDI)
- Thorough QT/QTc
- Organ impairment
- Pharmacogenomics
- Plans for an in vivo bridging trial of the formulation studied in the clinical development program to the to-be-marketed formulation
- Plans for conducting population pharmacokinetics, exposure-response modeling/simulation analyses
- Plans to describe dose modifications in labeling based on DDI, age, organ impairment, etc.
-

Nonclinical Pharmacology, Pharmacokinetics, and Toxicology

- Nonclinical studies completed, ongoing, and planned, including, the number and sex of animals per dose, doses, route of administration, toxicities, duration of study and study results. For studies planned timelines for initiation and submission of study reports. Examples of such studies include:
 - Subacute and chronic toxicology
 - Gene toxicology
 - Reproductive toxicology
 - Carcinogenicity studies
 - Animal models of disease and PK parameters associated with efficacy

- Evidence of mechanism of action
- Safety pharmacology, where appropriate
- Disease specific animal models

Chemistry, Manufacturing, and Controls:

- Drug product:
 - Dosage form
 - Formulation description
 - Administration instructions, delivery systems (e.g. vials, pre-filled syringes, etc.) proposed draft packaging, and disposal instructions
 - Critical quality attributes
 - Control and stability strategies
 - Proposed shelf life and required stability studies
- Drug substance:
 - Characterization
 - Critical quality attributes
 - Control and stability strategies
 - Proposed shelf life or retest period and required stability studies
- Proposed commercial processes:
 - Manufacturing process, in process controls, scale-up plans
 - Comparison of proposed commercial manufacturing processes to clinical manufacturing processes
 - Physico-chemical comparability of lots used in clinical studies and commercial lots or a plan to establish analytical comparability
 - Current manufacturing site(s) and proposed commercial site(s), if different, registration numbers, readiness, and manufacturing timelines
 - Current release and stability testing site(s) and proposed commercial testing site(s), if different
 - Anticipated market demand at launch
- Proposed validation approaches:
 - Drug substance and drug product manufacturing process
 - Microbial control and sterility assurance
 - Viral clearance
 - Analytical methods

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

/s/

PATRICIA KEEGAN
04/16/2014

Benton, Sandra J

From: Brounstein, Daniel
Sent: Thursday, April 10, 2014 1:06 PM
To: Temple, Robert; Jenkins, John K; Woodcock, Janet; Dal Pan, Gerald; Horn, Pamela; Birnkrant, Debra B; Hinton, Denise
Cc: Raggio, Miranda; Benton, Sandra J; Cox, Edward M; Unger, Ellis; Beitz, Julie G; Ganley, Charles J; Pazdur, Richard; Rosebraugh, Curtis; Benton, Sandra J; Scepura, Barbara; Blumenthal, Gideon; Griffin, Norma; Keegan, Patricia; Gootenberg, Joseph
Subject: RE: April 11, 2014 - Medical Policy Council – Breakthrough Therapy Designation - IND 117,879

As the Council agrees with DOP2's recommendation to grant AstraZeneca's breakthrough therapy designation request for IND 117,879, AZD9291 and do not believe a Council discussion is needed, this request will be cancelled from the 4/11/2014 meeting agenda.

Please let me know if you have any questions. Thanks!

Daniel Brounstein
Program Management Officer
CDER/Office of Medical Policy
(301) 796-0674
Daniel.Brounstein@fda.hhs.gov

From: Brounstein, Daniel
Sent: Friday, April 04, 2014 5:00 PM
To: Temple, Robert; Jenkins, John K; Woodcock, Janet; Dal Pan, Gerald; Horn, Pamela; Birnkrant, Debra B; Hinton, Denise
Cc: Raggio, Miranda; Brounstein, Daniel; Benton, Sandra J; Cox, Edward M; Unger, Ellis; Beitz, Julie G; Ganley, Charles J; Pazdur, Richard; Rosebraugh, Curtis; Benton, Sandra J; Scepura, Barbara; Blumenthal, Gideon; Griffin, Norma; Keegan, Patricia; Gootenberg, Joseph
Subject: April 11, 2014 - Medical Policy Council – Breakthrough Therapy Designation - IND 117,879

Hi! OMP has scheduled a Medical Policy Council discussion on April 11, 2014 regarding the breakthrough therapy designation request from AstraZeneca for its IND 117,879, AZD9291 for the treatment of (b) (4) metastatic non-small cell lung cancer (NSCLC) that has progressed with previous epidermal growth factor receptor (EGFR) tyrosine-kinase inhibitor (TKI) therapy and is EGFR mutation (EGFRm) positive (b) (4)

DOP2 recommends that this breakthrough therapy request be granted. Attached is DOP2's background on the breakthrough therapy designation with its rationale for granting the request.

DOP2 has asked if this request can be reviewed by email.

Would you please review DOP2's recommendation and let me know by COB April 9, if –

- You agree with DOP2's recommendation to grant this breakthrough therapy request and you do not believe a Council discussion is needed.

- You agree with DOP2's recommendation to grant this breakthrough therapy request. However, you would like a Council discussion regarding any questions you have.
- You disagree with DOP2's recommendation to grant this breakthrough therapy request.

If the Council agrees with bullet 1, I will cancel the discussion for IND 117,879.

Please let me know if you have any questions. Thank you.

Dan
(301) 796-0674

<< File: 2014IND 117879 CDER Medical Policy Council Brief Breakthrough Therapy De....doc >> << File: 2014Breakthrough AZD9291FRIDAY.PPT >> << File: request-comments-advice-ind.pdf >>

CDER Medical Policy Council Brief
Breakthrough Therapy Designation
Division of Oncology Products 2
April 11, 2014

Summary Box

1. IND 117879
2. Sponsor: AstraZeneca LLP
3. Drug: AZD9291
4. For the treatment of (b) (4) metastatic non-small cell lung cancer (NSCLC) that has progressed with previous epidermal growth factor receptor (EGFR) tyrosine-kinase inhibitor (TKI) therapy and is EGFR mutation (EGFRm) positive (b) (4)
5. Is the drug intended, alone or in combination with 1 or more other drugs, to treat a serious or life-threatening disease or condition? Yes.
6. Does the preliminary clinical evidence indicate that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints? Yes, AZD9291 has the potential to provide a substantial improvement over available therapies for the treatment of patients with (b) (4) NSCLC who develop the T790M resistance mutation following progression on first or second generation EGFR TKIs.

Division: Division of Oncology Products 2
Medical officer: Barbara Scepura
Clinical Team Leader: Gideon Blumenthal

1. Brief description of the drug

AZD9291 is an oral irreversible TKI of EGFR that is selective for both sensitizing and the T790M resistance mutations.

2. Brief description of the disease and intended population

Lung cancer is the third most common cancer in men and women in the United States, but it is the leading cause of cancer deaths. Approximately 85% of lung cancer cases are classified as non-small cell lung cancer (NSCLC). The majority of NSCLC patients are diagnosed at advanced stages, and have a median life expectancy of approximately 8-12 months and a 5 year survival rate of 1 - 5%.

Within the past decade, driver mutations such as mutations in the kinase domain of the EGFR gene have been identified, which can be targeted with EGFR TKIs. EGFR mutations occur in approximately 15% of NSCLC patients, and occur more frequently in patients with adenocarcinoma, never-smokers, females, and those of East Asian descent. First generation EGFR TKIs such as erlotinib and gefitinib yield high overall response rates (ORR 50-70%) and improve progression free survival (PFS) compared to

chemotherapy. Treatment with a second generation TKI, afatinib, has also demonstrated ORR and PFS improvements compared to chemotherapy. In the U.S., erlotinib and afatinib are approved for the first-line treatment of patients with metastatic NSCLC whose tumors have exon 19 deletion or exon 21 L858R substitution.

Unfortunately, all patients with EGFR mutations treated with first or second generation EGFR TKIs develop resistance. About half of patients acquire the T790M+ gatekeeper resistance mutation in the ATP-binding pocket of EGFR. There are currently no approved treatments specifically for tumors with EGFR T790M+ mutations. The only available treatment options for these patients are single agent chemotherapy agents such as pemetrexed and docetaxel, which have response rates of approximately 10% in unselected patients.

3. Endpoints used in the available clinical data, endpoints planned for later studies, and endpoints currently accepted by the review division in the therapeutic area

- *Describe the endpoints considered by the sponsor as supporting the breakthrough therapy designation and any other endpoints the sponsor plans to use in later studies.*

The sponsor's endpoint is overall (ORR) by RECIST 1.1 supported by duration of response (DOR).

- *The endpoint(s) that are accepted by the division as a clinically significant endpoint (outcome measure) for patients with the disease, such as:*

In NSCLC, the ultimate clinical benefit endpoint is overall survival (OS). The division has accepted PFS of large magnitude, with acceptable risk-benefit as evidence of direct clinical benefit. For accelerated approval, the division has accepted ORR of large magnitude with a long DOR.

- *Any other biomarkers the division would consider likely to predict a clinical benefit (e.g., metastatic effect), even if not yet a basis for accelerated approval.*

The sponsor also reports CNS response, which is a common sanctuary site of progression during EGFR TKI therapy.

4. Brief description of available therapies (if any)

There are no therapies approved specifically for EGFR mutation positive patients who progress on EGFR TKI therapy and acquire the T790M resistance mutation. Table 1 describes therapies approved in second or third line unselected NSCLC patients.

Table 1: FDA approved available therapies for second-line treatment of non-small cell lung cancer

	Median PFS/TTP (months)	Median OS (months)	ORR % (95% CI)
Docetaxel (n=125) vs Vinorelbine/Ifosfamide (n=123)	TTP 2.0 (1.6, 2.7) vs. 1.8 (1.5, 2.3)	5.7 (5.1, 7.1) vs. 5.6 (4.4, 7.9) p = 0.13	5.7% (2.3, 11.3) vs. 0.8% (0.0, 4.5)
Docetaxel (n=55) vs. BSC (n=49)	TTP 2.8 (2.1, 4.2) vs. 1.6 (1.4, 2.1)	7.5 (5.5, 12.8) vs. 4.6 (3.7, 6.1) p = 0.01	5.5% (1.1, 15.1) vs. N/A
Pemetrexed (n=283) vs. docetaxel (n=288) (non-inferiority) <i>No squamous subset (N=399)</i>	PFS 2.9 (2.4-3.1) vs. 2.9 (2.7-3.4) HR 0.97 (0.82-1.16)	8.3 (7.0-9.4) vs. 7.9 (6.3-9.2) HR 0.99 (0.82-1.20) 9.3 (7.8-9.7) vs. 8.0 (6.3-9.3) HR 0.89 (0.71-1.13)	8.5% (5.2-11.7) vs. 8.3% (5.1-11.5)
BSC, best supportive care; ORR, overall response rate; OS, overall survival; PFS, progression free survival; TTP, time to tumor progression			

Clinical Review, NDA205755, March 25, 2014. Sean Khozin, MD, MPH.

5. Brief description of any drugs being studied for the same indication that received breakthrough therapy designation

None.

6. Description of preliminary clinical evidence

- *Overview of clinical development program including completed and planned studies with the study endpoints and population, noting particularly troublesome and advantageous aspects of the design. If, for example, it is a single arm trial, there needs to be a consideration of the spontaneous variability of the condition.*

The clinical development program includes an ongoing Phase 1 study. The objectives of the study are to determine the safety and tolerability, maximum tolerated dose (MTD), biologically effective dose (BED), pharmacokinetics (PK), and preliminary anti-tumor activity of AZD9291 in adult subjects with advanced NSCLC who have progressed following prior therapy with an EGFR TKI.

