

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022433Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 022433

SUPPL #

HFD # 110

Trade Name Brilinta

Generic Name ticagrelor

Applicant Name AstraZeneca

Approval Date, If Known July 20, 2011

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

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:

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: Michael Monteleone
Title: Regulatory Health Project Manager
Date: July 18, 2011

Name of Office/Division Director signing form: Norman Stockbridge, MD, PhD
Title: Director, Division of Cardiovascular and Renal Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

MICHAEL V MONTELEONE
07/20/2011

NORMAN L STOCKBRIDGE
07/20/2011

**DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS
FOOD AND DRUG ADMINISTRATION**

WHITE OAK COMPLEX
10903 NEW HAMPSHIRE AVE
BLDG. 22
SILVER SPRING, MD 20993



US Mail address:

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

This document is intended only for the use of the party to whom it is addressed and may contain information that is privileged, confidential, and protected from disclosure under applicable law. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to:
FDA/CDER/DCaRP 5901-B Ammendale Rd. Beltsville, MD 20705-1266

Transmitted via Email: Emery.Gigger@astrazeneca.com

Attention: Emery Gigger

Company Name: AstraZeneca

Phone: 1.302.885.4048

Subject: Meeting Minutes

Date: May 19, 2011

Pages including this sheet: 5

From: Mike Monteleone

Phone: 301.796.1952

Fax: 301.796.9841

Meeting Minutes

Application: NDA 022433
Sponsor: AstraZeneca
Drug: Brilinta (ticagrelor)
Type of Meeting: Advice

Date of Meeting: April 20, 2011

List of FDA Meeting Participants:

** Office of Drug Evaluation I*

Robert Temple, MD	Director
Ellis Unger, MD	Deputy Director

** Division of Cardiovascular and Renal Products*

Norman Stockbridge, MD, PhD	Director
Stephen M. Grant, MD	Deputy Director
Mary Ross Southworth, PharmD	Deputy Director for Safety
Thomas Marciniak, MD	Clinical Team Leader
Melanie Blank, MD	Clinical Reviewer
Martin Rose, MD	Clinical Reviewer
Thomas Papoian, PhD	Pharmacology Team Leader
Elizabeth Hausner, DVM	Pharmacologist
Michael Monteleone, MS	Regulatory Project Manager

**Office of Biostatistics, Division of Biometrics I*

Jim Hung, PhD	Director
Jialu Zhang, PhD	Biostatistician

**Office of Clinical Pharmacology, Division of Clinical Pharmacology I*

Sudharshan Hariharan, PhD	Clinical Pharmacologist
Islam Younis, PhD	Clinical Pharmacologist

**Office of Surveillance and Epidemiology, Division of Risk Management*

Cynthia LaCivita, PharmD	Drug Risk Management Analyst
--------------------------	------------------------------

List of Sponsor Meeting Participants:

Kevin J. Carroll, MSc	Vice President Statistics, Chief Statistician
Simon Clowes, BSc (Hons)	Global Product Vice President
Jonathan C. Fox, MD, PhD	Vice President, Clinical Therapeutic Area, Cardiovascular and Gastrointestinal Diseases
Alex Gold, MD	Executive Director, Clinical Development
Peter Honig, MD	Vice President, Global Regulatory Affairs
Barry Sickels	Vice President, AZ Regulatory Affairs
Mary Whealy	Global Regulatory Affairs Director
Sven Nylander, PhD	Discovery Project Leader
Hans van Giezen, PhD	Innovative Medicines Project Director

Background:

The sponsor submitted an original NDA for Brilinta (ticagrelor) for treatment of ACS on November 16, 2009. The application was designated for standard review with a PDUFA goal date of September 16, 2010, which later was adjusted to December 16, 2010 because of submission of a major amendment. An Advisory Committee meeting was held on July 28, 2010. The Agency issued a Complete Response letter on December 16, 2010. The sponsor resubmitted their NDA on January 20, 2011 and the Agency acknowledged, in a letter dated February 3, 2011, that it was a complete, Class 2 resubmission with a July 20, 2011 PDUFA goal date. The sponsor requested a meeting with the Agency at the review cycle mid-point to discuss the progress of the review. That meeting took place on April 20, 2011. The minutes of that meeting follow.

Minutes:

After introductions, Dr. Temple opened the meeting by advising the applicant that primary reviews are not complete and so the Agency's review is still ongoing. Dr. Temple said that until a decision is made about the importance of the apparent interaction between dose of aspirin and ticagrelor, drafting labeling is problematic, though it should proceed quickly once a decision is reached.

The applicant's proposed REMS was briefly discussed. Dr. LaCivita commented that the proposed REMS was generally in line with Agency expectations. However, it is likely that some changes will be necessary with the changes being dependent on the completed label. She thought these changes would be relatively easy to implement. Dr. LaCivita advised that she may have specific comments for the sponsor once she completes her interim review.