Once the BED is determined, the sponsor plans two single arm studies. The first study will be a Phase 2 single-arm, open-label extension to the ongoing AURA study (AURA extension). This will be a protocol amendment to the currently ongoing Phase I study, and will assess the safety and efficacy of AZD9291 in patients with T790M+ advanced NSCLC (n=175) who have progressed following either one prior therapy

with an EGFR TKI (chemotherapy-naïve, n=50) or following treatment with both EGFR TKI and at least one other prior line of therapy, such as cytotoxic doublet chemotherapy or immunotherapy (n=125). The second study is AURA2, and will be a Phase II, open-label, single-arm study to assess the safety and efficacy of AZD9291 in patients with T790M+ advanced NSCLC (n = 175), whose disease has progressed following either one prior therapy with an EGFR TKI (chemotherapy-naïve, n=50) or following treatment with both EGFR TKI and at least one prior chemotherapy containing platinum-based doublet (n=125).

The primary endpoint of both Phase 2 studies is ORR, supported by DOR. The target response rate is > 40% with duration of response of > 6 months in > 50% of responding patients.

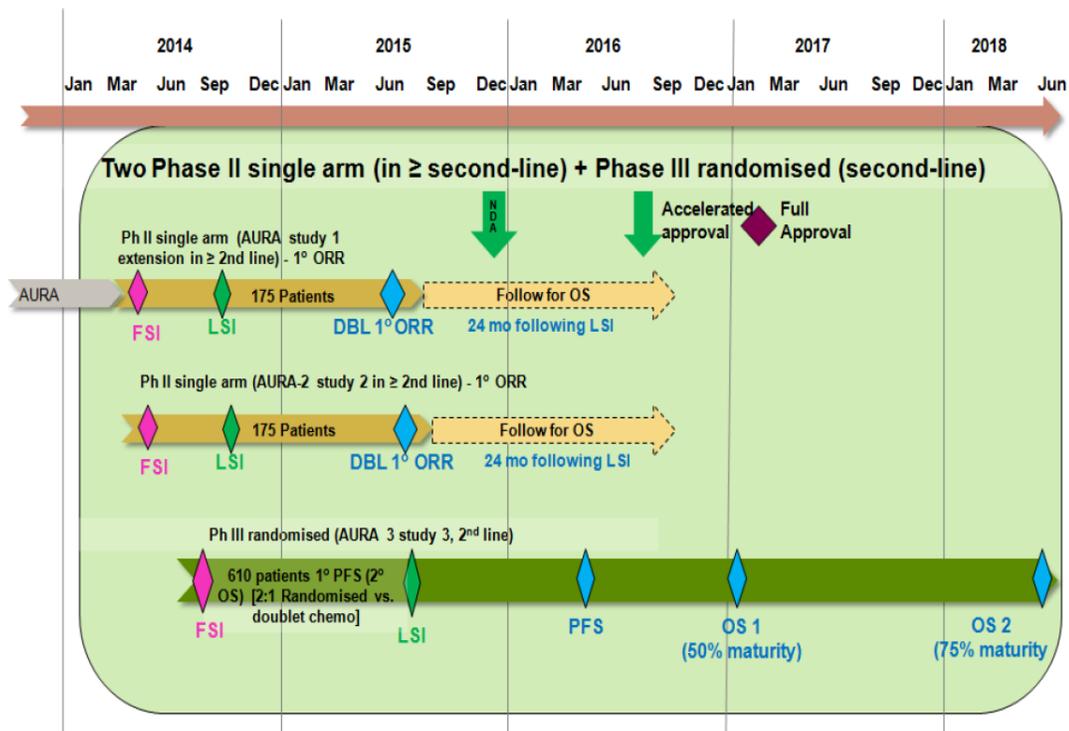
The confirmatory Phase 3 study is an open label, randomized study to assess the safety and efficacy of AZD 9291 versus platinum-based doublet chemotherapy (pemetrexed 500mg/m² + carboplatin AUC5 or pemetrexed 500mg/m² + cisplatin 75mg/m²) in second line patients with T790M+ advanced NSCLC (n+610) who have progressed on a prior EGFR TKI (chemotherapy-naïve patients).

The primary endpoint will be PFS but the study is powered for OS. The target hazard ratio (HR) for PFS is 0.67 (e.g., improvement from 6 to 9 months). The primary analysis will be conducted at approximately 65% maturity and will have >90% power. The study will also have adequate power (>80%) to characterize the secondary endpoint of OS. Figure 1 depicts the development plan.

The sponsor is planning to utilize a tissue based diagnostic test to identify T790M+ patients and has partnered with Roche Molecular Systems (RMS) to develop a test for detection of EGFR mutations including the T790M resistance mutation. A plan is in place to modify RMS's cobas® EGFR Mutation Test in order to obtain expanded label approval in United States for T790M directed EGFR mutation detection to select NSCLC patients for treatment with AZD9291. (b) (4)

. The development of (b) (4) diagnostic tests will be discussed with CDRH.

Figure 1.
Overall Development Plan



Taken from: Astra Zeneca's Pre-Phase III Briefing Document, page 8.

- *Efficacy data available to support breakthrough therapy designation (a table comparing the efficacy of the proposed breakthrough and available treatments, if any, would also be helpful). There should be an explanation of whether the data provided should be considered preliminary clinical evidence of a substantial improvement over available therapies. In all cases, actual results, in addition to reported significance levels, should be shown. Any major failings in the study that decrease its persuasiveness (small or missing data) should be identified.*

As of 16 January 2014, a total of 57 objective responses (35 confirmed partial responses (PRs), 22 awaiting confirmation) have been seen in 89 T790M+ patients with a baseline and at least one follow up assessment. The preliminary estimated response rate is 64% (95% CI 53% to 74%). This includes one patient with PR at initial scan who now has a complete response (CR) at their 12-week scan, and is ongoing on treatment. Objective tumor responses have been observed from the first dose escalation cohort of 6 patients at a once-daily dose of 20 mg. This information is depicted in table 2. Of the 35 confirmed PRs in T790M+ patients, 10 patients have a duration of response of approximately 3 months or more with the longest duration of response to date being approximately 6 months (the longest

duration of exposure in T790M+ patients is currently 7.2 months). This information is depicted in the spider plot (figure 2).

Table 2.

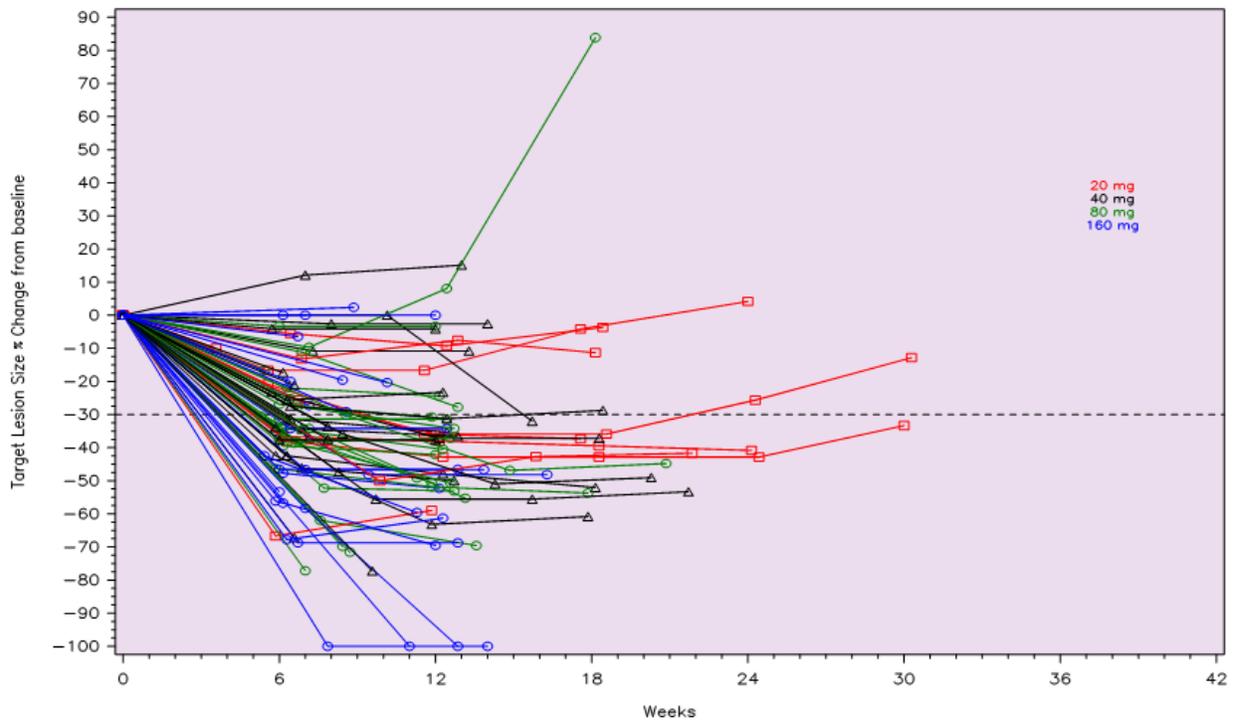
Number of responses by T790M status, confirmed and unconfirmed in patients with at least one follow up scan.

	Escalation Cohorts					Expansion T790M+				Expansion T790M-				Total	
	20 Mg N=6	40 Mg N=6	80 Mg N	160 Mg N=6	240 Mg N=7	20 Mg N=10	40 Mg N=28	80 Mg N=27	160 Mg N=24	20 Mg N=3	40 mg N=17	80 Mg N=	160 Mg N=9	T790M+ N=89	All N=177
Partial Response (%)	3	3	4	4	3	5	19	18	15	2	1	3	4	57 (64%)	91 (51%)
Confirmed (%)	3	3	3	4	1	5	8	11	11	2	0	2	2	35 (39%)	60 (33%)
Unconfirmed (%)	0	0	1	0	2	0	11	7	4	0	1	1	2	22 (24%)	31 (17%)

From Astra Zeneca's Request for Breakthrough Therapy Designation, page 19.

Figure 2.

Change in target lesions over time by dose: T790M+ patients (N=87)* by central testing of T790M status.



From Astra Zeneca's Request for Breakthrough Therapy Designation, page 20.

*Two patients who died prior to their first follow-up scan are excluded.

- *Any other factors regarding the clinical development program that were taken into consideration when evaluating the preliminary clinical evidence, such as trial conduct, missing data, any relevant nonclinical data, and whether the drug or its components have a novel MOA.*

Preliminary clinical evidence includes data in which 34 of the 199 patients had central nervous system (CNS) metastases at baseline that were followed as target or non-target lesions by RECIST 1.1. Thirty-one of these patients have had at least one post baseline scan, and the objective RECIST response in this subset of patients is similar to the overall study. In the subset of patients with non-target CNS metastasis there were 15 PR (10 confirmed, 5 un-confirmed), 4 stable disease, 4 progressive disease and 3 non-evaluable. Five patients had CNS target lesions with 2 confirmed PRs, 2 un-confirmed PRs, and 1 with stable disease.

Astra Zeneca, Request for Breakthrough Designation, Feb. 25, 2014, p 22.

- *Safety data (a brief explanation of the safety profile would be helpful, especially if it affects the division's recommendation)*

From the preliminary data in the Phase 1 study, AZD9291 may have an adverse event (AE) profile similar to the other EGFR TKIs currently approved. The sponsor reports that 84% of patients enrolled on the Phase 1 have had an AE, with 16% grade 3 or above. The most common AEs are rash, diarrhea and nausea and appear to be managed with standard medical therapy (e.g. loperamide, topical steroids, and anti-emetics). Serious AEs include pneumonia (4 cases), pleural effusion (4 cases), pneumonitis (3 cases), ischemic stroke (2 cases), pulmonary embolism (2 cases), and severe diarrhea (2 cases). Three patients on the Phase 1 study have died from causes other than from disease progression: two patients from pneumonia, and one from sepsis.

Table 5. Adverse Events by preferred term (PT) and dose

PT	20mg (N=21)	40mg (N=58)	80mg (N=60)	160mg (N=51)	240mg (N=9)	Total (N=199)
Any AE	18(86%)	46(79%)	50(83%)	45(88%)	8(89%)	167(84%)
Any AE≥CTCAE grade 3	3(14%)	10(17%)	9(15%)	10(20%)	0	32(16%)
Any SAE	2(10%)	6(10%)	13(22%)	14(28%)	1(11%)	36(18%)
Diarrhea	3(14%)	16(28%)	11(18%)	25(49%)	5(56%)	60(30%)
Rash	4(19%)	8(14%)	15(25%)	17(33%)	3(33%)	47(24%)
Nausea	2(10%)	11(19%)	8(13%)	10(20%)	3(33%)	34(17%)
Decreased Appetite	4(19%)	6(10%)	6(10%)	8(16%)	3(33%)	27(14%)
Dry Skin	1(5%)	4(7%)	5(8%)	15(29%)	1(11%)	26(13%)
Pruritis	4(19%)	7(12%)	8(13%)	4(8%)	2(22%)	25(13%)
Constipation	0	8(14%)	7(12%)	7(14%)	0	22(11%)
Anemia	0	4(7%)	6(10%)	10(20%)	1(11%)	21(11%)
Fatigue	3(14%)	7(12%)	4(7%)	7(14%)	0	21(11%)

From Astra Zeneca's Request for Breakthrough Therapy Designation, page 27.

7. Division's recommendation and rationale

- Our recommendation is to grant breakthrough status for the treatment of metastatic non-small cell lung cancer (NSCLC) whose disease has progressed on previous EGFR TK1 therapy ^{(b) (4)}
- Rationale: The ORR of 57% in 86 patients, which appears to be durable in patients with EGFRm positive NSCLC harboring a T790M resistance mutation who have progressed on a EGFR TKI represents evidence of a substantial improvement over available therapy in a serious disease with high unmet medical need.

8. Division's next steps and sponsor's plan for future development

- If recommendation is to grant the request – explain next steps and how the division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program).

We will schedule a multidisciplinary type B meeting to discuss all aspects of development including pharm-toxicology, clinical pharmacology, CMC, statistics, clinical, and CDRH. There will be further discussion of the size and timing of the clinical data necessary for accelerated approval, the design of the confirmatory studies, and plans for an expanded access program.



Request for Breakthrough Designation AZD 9291

Sponsor: AstraZeneca

Barb Sceपुरa, MS, CRNP

Gideon Blumenthal, MD, Team Leader

Division of Oncology Products 2

MPC Meeting: April 11, 2014

Goal Date: April 28, 2014

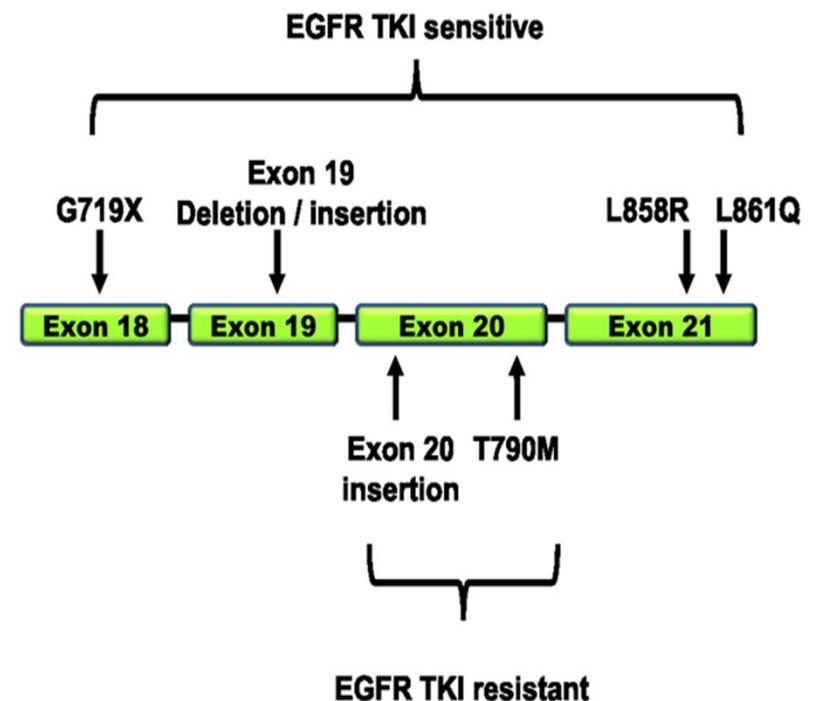


Background on NSCLC

- Lung cancer is the top cancer killer US and worldwide
- If no known mutation, standard first –line chemotherapy is platinum doublet – response rate is 25-35%
- Median Progression free survival (PFS) is ~5 months
- Median Overall survival (OS) is ~10-12 months
- In past decade, Non-Small Cell Lung cancer (NSCLC) subdivided into driver mutations which can be targeted with Tyrosine Kinase Inhibitors (TKIs)

EGFR mutant NSCLC

- EGFR mutations are present in about 15% of US NSCLC patients
- If EGFR mutation status is positive, first line treatment is TKI, ORR 60-65%
- 1st generation TKIs: erlotinib, gefitinib (pending NDA submission 8/2014)
- 2nd generation: afatinib
- Median PFS: 8-10 months
- Median OS: 22 months
- Resistance occurs in all patients, after about a year on TKI
- Most common mechanism of resistance: T790M (~50% of patients)





FDA approved available therapies for second-line treatment of non-small cell lung cancer

	Median PFS/TTP (months)	Median OS (months)	ORR % (95% CI)
Docetaxel (n=125) vs Vinorelbine/Ifosfamide (n=123)	TTP 2.0 (1.6, 2.7) vs 1.8 (1.5, 2.3)	5.7 (5.1, 7.1) vs 5.6 (4.4, 7.9) p = 0.13	5.7% (2.3, 11.3) vs 0.8% (0.0, 4.5)
Docetaxel (n=55) vs BSC (n=49)	TTP 2.8 (2.1, 4.2) vs 1.6 (1.4, 2.1)	7.5 (5.5, 12.8) vs 4.6 (3.7, 6.1) p = 0.01	5.5% (1.1, 15.1) vs N/A
Pemetrexed (n=283) vs docetaxel (n=288) (non-inferiority) <i>Nonsquamous subset (N=399)</i>	PFS 2.9 (2.4-3.1) vs 2.9 (2.7-3.4) HR 0.97 (0.82-1.16)	8.3 (7.0-9.4) vs 7.9 (6.3-9.2) HR 0.99 (0.82-1.20) 9.3 (7.8-9.7) vs 8.0 (6.3-9.3) HR 0.89 (0.71-1.13)	8.5% (5.2-11.7) vs 8.3% (5.1-11.5)

BSC, best supportive care; ORR, overall response rate; OS, overall survival; PFS, progression free survival; TTP, time to tumor progression.

Thanks to Sean Khozin.



AZD9291

AZD9291 is an irreversible inhibitor of both:

- EGFRm+(TKI-**sensitivity** conferring mutations such as del19 and L858R substitution)

and

- EGFR T790M+ (TKI-**resistance** conferring mutations- double mutant)



AZD9291 Proposed Indication

- For patients with metastatic NSCLC whose disease has progressed with previous EGFR TKI therapy

(b) (4)

[Redacted text block]



Phase I study – ongoing

Data cut-off January 16, 2014

- Eligibility criteria:
 - Confirmed EGFR mutation
 - Must have experienced clinical benefit from EGFR TKI therapy followed by progression
 - Radiologic disease progression while on treatment with EGFR-TKI
- Primary objective:
Safety and tolerability
- Secondary objectives:
MTD, PK, anti-tumor activity, biomarkers



Prior lines of therapy in Phase 1 Study

Prior lines of therapy	Dose escalation N=31	Expansion Cohorts N=168
Prior lines of therapy, median (range)	3 (1 to 12)	3 (1 to 9)
Number of lines		
1 (%)	24 (77%)	80 (48%)
2 (%)	2 (6%)	57 (34%)
3 (%)	2 (6%)	13 (8%)
≥4 (%)	3 (10%)	3 (2%)
Missing (%)	0	15 (9%)
Immediate prior use of EGFR TKI (Y,N,missing)	14/17/0	100/64/4



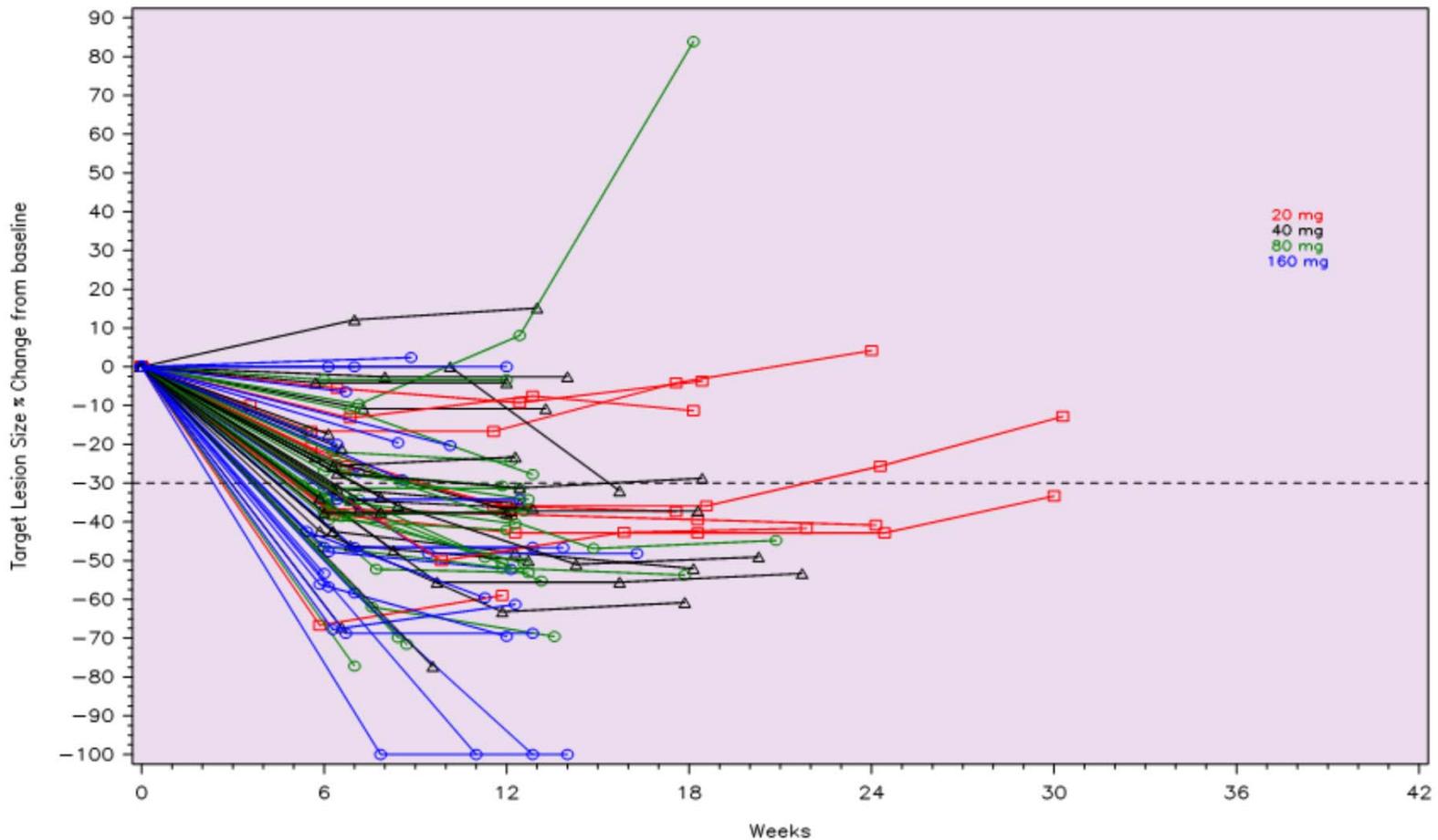
Best overall response by T790M status in patients with at least 1 follow up scan

	Escalation Cohorts T790M unknown					Expansion T790M+				Expansion T790M-			
	20 mg N=6	40 mg N=6	80 mg N=6	160 mg N=6	240 mg N=7	20 mg N=10	40 mg N=28	80 mg N=27	160 mg N=24	20 Mg N=3	40 Mg N=17	80 Mg N=14	160 Mg N=9
Part Resp (%)	3 (50)	3 (50)	4 (66)	4 (66)	3 (43)	5 (50)	19(67)	18(66)	15(62)	2(66)	1(.05)	3(21)	4(44)
Conf (%)	3 (50)	3 (50)	3 (50)	4 (66)	1 (14)	5 (50)	8 (28)	11(40)	11(45)	2(66)		2(14)	2(22)
Un-conf			1 (16)		2(28)		11(39)	7(25)	4(16)		1(.05)	1(.07)	2(22)

- **Total ORR (conf + unconf) T790M+: 57/89 (64%, 95% CI: 53, 74)**
- **Total ORR (conf + unconf) all pts: 91/177 (51%)**



Change in target lesions over time by dose: T790M+ patients by central testing of T790M.