Dr. Temple commented on the applicant's response to the Agency's Complete Response letter, stating that though the Agency's review is still ongoing, the finding of an interaction between dose of aspirin and ticagrelor appears robust to multiple methods of imputing aspirin dose and analyses of the interaction. Dr. Temple cautioned that he was mindful of the Advisory Committee's conclusion that the aspirin interaction was a chance finding. Dr. Temple stated that no one has been persuaded that a biologically plausible mechanism for an interaction between aspirin dose and ticagrelor has been identified.

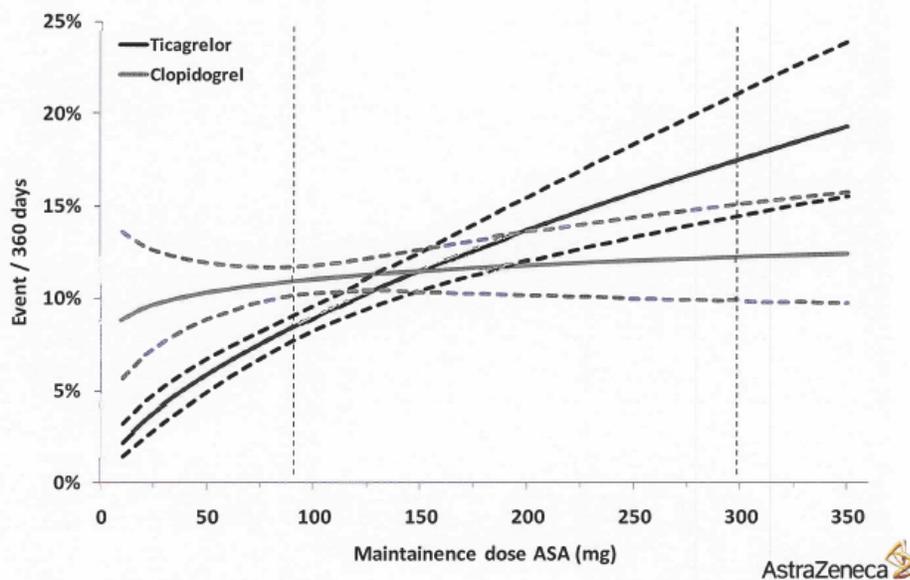
The biologic plausibility of the aspirin hypothesis was briefly discussed. Dr. Hausner advised that she had everything she needed from the applicant to complete her review. Dr. Papoian noted that the *in vitro* platelet data showed that although aspirin enhanced the anti-platelet effect when P2Y12 inhibition was partial, no additional platelet inhibition was observed when aspirin was increased from 30 uM to 120 uM, indicating that even concentrations of aspirin (30 uM) equivalent to exposure following a low dose (75 mg) in humans were already producing a maximal effect. Therefore, the sponsor's hypothesis that aspirin enhanced clopidogrel's partial P2Y12 blockade, but not ticagrelor's complete blockade, was not supported, at least by the *in vitro* data. The applicant appeared to agree with that interpretation.

The applicant mentioned the recent publication of a focused ACC/AHA Guideline that advises use of a low maintenance dose of aspirin (75-162 mg) for primary prevention. Dr. Blank asked the applicant to submit the reference and any other relevant information.

There was some discussion regarding an applicant handout, Figure 1, below. Dr. Temple commented that the graph showed that high dose aspirin has no effect on clopidogrel. The Division inquired why the confidence interval around the point estimate for event rates in subjects on ticagrelor at varying doses of aspirin does not splay out at lower doses of aspirin, as the one for clopidogrel does. The applicant commented that the splaying is a result of smaller numbers of patients on the different extremes of aspirin dose and resultant larger confidence intervals. The applicant commented that if ticagrelor were carried back to a zero dose of aspirin it would also splay. Dr. Papoian made the comment that the applicant's figure indicated that the lowest event rates were observed in ticagrelor subjects not administered any aspirin.

FIGURE 1

Event rates differ at lower ASA doses; at higher doses event rate CIs overlap.



There was some discussion regarding the applicant's internal procedures for handling of adverse event reporting. Dr. Marciniak asked why the applicant had not expedited the reporting of serious and unexpected adverse events in two PLATO subjects, one an out-of-hospital arrest with seizure in a patient with subsequent in-hospital AV block and the other a subject hospitalized with headache and an unspecified abnormality on cerebral scans. For both patients the investigator discontinued study drug because of the serious adverse event (SAE). The applicant replied that the investigator had indicated that the SAEs were unrelated to study drug and that it was company policy to accept investigator determination of relatedness. Dr. Marciniak noted that under FDA's new reporting rule it is the applicant's responsibility to determine relatedness of serious unexpected adverse events, although that was not clear at the time of reporting. Dr. Rose raised a question regarding a recent initial reporting of an AV block SAE. He asked why the name and address of the reporter were marked as private. The applicant commented that under German law they are limited in the information they can gather. Dr. Marciniak asked why the listing of prior AV block AEs included with the SAE report for this patient (see Figure 2) listed no prior AV block adverse events (AEs). The applicant responded that the listing only included AEs submitted post-marketing.