AE >15% by preferred term(PT) & dose

PT	20mg (n=21)	40 mg (n=58)	80mg (n=60)	160mg (n=51)	240mg (n=9)	Total (n=199)
Diarrhea	3 (14%)	16(28%)	11(18%)	25(49%)	5(56%)	60(30%)
Rash	4 (19%)	8(14%)	15(25%)	17(33%)	3(33%)	47(24%)
Nausea	2 (10%)	11(19%)	8 (13%)	10(20%)	3(33%)	34(17%)

Grade 3 and above AE and SAEs

AE n(%)	20mg (n=21)	40mg (n=58)	80mg (n=60)	160mg (n=51)	240mg (n=9)	Total (n=199)
Grade \geq 3	3 (14%)	10 (17%)	9 (15%)	10 (20%)	0	32 (16%)
SAE	2 (10%)	6 (10%)	13 (22%)	14 (28%)	1 (11%)	36 (18%)

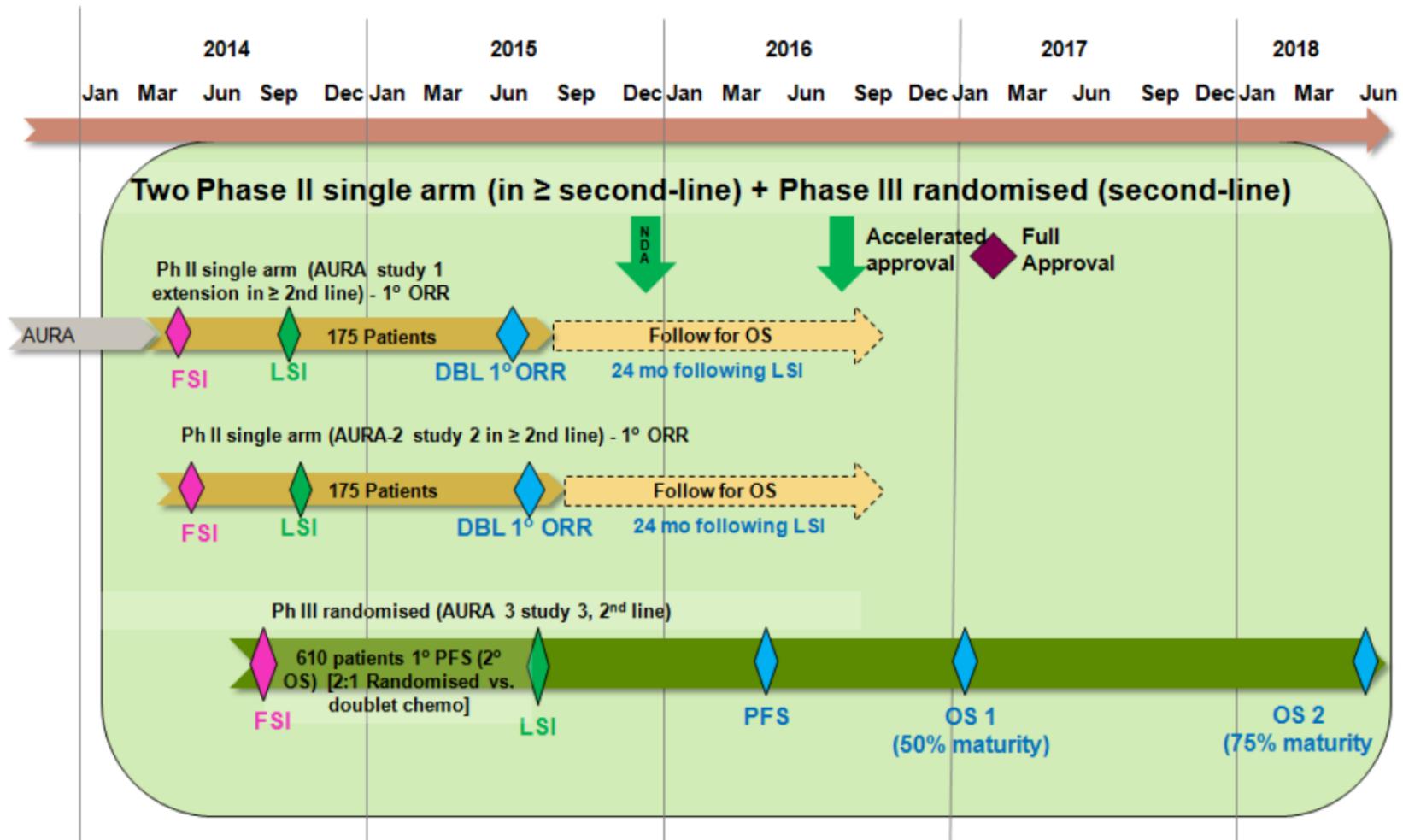


Safety

- **18% SAE:** pneumonia (4), pleural effusion (4), pneumonitis (3), CVA (2), PE (2), diarrhea (2)
- **7 patients discontinued due to AE's**
- **5 patients required dose reduction**
- **29 patients with dose interruptions due to AE**
- **3 deaths: 2 pneumonia, 1 sepsis**



Overall Development Plan





Requirements for BT designation

- Advanced NSCLC is a serious condition with high unmet medical need
- There are no approved therapies that exist to target T790M+ acquired EGFR TKI resistance
- Preliminary clinical evidence suggests substantial benefit over available therapy
- Recommendation: Grant BT

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

/s/

SANDRA J BENTON
04/15/2014

PATRICIA KEEGAN
04/16/2014



IND 117879

MEETING MINUTES

AstraZeneca Pharmaceuticals LP
Attention: Nicholas Troise
Regulatory Affairs Director
1800 Concord Pike
PO Box 8355
Wilmington, DE 19803-8355

Dear Mr. Troise:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for "AZD9291."

We also refer to the meeting between representatives of your firm and the FDA on January 14, 2014. The purpose of the meeting was to discuss the overall non-small cell lung cancer (NSCLC) clinical development program for AZD9291 to support initial registration as a treatment for (b) (4) T790M positive NSCLC patients.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-4255.

Sincerely,

{See appended electronic signature page}

Norma Griffin
Senior Regulatory Health Project Manager
Division of Oncology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C
Meeting Category: Other

Meeting Date and Time: Tuesday, January 14, 2014; 2:00-3:00 PM (ET)
Meeting Location: White Oak Building 22, Conference Room 1313

Application Number: IND 117879
Product Name: AZD9291
Indication: For the treatment of non-small cell lung cancer (NSCLC)
Sponsor/Applicant Name: AstraZeneca Pharmaceuticals LP

FDA ATTENDEES

Patricia Keegan, Division Director, DOP2
Joseph Gootenberg, Deputy Division Director, DOP2
Gideon Blumenthal, Clinical Team Leader, DOP2
Sean Khozin, Clinical Reviewer, DOP2
Barbara Scepura, Clinical, DOP2
Norma Griffin, Senior Regulatory Health Project Manager, DOP2
Ruth Maduro, Regulatory Health Project Manager, DOP2
Whitney Helms, Nonclinical Team Leader, DHOT
Shawna Weis, Nonclinical Reviewer, DHOT
Hong Zhao, Clinical Pharmacology Team Leader, DCPV
Shenghui Tang, Biometrics Team Leader, DBV
Somesh Chattopadhyay, Biometrics Reviewer, DBV
Timothy Schaefer, Reviewer, CDRH
Reena Phillip, Reviewer, CDRH

SPONSOR ATTENDEES

Hesham Abdullah	Vice President, Global Regulatory Affairs, Oncology
Cindy Lancaster	Executive Director, US Regulatory Affairs, Oncology
Kenneth Thress	Translational Scientist, Oncology iMED
Antoine Yver	Vice President, Oncology & New Opportunities, Head GMD
Darren Cross	AZD9291 Science Lead
Paul A Dickinson	Senior Clinical Pharmacology Scientist
Serban Ghiorghiu	AZD9291 Clinical Lead & Acting Global Product Team Director
Suzanne Jenkins	Dphil Diagnostics Expert
Nicola Schmitt,	Statistical Science Director
Wendy White	Global Regulatory Director, Oncology
Susan Galbraith	Vice President, Head of Oncology Innovative Medicines
(b) (4)	(b) (4)
(b) (4)	(b) (4)

BACKGROUND

AstraZeneca Pharmaceuticals LP (AstraZeneca) requested a meeting on October 30, 2013, to discuss the overall non-small cell lung cancer (NSCLC) clinical development program for AZD9291 to support initial registration as a treatment for (b) (4) T790M positive NSCLC patients.

AZD9291 is an irreversible third-generation inhibitor of EGFRm+ (TKI-sensitivity conferring mutations) and T790M+ (TKI-resistance conferring mutation) receptor forms of EGFR. AZD9291 was granted Fast Track designation as a treatment for patients with (b) (4) NSCLC (b) (4). AstraZeneca is also considering submitting an application for Breakthrough Designation in Q1 2014.

AstraZeneca plans to seek an initial registration for pre-treated patients with (b) (4) NSCLC (b) (4).

AstraZeneca notes that although there are approved and established therapies for patients with NSCLC known to have activating mutations in *EGFR* (EGFRm+), treatment with EGFR TKIs is not curative and the majority of patients will progress within 1 year. The emergence of a secondary T790M mutation in patients treated with an EGFR TKI agent has been described as a major route of development of resistance to this class of therapy in approximately 60% of patients. Treatment options are limited following progression on EGFR TKIs, with patients

generally receiving doublet chemotherapy before salvage single-agent cytotoxic therapy. AstraZeneca notes that there is thus a high unmet medical need for targeted anti-tumor therapy for patients with (b) (4) NSCLC (b) (4).

Nonclinical

AstraZeneca states that, consistent with its known activity as an EGFR inhibitor, toxicities observed in the 1-month, IND-enabling toxicology studies with AZD9291 in rats and dogs revealed gastrointestinal and ocular toxicities as the primary findings in both species. Although reproductive and dermal effects were also observed, the Sponsor states that they were of minimal to mild severity and therefore were not considered dose-limiting in these studies.

AstraZeneca states that AZD9291 has been fully characterized in safety pharmacology studies (cardiovascular, CNS, respiratory and ocular), and that AZD9291 was negative in the in vitro or in vivo genotoxicity studies and in vitro phototoxicity study conducted in support of the IND.

AstraZeneca states that they have initiated 13-week studies in rats and dogs to support ongoing clinical development of AZD9291. They anticipate completion of the in-life phase by mid-February 2014, and propose to submit interim reports (i.e. QA audited draft reports containing histopathology on main study animals, ophthalmology, clinical pathology, ECGs (dogs) toxicokinetics, and an assessment of male rat fertility) to enable progression into Phase 3 studies, and to follow up with the final reports with all remaining data, within 60 days of the start of the Phase 3 study.

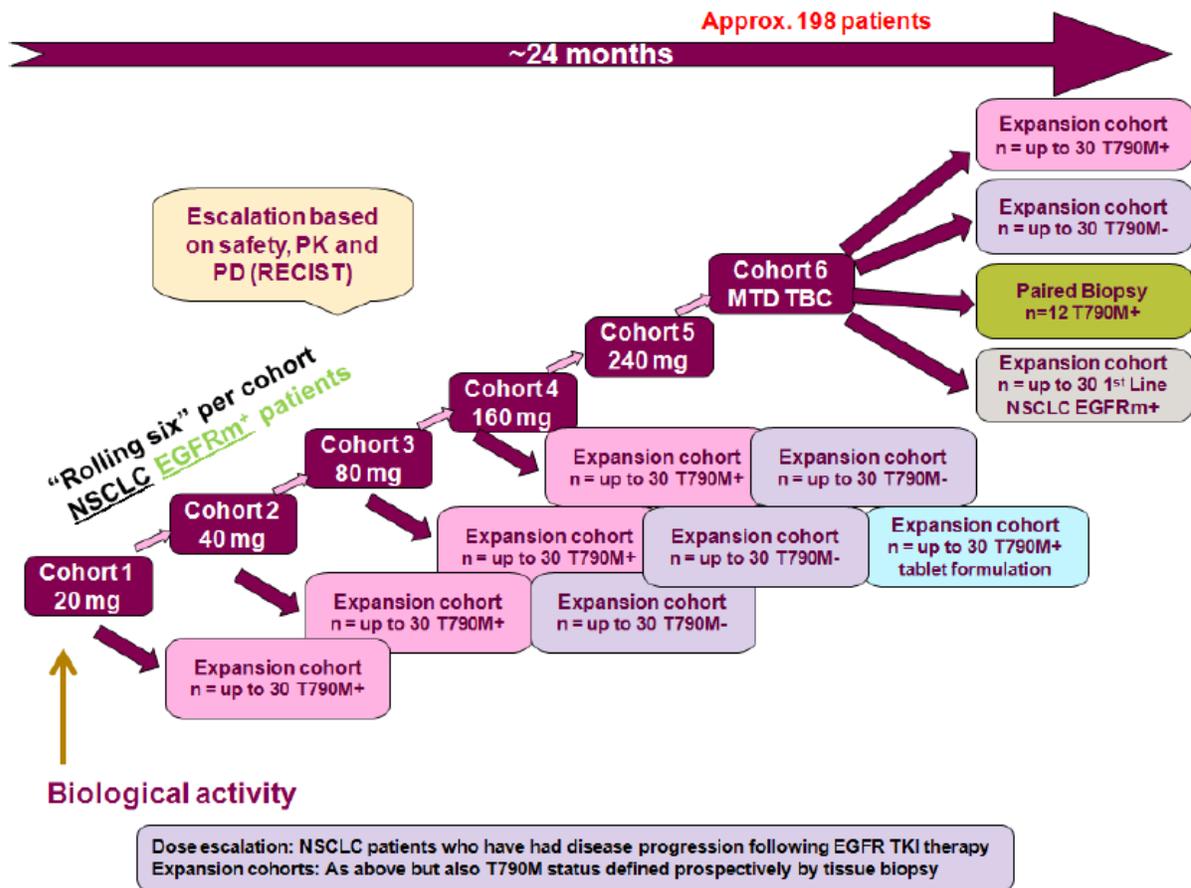
In addition, AstraZeneca proposes to complete a preliminary dose-ranging embryofetal toxicity study during 2014 to determine the feasibility of further reproductive toxicology assessments with AZD9291. Should AZD9291 demonstrate embryofetal toxicity in the preliminary dose-ranging studies, AstraZeneca proposes to conduct no further embryofetal studies and to provide label language to warn of the risks associated with the use of AZD9291 in pregnant women or nursing mothers.

AstraZeneca states that they intend to conduct no further studies beyond the 13-week toxicology and reproductive toxicity assessment (i.e. they propose not to conduct male and female fertility studies, or carcinogenicity studies).

Clinical Development

Two clinical studies of AZD9291 are currently ongoing. Study D5160C00001 (AURA) is a Phase I, first-time-in-human (FTIH), multi-center, open-label, dose-escalation, and dose-expansion study to determine the safety and tolerability, maximum tolerated dose (MTD), biologically effective dose, pharmacokinetics (PK), and preliminary anti-tumor activity of AZD9291 in adult subjects with advanced NSCLC who have progressed following prior therapy with an EGFR TKI agent. AURA's trial design includes expansion cohorts in each dose escalation group and the MTD cohort as shown in Figure 1.

Figure 1. . D5160C00001 (AURA) Trial Design



Study D5160C00005 is to determine the relative bioavailability of different oral formulations of AZD9291 and the effect of food in healthy volunteers. The first subject was dosed on November 5, 2013.

AstraZeneca states that to date, no DLTs have been reported across the active dose range of 20, 40, 80 or 160 mg/day in AURA. The MTD has not yet been defined and dose escalation is ongoing. The 240 mg dose is currently being evaluated. Preliminary data indicate the most commonly reported adverse events are diarrhea and skin toxicities.

In AURA, the first patient was dosed on March 6, 2013. The study is currently being conducted in the United Kingdom, Germany, France, Spain, Korea, Japan, Taiwan, Australia and the United States, with a ratio of Asian/non-Asian patients of 73%/27% as of November 19, 2013 data cut-off. According to AstraZeneca, efficacy results in AURA as follows:

- Objective tumor responses have been observed from the first dose escalation cohort of 6 patients at a once-daily dose of 20 mg
- 92 of 174 patients treated with AZD9291 have had at least 1 post-baseline follow-up assessment

- Out of the 92 patients above, 44 (48%; 18 [20%] confirmed) have had a partial response (PR)
- Of the 18 confirmed PRs, all are still ongoing with the longest duration of response to date being 6 months
- 21 (54%) responses have so far been observed in 39 T790M positive patients and 3 (16%) responses in 19 T790M negative patients

Assuming patients recruited to the dose extension component of the Phase I study, D5160C00001, continue to demonstrate the same level of efficacy, and are tolerant to AZD9291 treatment, AstraZeneca is proposing to conduct the following:

- AURA Extension - a Phase 2 single-arm, open label non-randomized study extension to the current Phase 1 AURA Study D5160C00001 in patients with T790M+ advanced NSCLC (n=175) who have progressed following either one prior therapy with an EGFR TKI (chemotherapy-naïve, n=50) or following treatment with both EGFR TKI and at least one other prior line of therapy, such as cytotoxic doublet chemotherapy or immunotherapy (n=125).
- AURA2 - a Phase 2, non-randomized study to assess the safety and efficacy of AZD9291 in patients with T790M+ advanced NSCLC (n = 175), whose disease has progressed following either one prior therapy with an EGFR TKI (chemotherapy-naïve, n=50) or following treatment with both EGFR TKI and at least one prior chemotherapy containing platinum-based doublet (n=125). The purpose of this study is to replicate the efficacy and safety data observed in the AURA extension.
- AURA3 - A confirmatory Phase 3, open label, randomized study to assess the safety and efficacy of AZD9291 versus platinum-based doublet chemotherapy (pemetrexed 500 mg/m² + carboplatin (AUC5 area under the plasma concentration–time curve [AUC] 5 mg/ml/minute) or pemetrexed 500 mg/m² + cisplatin 75mg/m²) in pre-treated (second-line) patients with T790M+, advanced NSCLC (n=610), who have progressed on a prior EGFR TKI (chemotherapy-naïve).
- Proposed - (b) (4)
[REDACTED]

AstraZeneca is currently planning to identify T790M+ patients, using a tissue based diagnostic test in the clinical development program, and has partnered with Roche Molecular Systems (RMS) to develop a tissue-based companion diagnostic test for detection of EGFR mutations, including the T790M resistance mutation. A plan is in place to modify RMS' cobas® EGFR Mutation Test in order to obtain expanded label approval in the United States for T790M directed EGFR mutation detection to select NSCLC patients for treatment with AZD9291.

(b) (4)

Regulatory

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

Preliminary responses were provided to AstraZeneca on January 13, 2013. AstraZeneca provided responses to FDA's preliminary responses on January 14, 2014, prior to the meeting. AstraZeneca requested discussion of Questions 7 and 17 during the meeting. A separate discussion was held after the meeting between AstraZeneca and FDA Nonclinical staff resulting in post-meeting communications. In addition, FDA Clinical Pharmacology staff agreed to provide additional response after the meeting to AstraZeneca's January 14, 2014 email response.

GENERAL RECOMMENDATION

FDA advises AstraZeneca to meet with FDA to further discuss AstraZeneca's Phase 3 protocols when the optimum biological dose has been determined.

SPONSOR SUBMITTED QUESTIONS AND FDA RESPONSES

Nonclinical

Refer to Background Information for Question 1 from pages 47-49 of AstraZeneca Briefing Document.

- AstraZeneca considers that the proposed non-clinical program of toxicology studies is sufficient to support the approval of AZD9291 as a proposed treatment for patients with (b) (4) EGFRm+/T790M+ non-small cell lung cancer (NSCLC) who have progressed on prior EGFR TKI, (b) (4) (b) (4) oes the FDA agree??**

FDA 1/13/2014 Response: The proposed nonclinical toxicology program appears sufficient to support the submission of an NDA for a drug to treat (b) (4)

Please note that the proposed dose-ranging embryofetal development study should include a toxicokinetic assessment of maternal and fetal plasma exposures as well as histopathology. In addition, if no clear findings of embryofetal risk are observed in this study, additional studies may be required.

The adequacy of the data to support approval of a marketing application for AZD9291 will be determined following a review of the reports submitted in the NDA.

AstraZeneca 1/14/2014 Email Response: AstraZeneca will request written clarification from FDA regarding the request to collect fetal plasma exposure under separate cover.

Discussion During 1/14/2014 Meeting: There was no discussion of this item during the meeting. FDA Nonclinical Reviewer discussed Question 1 with Hesham Abdullah of AstraZeneca immediately following the meeting and will provide further clarification.

FDA 1/15/2014 Post-Meeting Comments (provided as an Advice/Information Request Memorandum): The Nonclinical Reviewer provided the following additional comments/advice for clarification:

“To aid in interpretation of a dose-ranging embryofetal toxicity study, particularly if AstraZeneca hopes to use this study as the sole study for assessment of reproductive toxicity, it is necessary to distinguish specific drug-induced effects from effects that are elicited by indirect toxicity to the pregnant dam. To that end:

- (a) Perform histopathology on main study dams (or a subset of dams) at each dose level. Include known target organs, gross lesions and reproductive tissues from the animals selected and assess the dose-response for embryotoxicity against the toxicity of the drug as ascertained by histopathology in the dams. Collection of clinical pathology data (hematology and clinical chemistry) from those dams selected for histological assessment is also recommended.
- (b) Estimate the maternal/fetal plasma exposure ratios in the dams and fetuses. Typically, TK cohort dams and their fetuses, which are not evaluated for skeletal and/or soft-tissue alterations, are used. Fetal blood samples may be pooled by litter.”

AstraZeneca 1/17/2014 Email Response to FDA Advice/Information Request Memorandum of 1/15/2014:

“Thank you for providing further clarification and for your guidance regarding the design of the rat embryofetal development study. Based on our in house experience with other compounds from this pharmacological class (EGFR inhibitors), AstraZeneca will design a bespoke developmental toxicity study which includes an assessment of effects related to exposure to AZD9291 both during organogenesis and through to the early post-natal phase. AstraZeneca can confirm that this study will be designed to comply with

regulatory guidelines (ICH5) and will incorporate appropriate pharmacodynamic and pharmacokinetic endpoints. Given the availability of a sensitive analytical assay, AstraZeneca routinely collects blood samples for exposure monitoring from main study pregnant animals at the end of organogenesis and do not have satellite groups. Blood samples will also be collected from mothers and pups during the early post-natal phase to assess exposure. AstraZeneca anticipates developmental toxicity (in particular lethality) at maternal exposures that are below those which are minimally maternally toxic and below human therapeutic exposures. Once AstraZeneca has these developmental toxicity data and understands the timing and dose response of F1 losses, they will then assess options for placental transfer studies. AstraZeneca would like FDA to advise if their response is acceptable.”