FIGURE 2

AstraZeneca Pharmaceuticals
A Business Unit of AstraZeneca LP,
1800 Concord Pike, P.O. Box 15437,
Wilmington, DE 19850-5437

Mfr. Rep. #: 2011SE19562

Date: 14-APR-2011

LISTING OF PRIOR SAFETY REPORTS
SUBMITTED TO IND # 65,808

ADVERSE EVENT: Atrioventricular block
(all preferred and included coded terms)

Manufacturer Report # FDA Submission Date Protocol Number
No safety reports have been previously submitted to the IND for this adverse event.

Country of Origin

Signature, Meeting Chair: *{See appended electronic signature page}*
Robert Temple, MD

Reviewed:

MMonteleone	21 APR 11 (Drafted)
CLaCivita	21 APR 11
TMarciniak	28 APR 11
MBlank	28 APR 11
MRose	28 APR 11
EHausner	28 APR 11
TPapoian	28 APR 11
JZhang	29 APR 11
SGrant	09 MAY 11
NStockbridge	09 MAY 11
EUnger	11 MAY 11
RTemple	16 MAY 11

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

/s/

ROBERT TEMPLE
05/19/2011



NDA 022433

INFORMATION REQUEST

AstraZeneca LP
Attention: Emery Gigger
Regulatory Affairs Director
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803

Dear Mr. Gigger:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Brilinta, (ticagrelor) 90 mg tablets.

We are reviewing the carton and container labeling 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.

A. General Comments (All labels and Labeling)

1. We note the proprietary name is presented in all-caps. Consider revising the proprietary name to appear in title case (i.e., Brilinta). Words set in upper and lower case form recognizable shapes, making them easier to read than the rectangular shape that is formed by words set in all-caps.
2. Ensure the presentation of the established name is at least half the size of the proprietary name in accordance to 21 CFR 201.10(g)(2), which requires that the established name shall be printed in letters that are at least half as large and a prominence commensurate with the proprietary name, taking into consideration all pertinent factors, including typography, layout, contrast and other printing features.

B. Container Labels-180 count

1. We note that although the 180 count bottle may be a unit-of-use container, it may also be used for more than one patient. Ensure a sufficient number of medication guides are provided.
2. Minimize the size of the company name and logo.

C. Container Labels-60 count

1. See comment B.1. and B.2. above.

2. The principal display panel is crowded. To minimize overcrowding condense the manufacturer's address statement.

D. Professional Samples-8 count

The principal display panel of the container label is crowded. To minimize overcrowding, relocate the statement, "Each tablet contains 90 mg ticagrelor" to the top of the left side panel. In order to accommodate this, minimize or remove the statement "Brilinta is a trademark...AstraZeneca 2010".

If you have any questions, please call Michael Monteleone, Regulatory Project Manager, at (301) 796.1952.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, MD, PhD
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

NORMAN L STOCKBRIDGE
05/13/2011



NDA 022433

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

AstraZeneca LP
1800 Concord Pike
P.O. BOX 8355
Wilmington, DE 19803-8355

ATTENTION: Emery Gigger
Director, Regulatory Affairs

Dear Mr. Gigger:

Please refer to your New Drug Application (NDA) dated November 13, 2009, received November 16, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ticagrelor Tablets, 90 mg.

We also refer to your January 24, 2011, correspondence, received January 24, 2011, requesting review of your proposed proprietary name, Brilinta. We have completed our review of the proposed proprietary name, Brilinta, and have concluded that it is acceptable.

The proposed proprietary name, Brilinta, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your January 24, 2011 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nina Ton, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at 301-796-1648. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Michael Monteleone at 301-796-1952.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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

/s/

CAROL A HOLQUIST
04/15/2011

**DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS
FOOD AND DRUG ADMINISTRATION**

WHITE OAK COMPLEX
10903 NEW HAMPSHIRE AVE
BLDG. 22
SILVER SPRING, MD 20993



US Mail address:

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

This document is intended only for the use of the party to whom it is addressed and may contain information that is privileged, confidential, and protected from disclosure under applicable law. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to:

FDA/CDER/DCaRP 5901-B Ammendale Rd. Beltsville, MD 20705-1266

Transmitted via Email: Emery.Gigger@astrazeneca.com

Attention: Emery Gigger

Company Name: AstraZeneca

Phone: 1.302.885.4048

Subject: Meeting Minutes

Date: February 16, 2011

Pages including this sheet: 4

From: Mike Monteleone
Phone: 301.796.1952
Fax: 301.796.9841

Meeting Minutes

Application: NDA 022433
Sponsor: AstraZeneca
Drug: Brilinta (ticagrelor)
Type of Meeting: Advice

Date of Meeting: February 4, 2011

List of FDA Meeting Participants:

** Office of Drug Evaluation I*

Robert Temple, MD	Director
Ellis Unger, MD	Deputy Director

** Division of Cardiovascular and Renal Products*

Norman Stockbridge, MD, PhD	Director
Stephen M. Grant, MD	Deputy Director
Mary Ross Southworth, PharmD	Deputy Director for Safety
Tom Marciniak, MD	Clinical Team Leader
Melanie Blank, MD	Clinical Reviewer
Elizabeth Hausner, DVM	Pharmacologist
Ed Fromm, RPh, RAC	Chief Project Manager
Michael Monteleone, MS	Regulatory Project Manager