FDA 2/6/2014 Response to 1/17/2014 AstraZeneca Email Correspondence:

AstraZeneca’s proposal to characterize fetal plasma levels of AZD9291 appears to be acceptable; however, should the study fail to demonstrate clear signs of teratogenic activity, a standard panel of embryofetal studies (i.e. studies in two species, sufficiently powered to detect dose-related effects) should be conducted.

Refer to Background Information for Question 2 from pages 49-50 of AstraZeneca Briefing Document.

- 2. The proposed toxicology data to support commencement of the proposed Phase III clinical study will include completed 1-month toxicology data and ongoing 3-month toxicology studies.** (b) (4)

Does the FDA agree with this proposal?

FDA 1/13/2014 Response: No, FDA does not agree. Submit the complete results from repeat dose studies of 3 months’ duration prior to initiating Phase 3 studies.

AstraZeneca 1/14/2014 Email Response: AstraZeneca will provide further written clarification for FDA under separate cover.

Discussion During 1/14/2014 Meeting: There was no discussion of this item during the meeting.

FDA 1/15/2014 Post-Meeting Comments (provided as an Advice/Information Request Memorandum): Although AstraZeneca did not provide written clarification under separate cover, FDA Nonclinical Reviewer provided the following additional comments:

“Submission of draft 13-week study reports is acceptable to support initiation of a Phase 3 trial, provided that the data are audited and complete (i.e. in-life data such as clinical pathology, ECG, a signed histopathology report, bioanalysis/TK, etc., are available for all animals on-study, including recovery cohort animals).”

AstraZeneca 1/17/2014 Email Response to FDA Advice/Information Request Memorandum of 1/15/2014: By way of an email communication from Nicholas Troise on 1/17/2014, AstraZeneca concurs with FDA’s additional comments:

“For Q2, we have concurrence with FDA.”

Clinical

Refer to Background Information for Question 3 from pages 50-53 of AstraZeneca Briefing Document.

- 3. AstraZeneca is intending to select a biologically effective dose with a tolerable safety profile from the Phase I study for the Phase II and Phase III clinical studies. Does the FDA agree with the proposed approach for dose regimen selection for the Phase II and Phase III clinical studies?**

FDA 1/13/2014 Response: FDA does not object to the selection of an optimum biologic dose (OBD) lower than the maximum tolerated dose (MTD) as the recommended phase 2 dose (RP2D) as described in section 3.2.1 of the briefing package. Please provide more detail on the biologic criteria to be used to identify the OBD including the relationship to EGFR plasma ctDNA levels. The appropriate dose of AZD9291 to be included in the potential label, including any dose adjustments in clearly-defined specific populations (e.g. modifying dose in patients with brain metastasis) will be determined based on the data submitted at the time of review.

AstraZeneca 1/14/2014 Email Response: AstraZeneca has provided the following clarification of information:

The overall aim is to select a dose that maximizes clinical efficacy and minimizes wild-type EGFR associated AEs for patients. To select the OBD for the single arm registrations studies (anticipate n=30 patients for each T790M+ cohort for 40 mg to 160 mg) and the Phase 3 randomized study the following clinical data and analyses of clinical data will be used:

- 1) Dose vs. ORR, duration of response (DoR), depth of response and AEs
- 2) Exposure (AZD9291, AZ5104 and AZ7550) vs. ORR, DoR and depth of response and AEs.
- 3) Population PK response (ORR, DoR, depth of response and AEs) analysis

Additionally inter patient variability and population PK assessment of exposure by dose (including the variability in exposure due to potentially important covariates such as ethnicity) will be compared to the exposures (directly and through input of clinical PK parameters in to the preclinical PK-PD-efficacy model) that led to tumors responses (including in brain metastases model) and pathway biomarker knock down in preclinical species will inform dose choice.

At the time of dose selection for the single arm registration studies and the Phase 3 randomized study, clinical data on the impact of AZD9291 administration on biomarkers of target (EGFR) and pathway engagement will not be available. Currently, AstraZeneca plans, at the time of submission, are to provide data on target and pathway engagement using paired biopsies at OBD or MTD for pEGFR, pAKT, pERK and pS6K.

Additionally, ctDNA will be collected every 6 weeks from all patients in the Phase II and III clinical studies during the course of AZD9291 treatment. ctDNA will not be used to inform dose selection but will be analyzed retrospectively.

Discussion During 1/14/2014 Meeting: There was no discussion of this item during the meeting. FDA Clinical Pharmacology Reviewer agreed to provide a response to AstraZeneca's 1/14/2014 Email Response for Question 3.

FDA 1/15/2014 Post-Meeting Comment: FDA agrees that the proposed approach appears reasonable.

Refer to Background Information for Question 4 from pages 54-55 of AstraZeneca Briefing Document.

4. **AstraZeneca considers that there is high unmet medical need for patients with acquired resistance to EGFR TKI (Jackman et al 2010),** (b) (4)
(b) (4). **According to NCCN guidelines, single agent cytotoxic chemotherapy (e.g., docetaxel 60-75 mg/m² q 3-week or pemetrexed 500 mg/m² q 3-week) is the main systemic treatment option, but is associated with low response rate and duration of response and significant toxicity. Considering the high unmet medical need, the primary AZD9291 development plan is designed to support initial approval for the proposed indication as**

(b) (4)
(b) (4)

Does the Agency agree that an unmet medical need exists in this patient population and that the AZD9291 clinical development program could address it and support the proposed indication?

FDA 1/13/2014 Response: FDA agrees that there is an unmet need for patients with EGFR mutation positive NSCLC (b) (4) following appropriate EGFR TKI therapy. AstraZeneca's clinical development program summarized in the briefing package can potentially generate sufficient data for adequate benefit-risk evaluation of AZD9291 in the proposed patient population.

AstraZeneca 1/14/2014 Email Response: AstraZeneca acknowledged FDA’s response. No further discussion was required during the meeting.

Refer to Background Information for Question 5 from pages 55-56 of AstraZeneca Briefing Document.

5. **Given the unmet medical need that exists in the aforementioned patient population, AstraZeneca is proposing that registration is based on demonstrating compelling efficacy, based on frequency, depth and durability of response and appropriate tolerability in two separate single arm studies (in a well defined and molecularly characterized population of approximately 250 patients with acquired resistance to EGFR TKI, who have progressed on prior therapy and harbor a T790M+ resistance mutation, of whom a significant proportion have bulky or clinical relevant tumor burden), with an appropriate confirmatory trial well under way at time of initial approval (see related question on confirmatory study). Does the Agency agree?**

FDA 1/13/2014 Response: Yes, FDA agrees that demonstration of a favorable benefit-risk profile based on overall response (ORR) of clinically meaningful duration and magnitude in approximately 250 patients can potentially support approval under the provisions of 21 CFR 314 Subpart H in the proposed patient population.

AstraZeneca 1/14/2014 Email Response: AstraZeneca acknowledged FDA’s response. No further discussion was required during the meeting.

Refer to Background Information for Question 6 from pages 57-59 of AstraZeneca Briefing Document.

6. **AstraZeneca intend to demonstrate the benefit of AZD9291 in a** (b) (4)

Does the Agency agree?

FDA 1/13/2014 Response: FDA generally agrees that the proposed 350-patient dataset of approximately 100 second-line patients and 250 later-line patients generated from the single arm trials may be sufficient to support an indication under the provisions of 21 CFR 314 Subpart H for the treatment of patients (b) (4)

however, the precise indication will be determined in a benefit-risk evaluation at the time of review.

AstraZeneca 1/14/2014 Email Response: AstraZeneca acknowledged FDA's response. No further discussion was required during the meeting.

Refer to Background Information for Question 7 from pages 59-60 of AstraZeneca Briefing Document.

- AstraZeneca acknowledges that a Phase III study versus docetaxel in patients with acquired resistance to TKI, who have progressed on a prior platinum-contained doublet chemotherapy and a T790M+ resistance mutation could be regarded as an appropriate clinical study to confirm clinical benefit. However, due to the modest improvement in survival and toxicity profile associated with docetaxel as well as the need for the conduct of clinically meaningful trials with highly active and well tolerated agents in a selected patient population (T790M+), AstraZeneca is proposing to conduct a confirmatory randomized Phase III study versus platinum-contained doublet chemotherapy in chemo-naïve patients with acquired resistance to TKIs and a T790M+ resistance mutation. Does the Agency agree?**

FDA 1/13/2014 Response: FDA generally agrees with AstraZeneca's proposal to conduct the confirmatory randomized trial with AZD9291 versus standard platinum-based doublet chemotherapy in chemotherapy-naïve patients with acquired resistance to EGFR TKIs and T790M resistance mutations. However, for any randomized trial, the condition of equipoise must exist. Please see FDA response to Question 13.

AstraZeneca 1/14/2014 Email Response: AstraZeneca would like discussion of Question 7 and FDA response.

Discussion During 1/14/2014 Meeting: AstraZeneca stated that the proposed randomized study of AZD 9291 versus doublet chemotherapy would maintain equipoise, and the proposed control arm represents an acceptable standard of care in the U.S. FDA has no objections to the study provided that the conditions of equipoise are maintained. AstraZeneca will meet with FDA should standards of care change in the U.S.

Refer to Background Information for Question 8 from pages 60-61 of AstraZeneca Briefing Document.

8. **The primary endpoint of the confirmatory Phase III study will be PFS, assessed by RECIST and the secondary endpoint will be OS. The target hazard ratio for PFS is 0.67 (e.g., an improvement from 6 to 9 months). The study will also be powered to characterize effects on OS. AstraZeneca considers that this Phase III study is optimally designed to** (b) (4)

Does the FDA agree?

FDA 1/13/2014 Response: Yes, FDA agrees with PFS as the primary endpoint and OS as a key secondary endpoint in the proposed randomized trial. However, (b) (4) would require demonstration of a highly statistically significant and clinically important magnitude of PFS improvement with an acceptable benefit-risk profile and no decrement in OS. Whether a 3-month improvement in median PFS will be clinically meaningful will be determined at time of the review.

Revise the clinical protocol to conduct an interim OS analysis at the time of PFS analysis. Use O'Brien Fleming boundary for the interim analyses of OS.

FDA also notes that the study is overpowered for PFS. Hence, it may achieve statistical significance with marginal improvement in PFS that is not clinically meaningful.

AstraZeneca 1/14/2014 Email Response: AstraZeneca acknowledged FDA's response. No further discussion was required during the meeting.

Refer to Background Information for Question 9 from pages 61-62 of AstraZeneca Briefing Document.

9. **AstraZeneca considers that the proposed platinum-based doublet-chemotherapy for the comparator in the Phase III study (pemetrexed (500mg/m²) + carboplatin (AUC5 area under the plasma concentration–time curve (AUC) 5 mg ml⁻¹ per minute) or pemetrexed (500mg/m²) + cisplatin (75mg/m²)) is an acceptable standard of care for T790M+ advanced NSCLC patients with acquired resistance to TKIs (chemotherapy-naïve). Does the FDA agree?**

FDA 1/13/2014 Response: Yes, FDA agrees with the proposed standard dose and schedule of platinum-based doublet chemotherapy in the proposed confirmatory randomized clinical trial in chemotherapy-naïve metastatic non-squamous NSCLC patients with EGFR mutation positive tumors and acquired T790M resistance mutations.

AstraZeneca 1/14/2014 Email Response: AstraZeneca acknowledged FDA's response. No further discussion was required during the meeting.

Refer to Background Information for Question 10 from page 62 of AstraZeneca Briefing Document.

- 10. Given the preliminary level of activity observed in monotherapy study with AZD9291, AstraZeneca considers that a 2:1 open-label randomization is an appropriate study design for the Phase III trial. Does the FDA agree?**

FDA 1/13/2014 Response: Equal randomization ratio is the most statistically efficient design to maximize the power of a trial for a given sample size and double-blinding is preferred to minimize bias in randomized trials. However, FDA does not object to a 2:1 randomization ratio or an open-label design for the proposed confirmatory randomized phase 3 trial. (b) (4)

Please refer to
FDA response to Question 13.