**Office of Biostatistics, Division of Biometrics I*

Jim Hung, PhD	Director
Jialu Zhang, PhD	Biostatistcian
John Lawrence, PhD	Biostatistcian

**Office of Surveillance and Epidemiology, Division of Risk Management*

LCDR Latonia Ford	Patient Labeling Reviewer
Cynthia LaCivita	REMS Reviewer

List of Sponsor Meeting Participants:

Peter Honig, MD	Vice President, Global Regulatory Affairs
Jonathan C. Fox, MD	Vice President, Clinical Therapeutic Area, Cardiovascular and Gastrointestinal Diseases
Kevin J. Carroll, MSc	Vice President Statistics, Chief Statistician
Simon Clowes, BSc (Hons)	Global Product Vice President
Alex Gold, MD	Executive Director, Clinical Development

Background:

The applicant submitted an original NDA to market Brilinta (ticagrelor) for treatment of ACS on 16 November 2009. An Advisory Committee (AC) meeting was held to discuss aspects of the application on 28 July 2010. The Agency issued a Complete Response letter to the applicant on 16 December 2010. The applicant resubmitted their NDA on 20 January 2011. In a letter dated 03 February 2011, the Agency acknowledged the resubmission was a complete, Class 2 resubmission with a 20 July 2011 PDUFA goal date. In response to a request from the applicant, a meeting was held to discuss their resubmission on 04 February 2011.

Minutes:

The applicant began the meeting by thanking the Agency for its time and confirming receipt of the Agency's Acknowledgment letter the day before. The sponsor also indicated that they realized that the decision on their

NDA would be difficult and expressed a desire to work with the Agency to conduct an efficient and expeditious review.

The applicant presented a number of slides giving an overview of their Resubmission [see attached]. They commented that they believe the submitted analyses confirm their conclusion in the original submission that the regional interaction observed in North America is explained by an interaction of ticagrelor with aspirin (ASA).

There was some discussion around slide 7, describing a particular PLATO subject's ASA records; Dr. Marciniak commented that patients without aspirin records probably did not receive aspirin and should be assigned a dose of zero. The applicant responded that they analyzed all patients using a number of possible imputation methods as requested in the Agency's Complete Response letter, including assigning zero dose for patients without ASA records.

There was some discussion around how and when aspirin dosage was recorded.

There was also discussion exploring stenting and other factors that may have influenced the ASA dose that subjects received (so that such a factor might explain the outcome effect being attributed to aspirin). The applicant said that they had looked at numerous factors and were not able to find one that influenced ASA dosage. Dr. Marciniak commented that he thought there were factors that influenced ASA dosage and he is also looking at what other factors correlate with outcomes. He noted that for all cause mortality there are interactions between ticagrelor use and CYP3A4 statin use and stenting and none with ASA dosage. He agreed to provide his analyses to the applicant.

Dr. Temple asked the applicant to comment on slide 16 of their presentation because this was the one analysis that did not show a strong aspirin dose interaction. The sponsor commented that this analysis includes the first day ASA dose.

Dr. Temple noted that most of the AC members believed that the discrepancy in US/OUS outcomes was a chance finding. The applicant responded that chance can never be eliminated as a possibility but given the current evidence, ASA seems to be the most likely explanation. There was discussion of the fact that ASA dose is a post-randomization characteristic and that it could be a consequence of some subject characteristics that themselves correlated with outcomes. If that were the case it could be the characteristic, not ASA, creating the disparate results. For this to be so, however, it was pointed out, the characteristic that led to high aspirin dose would need to have its effect only on the ticagrelor patients.

Dr. Grant asked the applicant to comment on whether they had additional data that would provide a biologic explanation for the ASA interaction. The applicant responded that they are not much further along in their understanding of the interaction than they were at the AC. There is no direct evidence of a harmful effect on the endothelium from the interaction between high dose aspirin and ticagrelor but they have done some animal work that they have submitted to the NDA that they want us to consider. The applicant commented that given the dearth of data showing any benefit of high dose over low dose ASA they did not see a need to define a population that may require high dose ASA in conjunction with ticagrelor.

The sponsor asked if an additional clinical trial will be required before approval. Dr. Temple commented that although the AC and the applicant's advisor wanted another confirmatory clinical trial, perhaps after approval, the Agency has not determined whether an additional trial is necessary. Dr. Temple reiterated that, as described in the Agency's Complete Response letter, before an Approval decision can be contemplated the Agency must have a thorough understanding of the ASA interaction in the trial. Dr. Temple also advised that there are still a number of analyses underway and that the Division would provide feedback on those following the meeting.