AstraZeneca 1/14/2014 Email Response: AstraZeneca acknowledged FDA's response. No further discussion was required during the meeting.

Refer to Background Information for Question 11 from page 63 of AstraZeneca Briefing Document.

- 11. AstraZeneca propose that the primary analysis of PFS in the Phase III open-label study would be programmatically derived and based on investigator recorded assessments. To support this, a blinded independent central review (BICR) of radiological scans would be performed to confirm the robustness of the PFS endpoint. Does the FDA agree with this approach?**

FDA 1/13/2014 Response: Yes, FDA agrees with the primary analysis of PFS in the intention-to-treat (ITT) population based on investigator assessment. However, a pre-specified auditing procedure by independent reader to audit a subset should be designed, which should include the percentage of patients to be audited, the method used to identify the subset of images to be audited, the method for comparing the PFS results obtained by local review with the PFS results of the audit, and the criteria for determining whether all images need to be audited. All images should be archived and easily accessible. If bias cannot be excluded based upon the audit, then FDA will consider an independent evaluation of all radiographic images to be necessary for assessment of the primary PFS endpoint. Please also refer to the paper by Zhang et al, Clinical Cancer Research, (May 15, 2013).

AstraZeneca 1/14/2014 Email Response: AstraZeneca acknowledged FDA's response. No further discussion was required during the meeting.

Refer to Background Information for Question 12 from page 63 of AstraZeneca Briefing Document.

12. Does the FDA agree that the [REDACTED] (b) (4)

FDA 1/13/2014 Response: No, FDA recommends that the primary analysis of ORR be conducted by an IRC blinded to investigator assessment. AstraZeneca should perform concordance analyses of ORR, and response duration between investigator and BICR assessments.

AstraZeneca 1/14/2014 Email Response: AstraZeneca acknowledged FDA's response. No further discussion was required during the meeting.

Refer to Background Information for Question 13 from pages 64-65 of AstraZeneca Briefing Document.

13. AstraZeneca acknowledge, in the context of the high unmet medical need, the desire of patients and of investigators to enable patients access to promising investigational agents in development. This poses a challenge however to being able to fully characterize effects on overall survival. Can the Agency provide their perspective on the challenges and considerations associated with cross-over in randomized controlled registration trials involving highly active investigational agents?

FDA 1/13/2014 Response: Randomized trials should only be performed in the setting of clinical equipoise of the treatment arms. If clinical equipoise is lacking, then the proposed randomized trial should not be conducted. Although FDA does not object to cross-over in randomized trials, allowing cross-over for the primary purpose of addressing lack of equipoise would not be appropriate.

AstraZeneca 1/14/2014 Email Response: AstraZeneca acknowledged FDA's response. No further discussion was required during the meeting.

Refer to Background Information for Question 14 from pages 65-66 of AstraZeneca Briefing Document.

14. AstraZeneca is intending to collect data and analyze the tumor de-bulking response (i.e., responses in tumor of a size and/or location which are clinically meaningful to individual patients, and not isolated image-based evidence of anti-tumor activity e.g., nodule in the liver or lung) to further enable the characterization of clinical benefit of AZD9291. Can FDA provide advice on the relevance and definition of tumor de-bulking response?

FDA 1/13/2014 Response: FDA considers assessment of ORR based on RECIST 1.1 as the standard in metastatic NSCLC for evaluating anti-tumor response. FDA does not object to characterization of the clinical activity of AZD9291 based on “tumor de-bulking response” as an exploratory endpoint with definitions for “bulky disease” and “tumor de-bulking response” proposed by AstraZeneca. FDA is not aware of any validated or qualified methodologies for measuring responses in tumor of a size and/or location which are clinically meaningful to individual patients. FDA encourages engagement with other stakeholders to pursue the development of such methodologies as drug development tools through the CDER biomarker qualification program
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/default.htm> .

AstraZeneca 1/14/2014 Email Response: AstraZeneca acknowledged FDA’s response. No further discussion was required during the meeting.

Refer to Background Information for Question 15 from pages 67-69 of AstraZeneca Briefing Document.

15. **AstraZeneca is committed to improving a patient centric approach to Drug Development in our current and future trials, and implementing this alignment with regulatory guidance and good practice (e.g., FDA’s Benefit-Risk Assessment Framework PDUFA V commitments). Specific to the AZD9291 trials, this patient-centric approach will enable us to enhance our understanding of the overall patients’ perspective of the risk/benefit evaluation for AZD9291.**

In the ongoing Phase I study, AstraZeneca is collecting patient-reported outcome (PRO) data on symptoms and Health-related quality of life (HRQL). The PRO instruments that will be used to collect HRQL, symptoms and tolerability concerns in the AZD9291 registration program are the EORTC QLQ-C30, LC-13 questionnaires, and the PRO-CTCAE. These PRO’s will be complemented with in-depth qualitative patient interviews from the Phase I study in a number of countries. Patients included in these interviews will be patients who are/have participated in the ongoing Phase I study. It is believed that including these three PRO instruments within the trial designs combined with the results of the qualitative patient interviews, will provide data on overall quality of life, efficacy, and tolerability concerns patients might have whilst being treated with AZD9291 for their ^{(b) (4)} conditions.

AstraZeneca seeks to evaluate how important these concerns and/or improvements are, and how patients evaluate these effects in relation to overall treatment benefit. The intention of this approach is to add the patient perspective to support the risk/benefit evaluation of AZD9291 at this stage, and to inform the design of subsequent trials, with a view to implementing the PRO instruments as secondary endpoints in the Phase II single-arm and Phase III randomized trials. Ultimately

these data will contribute to the future assessment of cancer patients and the role of AZD9291 in the treatment paradigm “i.e., the physician and patient assessment”.

Does FDA agree that this approach, using PROs in combination with qualitative interviews, is an acceptable approach to support the overall risk/benefit evaluation for AZD9291?

FDA 1/13/2014 Response: FDA does not object to the collection of data on patient-reported outcomes (PROs) in combination with qualitative interviews as described in the briefing package. In general, PRO instruments can generate the most reliable data if used in double-blinded randomized trials. FDA encourages AstraZeneca to meet with FDA SEALD to discuss development or incorporation of validated PROs for metastatic NSCLC in the AZD9291 clinical development program. For further information, please refer to the Guidance for Industry “Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims” available at <http://www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf>.

In addition, in response to a polling question at an FDA Public Meeting on Lung Cancer Patient-Focused Drug Development (June 28, 2013), fatigue, shortness of breath, and chronic pain were mentioned as the most significant symptoms affecting patients’ daily lives. The final report is located at the following link: <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm368342.htm>. AstraZeneca could utilize this report to pursue an appropriate PRO for this patient population.

Finally, AstraZeneca should consider collaborating with the Critical Path Institute PRO Consortium Lung Cancer Working Group, which is currently conducting research for a new PRO symptom measure in NSCLC. Information is located at: <http://c-path.org/programs/pro/>.

AstraZeneca 1/14/2014 Email Response: AstraZeneca acknowledged FDA’s response. No further discussion was required during the meeting.

Diagnostic Development

Refer to Background Information for Question 16 from pages 69-73 of AstraZeneca Briefing Document.

16. **AstraZeneca is currently planning to identify T790M+ patients, using a tissue based diagnostic test in the clinical development program, with a view to development of a tissue-based companion diagnostic for pre-market approval. We are also exploring the possibility of** (b) (4)

AstraZeneca is planning to discuss the development of both diagnostic tests with CDRH.

Does FDA consider that utilization of a (b) (4)

FDA 1/13/2014 Response: Yes, FDA agrees tha (b) (4)
(b) (4). CDER encourages
AstraZeneca to further discuss the development plan of the proposed (b) (4) with
CDRH, including the requirements for analytic and clinical validation.

In order to receive marketing approval for the (b) (4)

(b) (4)

AstraZeneca 1/14/2014 Email Response: AstraZeneca acknowledged FDA's response.
No further discussion was required during the meeting.

Application of Molecular Monitoring to First-Line Disease

Refer to Background Information for Question 17 from pages 74-76 of AstraZeneca Briefing Document.

17. **Recent emergent evidence substantiates the hypothesis of a polyclonal and dynamic resistance to various treatment modalities in NSCLC patients with EGFR activating mutations. AstraZeneca believes that a prospective molecular characterization over time of EGFRm+ patients treated with erlotinib or gefitinib as first-line monotherapy might help inform the design of a first-line AZD9291 study in this patient population. Whilst not yet validated, noninvasive methods for monitoring the molecular mechanisms of response and resistance, such as quantitative mutational profiling of (b) (4) are likely to be informative. In particular, the relationship of the molecular profile over time with the image-based and clinical progression pattern is considered to be an essential step.**

AstraZeneca would therefore welcome a discussion with the Agency regarding the level of evidence that would be required to consider a (b) (4) molecular endpoint as a valid secondary endpoint in a prospective AZD9291 randomized controlled study, in order to support a shift in treatment paradigm similar to the registration of imatinib in chronic phase CML.

FDA 1/13/2014 Response: It appears that AstraZeneca is seeking advice on:

- 1) the use of molecular characterization to identify an enriched subset of patients likely to achieve greater benefit with AZD9291 as compared to erlotinib or gefitinib; and
- 2) the use of a novel endpoint for clinical benefit.

FDA encourages the exploration of enrichment studies designed to define the most appropriate patient population. For example, AstraZeneca could explore the possibility of a first-line study of EGFRm mNSCLC patients (deletion 19 or L858R) where all patients initially receive an approved EGFR TKI and then are randomized to continue approved EGFR TKI versus AZD9291 at the time of rise in T790M+ (b) (4) above a specific (pre-specified) threshold.

FDA recommends AstraZeneca submit a detailed proposal for establishing the use of a (b) (4) molecular endpoint as clinical benefit. Please also see FDA response to Question 14 regarding CDER's biomarker qualification program.

AstraZeneca 1/14/2014 Email Response: AstraZeneca would like discussion of Question 17 and FDA response.

Discussion During 1/14/2014 Meeting: AstraZeneca stated their strong interest in exploring an enrichment strategy to identify patients with metastatic NSCLC containing EGFR mutations who:

- a) may identify a poor prognostic population based on (b) (4) (s) for response to standard EGFR TKI therapy and;
- b) can potentially achieve greater benefit with AZD9291 as compared to treatment with standard EGFR TKI therapy.

Furthermore, AstraZeneca stated their intention to investigate (b) (4) reduction as a surrogate endpoint for clinical benefit. FDA stated that both approaches (enrichment and surrogacy) could be considered in the design of clinical trials with AZD9291. However, the amount of data required to establish (b) (4) level(s) as a validated and clinically meaningful surrogate endpoint will have to be much more comprehensive compared to the amount of data required to support an enrichment strategy based on (b) (4) level(s). FDA emphasized that early involvement by CDRH will be necessary in both cases. FDA also recommended that AstraZeneca consider submitting these drug development tool strategies to the CDER biomarker qualification team for review.

Additional Comments sent on 1/13/2014

Clinical Pharmacology:

During the development of AZD9291, address the following:

18. Assess the effect of body size (such as body weight and body surface area) on the pharmacokinetics and pharmacodynamics of AZD9291 to determine the optimal dosing approach (body size-based or fixed dosing) that minimizes inter-patient variability for the registration trials.

AstraZeneca 1/14/2014 Email Response: AstraZeneca acknowledged FDA’s comment. No further discussion was required during the meeting.

19. Conduct population pharmacokinetic analyses to evaluate the effect of intrinsic and extrinsic factors on the pharmacokinetics of AZD9291 and its active metabolites (AZ5104 and AZ7550) in humans. Refer to the FDA Guidance for Industry entitled “*Population Pharmacokinetics*” found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf>.

AstraZeneca 1/14/2014 Email Response: AstraZeneca acknowledged FDA’s comment. No further discussion was required during the meeting.