Signature, Meeting Chair: *{See appended electronic signature page}*
Robert Temple, MD

Reviewed:

MMonteleone	07 FEB 11 (drafted)
EFromm	07 FEB 11
JZhang	09 FEB 11
JHung	09 FEB 11
MBlank	09 FEB 11
TMarciniak	10 FEB 11
SGrant	10 FEB 11
NStockbridge	11 FEB 11
RTemple	15 FEB 11
MMonteleone	16 FEB 11 (finalized)

Attachment:

Applicant's Slides

45 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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

/s/

ROBERT TEMPLE
02/16/2011



NDA 022433

**ACKNOWLEDGE –
CLASS 2 RESPONSE**

AstraZeneca LP
Attention: Emery Gigger
Regulatory Affairs Director
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803

Dear Mr. Gigger:

We acknowledge receipt on January 20, 2011, of your January 20, 2011, resubmission of your new drug application submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Brilinta (ticagrelor) 90 mg tablets.

We acknowledge your request that this resubmission be considered a class 1 resubmission, but because of the critical and extensive nature of the submitted analysis, as well as your submission of a proposed REMS containing a communication plan we consider this a complete, class 2 resubmission to our December 16, 2010, action letter. Therefore, the user fee goal date is July 20, 2011.

If you have any questions, call Michael Monteleone, Regulatory Project Manager, at (301) 796-1952.

Sincerely,

{See appended electronic signature page}

Edward Fromm, RPh, RAC
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

EDWARD J FROMM
02/03/2011

Monteleone, Michael V.

Subject: RE: Call from AZ

From: Jenkins, John K
Sent: Tuesday, December 14, 2010 3:32 PM
To: Temple, Robert; Stockbridge, Norman L; Unger, Ellis; Woodcock, Janet
Cc: Kweder, Sandra L; Jenkins, John K
Subject: Call from AZ

Bob and others

I [REDACTED] (b) (5)

[REDACTED]

[REDACTED]

John

John K. Jenkins, M.D.
Director, Office of New Drugs
10903 New Hampshire Avenue
Bldg #22, Room 6304
Silver Spring, MD 20993
301-796-0700
301-796-9856 (fax)
NOTE, New E-mail Address: john.jenkins@fda.hhs.gov

Reference ID: 2877809

12/14/2010

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

/s/

MICHAEL V MONTELEONE
12/14/2010



PDUFA GOAL DATE EXTENSION

NDA 022433

AstraZeneca LP
Attention: Emery Gigger
Regulatory Affairs Director
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803

Dear Mr. Gigger:

Please refer to your new drug application (NDA) originally submitted on November 13, 2009 and received November 16, 2009 under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Brilinta (ticagrelor) 90 mg tablets.

On June 21, 2010, we received your June 21, 2010, major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is December 16, 2010.

If you have any questions, please call Michael Monteleone, Regulatory Project Manager, at (301) 796-1952.

Sincerely yours,

{See appended electronic signature page}

Edward Fromm, RPh, RAC
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22433	ORIG-1	ASTRAZENECA LP	AZD6140

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

/s/

EDWARD J FROMM
09/14/2010

MEMORANDUM OF MEETING MINUTES

APPLICATION: NDA 022433

DRUG NAME: Brilinta (ticagrelor) Tablets

SPONSOR: AstraZeneca

TYPE OF MEETING: Regulatory Briefing

TIME: 11:00 a.m. – 1:00 p.m. EST

MEETING CHAIR: John Jenkins, MD, Director, Office of New Drugs

MEETING FACILITATOR: Liz Hespeneide, MSN, RN

MEETING RECORDER: Mike Monteleone, MS, RPM, Division of Cardiovascular and Renal Products

REGULATORY BRIEFING PANEL: (This list may be incomplete.)

John Jenkins, MD, Director, Office of New Drugs
Larry Lesko, PhD, Director, Office of Clinical Pharmacology
Curtis Rosebraugh, MD, Director, Office of Drug Evaluation II
Douglas Throckmorton, MD, Deputy Director, Center for Drug Evaluation and Research
Issam Zineh, PhD, Associate Director of Genomics, Office of Clinical Pharmacology
Janet Woodcock, MD, Director, Center for Drug Evaluation and Research
Robert Temple, MD, Director, Office of Drug Evaluation 1 (acting)

FDA PRESENTERS:

Robert Fiorentino, MD, MPH, Clinical Reviewer, DCRP
Jialu Zhang, PhD, Statistical Reviewer, Office of Biostatistics
Robert Temple, MD, Director, Office of Drug Evaluation 1 (acting)

DIVISION OF CARDIOVASCULAR AND RENAL REPRESENTATIVES:

Norman Stockbridge, MD, PhD, Director, DCRP
Stephen Grant, MD, Deputy Director, DCRP

OTHER FDA ATTENDEES: *(See attached sign-in lists)*

TOPIC

Brilinta, for the treatment of Acute Coronary Syndrome (ACS)

MEETING OBJECTIVE

To discuss the regulatory implication of the results of PLATO, a single pivotal study submitted to support approval of a new oral antiplatelet agent for the treatment of acute coronary syndromes (ACS). PLATO met its primary endpoint in the overall study population, though the outcomes in the U.S. subset of the study (n=1,413), however, did not show a benefit and indeed, were unfavorable.

(b) (5)



(b) (5)



81 Pages Have Been Withheld As b5 Immediately Following This Page

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

/s/

MICHAEL V MONTELEONE
11/10/2010

ROBERT TEMPLE
11/10/2010



NDA 022433

INFORMATION REQUEST

AstraZeneca LP
Attention: Emery Gigger
Regulatory Affairs Director
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803

Dear Mr. Gigger:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Brilinta, (ticagrelor) 90 mg tablets.

We also refer to your November 13, 2009 submission, containing a New Drug Application for Brilinta (ticagrelor).

We are reviewing the carton and container labeling 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.

A. General Comments (All labels and Labeling)

1. We note the proprietary name is presented in all-caps. Consider revising the proprietary name to appear in title case (i.e. Brilinta). Words set in upper and lower case form recognizable shapes, making them easier to read than the rectangular shape that is formed by words set in all-caps.
2. Ensure the presentation of the established name is at least half the size of the proprietary name in accordance to 21 CFR 201.10(g)(2), which requires that the establish name shall be printed in letters that are at least half as large and with a prominence commensurate to the proprietary name, taking into consideration all pertinent factors, including typography, layout, contrast and other printing features.
3. Increase the prominence of the strength. The current presentation is difficult to read.

B. Container Labels-180 count

1. Relocate the statement "Dispense with Medication Guide" to the Principal Display Panel (PDP) to ensure the statement is not overlooked by health care practitioners. To accommodate this modification and prevent over-crowding of the PDP, relocate the statement, "Each tablet contains 90 mg ticagrelor" to the side panel of the container label.

2. We note that although the 180 count bottle may be a unit-of-use container, it may also be used for more than one patient. Ensure a sufficient number of medication guides are provided.

C. Container Labels-60 count

See comment B.1. above

If you have any questions, please call Michael Monteleone, Regulatory Project Manager, at (301) 796.1952.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, MD, PhD
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22433	ORIG-1	ASTRAZENECA LP	AZD6140

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

/s/

NORMAN L STOCKBRIDGE
08/13/2010



NDA 022433

ADVICE

AstraZeneca LP
Attention: Emery Gigger
Regulatory Affairs Director
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803

Dear Mr. Gigger:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Brilinta, (ticagrelor) 90 mg tablets.

We also refer to your November 13, 2009 submission, containing a New Drug Application for Brilinta (ticagrelor).

We are reviewing the pharmacology section of your submission and have the following comments.

The Division met with the Executive Carcinogenicity Assessment Committee to discuss Astra Zeneca's proposed prolactin mechanism of carcinogenesis. Information provided to the Executive CAC included the material provided by Astra Zeneca (SDN 042, submitted July 16, 2010), the incidence tables for pituitary and mammary tumors and the minutes of the Executive CAC meeting where the rodent carcinogenicity studies were originally reviewed.

The Committee felt that since the proposed hypothesis is predicated upon a change in hormonal levels, it would be reasonable to demonstrate that change by measuring prolactin levels. However, even if decreased prolactin levels are found, those decreased levels are not necessarily linked to increased uterine tumors. Circulating hormone levels measured only in animals do not necessarily support that the uterine tumors will not occur in humans. As presented, the Executive CAC felt that there were insufficient data to support the hypothesis and insufficient evidence to discount the possible relevance of the observed carcinogenic effect to humans.

If you have any questions, please call Michael Monteleone, Regulatory Project Manager, at (301) 796.1952.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, MD, PhD
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22433	ORIG-1	ASTRAZENECA LP	AZD6140

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

/s/

NORMAN L STOCKBRIDGE
08/12/2010

Minutes of Division Discussion with Executive CAC for Ticagrelor

Executive CAC

Date of Meeting: August 3, 2010

Committee: David Jacobson-Kram, Ph.D. OND-IO, Chair
Abby Jacobs, Ph.D., OND-IO, Member
Paul Brown, Ph.D., OND-IO, Member
Haleh Saber, Ph.D., DHP, Alternate Member
Muriel Saulnier, D.V.M., Ph.D., Acting Supervisor
Elizabeth Hausner D.V.M, Reviewer

Coordinator: Adele Seifried, M.S. OND-IO

Author of minutes: E. Hausner, D.V.M.

NDA:22-433

Drug Name: ticagrelor (Brilinta™)

Sponsor: AstraZeneca

The Division met with the Executive CAC to request the committee's opinion on the sponsor's proposed hypothesis that the uterine tumors (a decreased prolactin mechanism proposed) and hepatic tumors (hepatic adaptation proposed) seen in the rat two year study were due to mechanisms that made the tumors irrelevant to humans.

The Committee felt that if a change in prolactin levels are cited as the mechanism, a change in the hormone level should at least be demonstrated. However, even if decreased prolactin levels are found, those decreased levels are not necessarily linked to increased uterine tumors. Circulating levels of prolactin measured only in animals also does not provide support that the uterine tumors will not occur in humans.

The consensus opinion of the Exec CAC was that there was insufficient evidence to support the hypotheses and insufficient evidence to discount the possible relevance of the observed carcinogenic effect to humans.