20. Explore the exposure-response relationships for AZD9291 and its active metabolites (AZ5104 and AZ7550) for measures of effectiveness, toxicity and pharmacodynamic biomarkers. Refer to the FDA Guidance for Industry entitled “*Exposure-Response Relationships – Study Design, Data Analysis, and Regulatory Applications*” found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf>.

AstraZeneca 1/14/2014 Email Response: AstraZeneca acknowledged FDA’s comment. No further discussion was required during the meeting.

21. Submit the proposed QT evaluation plan to the FDA for QT-IRT review.

AstraZeneca 1/14/2014 Email Response: AstraZeneca acknowledged FDA’s comment. No further discussion was required during the meeting.

22. Submit the results of the relative bioavailability and food effect study (D5160C00005) when available for FDA review. In general, the dedicated food effect study should be conducted with the (b) (4) Evaluate adequately the effect of food on the bioavailability of AZD9291 to guide dosing recommendations with regard to food intake in the clinical efficacy and safety trials. Conduct a food effect trial per the FDA Guidance for Industry entitled “*Food-Effect Bioavailability and Fed Bioequivalence Studies*” found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070241.pdf>.

AstraZeneca 1/14/2014 Email Response: AstraZeneca acknowledged FDA’s comment. No further discussion was required during the meeting.

23. Conduct the study to assess the effect of pH-elevating agents on the absorption of AZD9291 in a gated manner, first assessing the effect of a proton pump inhibitor (PPI) on the exposure of AZD9291. In the event that concomitant administration of a PPI has a large impact on the drug exposure, an H₂ antagonist and an antacid should be subsequently evaluated.

AstraZeneca 1/14/2014 Email Response: AstraZeneca acknowledged FDA's comment. No further discussion was required during the meeting.

24. Submit the in vitro study report that determined AZD9291 is a P-gp substrate and also a BCRP substrate to help decide if further in vivo drug-drug interaction studies are needed.

AstraZeneca 1/14/2014 Email Response: AstraZeneca acknowledged FDA's comment. No further discussion was required during the meeting.

25. Determine whether AZD9291 is a substrate of OAT1/3 and OCT2 in vitro if renal active secretion is $\geq 25\%$ of total clearance of AZD9291.

AstraZeneca 1/14/2014 Email Response: AstraZeneca acknowledged FDA's comment. No further discussion was required during the meeting.

26. Evaluate the potential for AZD9291 to inhibit OAT1/OAT3 and OCT2 in vitro.

AstraZeneca 1/14/2014 Email Response: AstraZeneca acknowledged FDA's comment. No further discussion was required during the meeting.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

ATTACHMENTS AND HANDOUTS

- Meeting Attendance List
- AstraZeneca's 1/14/2014 Slide Presentation for the Meeting

MEETING ATTENDANCE LIST

Meeting between AstraZeneca (IND 117879) and
the Center for Drug Evaluation and Research.

DATE: January 14 , 2014 TIME: 2:00-3:00 PM (ET) ROOM: Bldg 22/Room1313

NAME - Please print	AFFILIATION
Norma Griffin	FDA / OHOP / DOP2
Ruth MADURO	FDA / OHOP / DOP2
WENDY WHITE	AZ
PARREN CROSS	AZ
SERBAN GHIOGHIU	AZ
PAUL DICKINSON	AZ
ANTOINE YVER	AZ
(b) (4)	
SUSAN GALICIAN	AZ
(b) (4)	
SUZANNE JENKINS	AZ
NICOLA SCHMITZ	AZ
Candy Larcajien	AstraZeneca
Kenneth Thress	AZ
Heham Abdullah	AZ
SOMESH CHATTOPADHYAY	FDA
Gidan Blumenthal	"
Sean Khazin	"
Hong Zhao	OTS/OCP/DCPV
Barb Scopura	DOP2
KEENA PHILIP	FDA / CDRH
Timothy Schaefer	FDA / CDRH
SHENGHUI TANG	FDA
Shauna Wells	FDA
Whitney Helms	FDA
PATRICIA KEEGAN	FDA / ODEA / OND / OHOP / DOP2

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/s/

NORMA S GRIFFIN
02/06/2014

LATE-CYCLE COMMUNICATION
DOCUMENTS



NDA 208065

LATE-CYCLE MEETING MINUTES

AstraZeneca Pharmaceuticals LP
Attention: Jonathan Jazayeri, Pharm.D., M.S., R.A.C.
Regulatory Affairs Director, Oncology
One MedImmune Way
Gaithersburg, MD 20878

Dear Dr. Jazayeri:

Please refer to your New Drug Application (NDA) dated June 5, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for TAGRISSO (Osimertinib), 40 mg and 80 mg tablets.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on October 13, 2015.

A copy of the official minutes of the LCM is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Ingrid Fan, Regulatory Project Manager, at (301) 796-5053.

Sincerely,

{See appended electronic signature page}

Gideon Blumenthal, M.D.
Cross-Discipline Team Leader
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: Tuesday, October 13, 2015, 11:00AM – 12:00PM
Meeting Location: Teleconference

Application Number: NDA 208065
Product Name: TAGRISSO
Applicant Name: AstraZeneca Pharmaceuticals LP

Meeting Chair: Gideon Blumenthal
Meeting Recorder: Ingrid Fan

FDA ATTENDEES

Patricia Keegan,	Division Director
Gideon Blumenthal,	Medical Officer (TL and CDTL)
Chana Weinstock,	Medical Officer (Safety)
Ingrid Fan,	Regulatory Project Manager
Joyce Cheng,	Statistics
Shawna Weis	Non-clinical Reviewer
Whitney Helms,	Non-Clinical Supervisor
Jun Yang,	Clinical Pharmacology Reviewer
Hong Zhao,	Clinical Pharmacology Team Leader
Rosane Charlab Orbach,	Genomics (TL)
William Adams,	CMC ONDP
Olen Stephens	CMC Team Leader
Shaily Arora	OSE Reviewer
Karen Bijwaard	CDRH Representative
Carolyn L. Yancey	OSE/DRISK Reviewer
Carolyn McCloskey	OSE/DEPI Reviewer

EASTERN RESEARCH GROUP ATTENDEES

Christopher Sese, Independent Assessor

APPLICANT ATTENDEES

Jonathan Jazayeri,	Regulatory Affairs Director
Eric Richards,	Regulatory Affairs Senior Director
Hesham Abdullah,	Regulatory Affairs VP - Oncology
Marilyn Tsourounis,	Regulatory Affairs - Labeling
Silke Klick,	Regulatory Affairs - CMC
Simon Collett,	Pharmaceutical Development Lead
Dawn Sievwright,	Pharmaceutical Development Project Manager

Maria Eriksson,	New Product Director
Mireille Cantarini,	Clinical Development
Serban Ghiorghiu,	Clinical Development Lead
Klaus Edvardsen,	Clinical Development VP - Oncology
Paul Howarth,	Patient Safety Physician
Andrew Walding,	Patient Safety Scientist
Jim Kotsanos,	Patient Safety Head - Oncology
Karthick Vishwanathan,	Clinical Pharmacology - Oncology
Kathryn Brown,	Clinical Pharmacometrics
Helen Mann,	Biometrics & Informatics Lead
Renee Iacona,	Biometrics & Informatics Head - Oncology
Mei Dey,	Programming Lead
Suzanne Jenkins,	Personalized Healthcare and Biomarkers
Antoine Yver,	Global Head – Oncology

BACKGROUND

NDA 208065 was submitted on June 5, 2015 for TAGRISSO (Osimertinib).

Proposed indication: [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 TKI therapy.

PDUFA goal date: 02/05/2016

FDA issued a Background Package in preparation for this meeting on October 7, 2015.

DISCUSSION

1. Information Requests

Discussion:

FDA noted that CMC-specific information requests will be sent to AstraZeneca and will request a quick response. AstraZeneca agreed that they will send their response as requested.

2. Postmarketing Requirements/Postmarketing Commitments

Discussion:

FDA noted that AstraZeneca proposed the same date for both Study/Trial Completion date and Final Report Submission date for one PMR study. AstraZeneca clarified that the date of

final sign off of the clinical study report is their proposed Study/Trial Completion date. FDA stated that AstraZeneca should use a standard definition of the Study/Trial Completion date for the PMRs. AstraZeneca stated that they will re-think this definition and propose an alternate definition and corresponding Study/Trial Completion date for the PMRs to FDA.

(b) (4)

3. Major Labeling Issues

Discussion:

FDA noted that the TAGRISSO label with FDA proposed edits will be sent to AZ this week.

FDA noted that the labeling discussion should focus on the US patient population not a population of patients from a single ex-US country.

4. Review Plans:

Discussion:

FDA stated that the target action date is Nov. 16th.

FDA also noted that at this time there is no PMR/C planned regarding the male fertility findings. FDA comments regarding further investigation of sperm motility in the ongoing dog toxicity study may be sent to the IND. Current thinking on the duration of male contraception will be included in the initial FDA labeling recommendations.

5. Wrap-up and Action Items

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

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/s/

GIDEON M BLUMENTHAL
10/14/2015



NDA 208065

**LATE CYCLE MEETING
BACKGROUND PACKAGE**

AstraZeneca Pharmaceuticals LP
Attention: Jonathan Jazayeri, Pharm.D., M.S., R.A.C.
Regulatory Affairs Director, Oncology
One MedImmune Way
Gaithersburg, MD 20878

Dear Dr. Jazayeri:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TAGRISSO (Osimertinib), 40 mg and 80 mg tablets.

We also refer to the Late-Cycle Meeting (LCM) scheduled for October 13, 2015. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Ingrid Fan, Regulatory Project Manager, at (301) 796-5053.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: Tuesday, October 13, 2015, 11:00AM – 12:00PM
Meeting Location: WO Building 22, Room 1311

Application Number: NDA 208065
Product Name: TAGRISSO
Proposed Indication: (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.

Applicant Name: AstraZeneca Pharmaceuticals LP

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

No Discipline Review letters have been issued to date.

2. Substantive Review Issues

No substantive review issues have been identified to date.

3. Advisory Committee Meeting

An Advisory Committee meeting is not planned.

4. REMS or Other Risk Management Actions

REMS will not be required; please see proposed post-marketing requirements and commitments identified below.

LCM AGENDA

1. Introductory Comments – 5 minutes (RPM/CDTL)

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Information Requests – 5 minutes

CMC: Pending information request sent September 29, 2015, regarding content uniformity testing and tablet weight checks

3. Postmarketing Requirements/Postmarketing Commitments – 10 minutes

- a. (b) (4) to Assess the Effect of (b) (4) (a CYP3A4 Inhibitor) on the Pharmacokinetics of a (b) (4) of AZD9291 (b) (4)

Final Protocol Submission: Submitted

Study/Trial Completion: September 2015

Final Report: April 2016

- b. (b) (4) to Assess the Effect of (b) (4) (a CYP3A4 Inducer) on the Pharmacokinetics of AZD9291 (b) (4)

Final Protocol Submission: Submitted

Study/Trial Completion: November 2015

Final Report : April 2016

- c. (b) (4) to Assess the Effect of AZD9291 on the Pharmacokinetics of (b) (4) CYP3A4 (b) (4)

Substrate) [REDACTED] (b) (4)

Final Protocol Submission: Submitted
Study/Trial Completion: November 2015
Final Report: April 2016

d. [REDACTED] (b) (4) to Assess the Effect
of AZD9291 on the Pharmacokinetics of [REDACTED] (b) (4) BCRP
Substrate) [REDACTED] (b) (4)

Final Protocol Submission: Submitted
Study/Trial Completion: December 2015
Final Report: April 2016

e. Phase III, Open Label, Randomized Study of AZD9291 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 and [REDACTED] (b) (4)

Final Protocol Submission: Submitted
Study/Trial Completion: December 2016
Final Report: June 2017

f. [REDACTED] (b) (4)

Final Protocol Submission: Submitted
Study/Trial Completion: November 2018
Final Report: November 2018

4. Major labeling issues – 30 minutes
5. Review Plans – 5 minutes
6. Wrap-up and Action Items – 5 minutes

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/s/

PATRICIA KEEGAN
10/07/2015