The Division requested that the Exec CAC address the following three questions:

1. Does the Executive CAC agree with the sponsor's proposed prolactin hypothesis?

Exec CAC answer: No.

2. Does the Executive CAC agree that the hepatic tumors are irrelevant to humans?

Exec CAC answer: It is not certain, although usually hepatic tumors in rodents are not considered relevant to humans..

3. 3. Does the Exec CAC agree that ticagrelor has no carcinogenic potential for humans?

Exec CAC answer: No.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\

- /Division File, DCRP
- /M Saulnier, DCRP
- /L Hausner, DCRP
- /M Monteleone, DCRP
- /ASeifried, OND IO

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22433	ORIG-1	ASTRAZENECA LP	AZD6140

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

/s/

ADELE S SEIFRIED
08/10/2010

DAVID JACOBSON KRAM
08/10/2010



NDA 022433

INFORMATION REQUEST

AstraZeneca LP
Attention: Emery Gigger
Regulatory Affairs Director
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803

Dear Mr. Gigger:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Brilinta, (ticagrelor) 90 mg tablets.

We also refer to your November 13, 2009 submission, containing a New Drug Application for Brilinta (ticagrelor).

We are reviewing the pharmacology section 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.

There are insufficient data to support the qualification of the impurity (b) (4) at a level of (b) (4) as requested in the NDA. Based on our concern that this impurity may possess genotoxic potential, it is recommended, as outlined in the ICH Guidance Q3A Impurities in New Drug Substances (Feb 2003), that a Bacterial Reverse Mutation (Ames) Test and a mammalian chromosomal aberration test be conducted with ticagrelor containing the impurity (b) (4) at a level (b) (4)

If you have any questions, please call Michael Monteleone, Regulatory Project Manager, at (301) 796.1952.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, MD, PhD
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- NDA-22433	----- ORIG-1	----- ASTRAZENECA LP	----- AZD6140

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

/s/

NORMAN L STOCKBRIDGE
07/12/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Office/Division): PMHS		FROM (Name, Office/Division, and Phone Number of Requestor): Michael Monteleone, Division of Cardiorenal, x61952		
DATE 7-9-10	IND NO.	NDA NO. 22433	TYPE OF DOCUMENT Labeling	DATE OF DOCUMENT 7-9-10
NAME OF DRUG Brilinta (ticagrelor)	PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG NME	DESIRED COMPLETION DATE August 10, 2010	
NAME OF FIRM: AstraZeneca				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL	<input type="checkbox"/> PRE-NDA MEETING	<input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER		
<input type="checkbox"/> PROGRESS REPORT	<input type="checkbox"/> END-OF-PHASE 2a MEETING	<input type="checkbox"/> FINAL PRINTED LABELING		
<input type="checkbox"/> NEW CORRESPONDENCE	<input type="checkbox"/> END-OF-PHASE 2 MEETING	<input checked="" type="checkbox"/> LABELING REVISION		
<input type="checkbox"/> DRUG ADVERTISING	<input type="checkbox"/> RESUBMISSION	<input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE		
<input type="checkbox"/> ADVERSE REACTION REPORT	<input type="checkbox"/> SAFETY / EFFICACY	<input type="checkbox"/> FORMULATIVE REVIEW		
<input type="checkbox"/> MANUFACTURING CHANGE / ADDITION	<input type="checkbox"/> PAPER NDA	<input type="checkbox"/> OTHER (SPECIFY BELOW):		
<input type="checkbox"/> MEETING PLANNED BY	<input type="checkbox"/> CONTROL SUPPLEMENT			
II. BIOMETRICS				
<input type="checkbox"/> PRIORITY P NDA REVIEW		<input type="checkbox"/> CHEMISTRY REVIEW		
<input type="checkbox"/> END-OF-PHASE 2 MEETING		<input type="checkbox"/> PHARMACOLOGY		
<input type="checkbox"/> CONTROLLED STUDIES		<input type="checkbox"/> BIOPHARMACEUTICS		
<input type="checkbox"/> PROTOCOL REVIEW		<input type="checkbox"/> OTHER (SPECIFY BELOW):		
<input type="checkbox"/> OTHER (SPECIFY BELOW):				
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE		
<input type="checkbox"/> BIOAVAILABILTY STUDIES		<input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS		
<input type="checkbox"/> PHASE 4 STUDIES		<input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG SAFETY				
<input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY		
<input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES		<input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE		
<input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)		<input type="checkbox"/> POISON RISK ANALYSIS		
<input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP				
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> NONCLINICAL		
COMMENTS / SPECIAL INSTRUCTIONS: Please review the PI for new NDA 022433 Brilinta (ticagrelor), the pharmtox review is in DARRTS and labeling has been commented on by the tox reviewer, Dr. Elizabeth Hausner. I will send a word version of the commented upon labeling to Tammy Brent Howard via email.				
SIGNATURE OF REQUESTOR Mike Monteleone		METHOD OF DELIVERY (Check one) <input type="checkbox"/> DFS <input checked="" type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND		
PRINTED NAME AND SIGNATURE OF RECEIVER		PRINTED NAME AND SIGNATURE OF DELIVERER		

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22433	ORIG-1	ASTRAZENECA LP	AZD6140

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

/s/

MICHAEL V MONTELEONE
07/09/2010

**DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS
FOOD AND DRUG ADMINISTRATION**

WHITE OAK COMPLEX
10903 NEW HAMPSHIRE AVE
BLDG. 22
SILVER SPRING, MD 20993



US Mail address:

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

This document is intended only for the use of the party to whom it is addressed and may contain information that is privileged, confidential, and protected from disclosure under applicable law. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to:
FDA/CDER/DCaRP 5901-B Ammendale Rd. Beltsville, MD 20705-1266

Transmitted via Email: Emery.Gigger@astrazeneca.com

Attention: Emery Gigger

Company Name: AstraZeneca

Phone: 1.302.885.4048

Subject: Meeting Minutes

Date: June 11, 2010

Pages including this sheet: 5

From: Mike Monteleone

Phone: 301.796.1952

Fax: 301.796.9841

Meeting Minutes

Application: NDA 022433
Sponsor: AstraZeneca
Drug: Brilinta (ticagrelor)
Type of Meeting: Advice
Classification: C

Date of Meeting: June 7, 2010

List of FDA Meeting Participants:

Norman Stockbridge, MD, PhD	Director, Division of Cardiovascular and Renal Products
Tom Marciniak, MD	Medical Team Leader
Robert Fiorentino, MD, MPH	Medical Officer
Melanie Blank, MD	Medical Officer
Jim Hung, PhD	Biostatistics, Director, Division of Biometrics I
Jialu Zhang, PhD	Biostatistics
Rajnikanth Madabushi, PhD	Clinical Pharmacology, Team Leader
Islam Younis, PhD	Clinical Pharmacology
Kevin Krudys, PhD	Pharmacometrics
Mike Pacanowski, PharmD, MPH	Pharmacogenomics
Patricia Harlow, PhD	Pharmacology, Acting Team Leader
Elizabeth Hausner, DVM	Pharmacology
Ed Fromm, RPh, RAC	Project Management, Chief
Michael Monteleone, MS	Project Management

List of Sponsor Meeting Participants:

Elizabeth Bjork, MD, PhD	VP Late Phase Clinical Development Director CVGI TA
Kristin Buck, MD	Director Clinical Research
Richard Caplan, PhD	Director of Statistical Science
Kevin Carroll PhD	VP Statistics and Chief Statistician
Simon Clowes, BSc (Hons)	Global Product Vice President
Sandy Fitt	Information Science Director
Jonathan Fox, MD, PhD, FACC	Vice President of Clinical Development CVGI TA
Emery Gigger	Regulatory Affairs Director
Alex Gold, MD	Executive Director Clinical Development
Johannes Harleman, PhD	Senior Director of Pathology
Jay Horrow, MD, MS	Executive Director Medical Science
David Stong, PhD	Director Preclinical Team Leader
Renli Teng, PhD	Senior Director Clinical Pharmacology
Mary Whealy	Global Regulatory Affairs Director
Margaret Melville	Executive Director, Regulatory Affairs CVGI TA

Background: The sponsor submitted an original NDA for Brilinta (ticagrelor) for treatment of ACS on November 16, 2009. The application was designated for standard review with a PDUFA goal date of September 16, 2010. An Advisory Committee meeting is scheduled for July 28, 2010. On April 27, 2010 the sponsor requested a Type C meeting to discuss issues to be presented at the Advisory Committee and discuss any additional information requests by the Division. The sponsor's meeting

request was granted on May 10, 2010. The Division met with the sponsor on June 7, 2010, the minutes of that meeting follow:

The following topics were addressed:

Topic 1: *Feedback on the Division's key NDA review issues and opportunities for clarification.*

Discussion at the meeting:

Dr. Stockbridge stated at the opening of the meeting that it was the Division's intention to have an open and collegial discussion about the ongoing review of the NDA.

There was some discussion about a recent exchange of emails regarding the median acetylsalicylic acid (ASA) dose calculation in PLATO. The sponsor offered background on the recent correction to and revision of the ASA datasets. The sponsor offered that they do not believe the revised analysis significantly affects the original conclusions and agreed to submit an updated dataset for ASA.

The sponsor asked for feedback regarding clinical safety. Dr. Blank said that she did have some concerns that there were more renal AEs, including renal failure, in the few enrolled patients with preexisting advanced chronic renal disease (stage 4) and that these patients had worse outcomes when treated with ticagrelor. She stated, however, that there were not enough data in this population to explore this issue. Dr. Blank offered that while she was still completing her safety review, there are no current major safety concerns.

There was some discussion about an inactive metabolite and how the sponsor had determined that it was inactive. The sponsor related that the results of those studies had not yet been submitted. The sponsor agreed to submit the data to the Division.

There was some discussion regarding the sponsor's recent submission relating to prolactin. Without actual measurement of prolactin levels, the proposed mechanism of carcinogenicity is hypothetical. There was further discussion on what might be included in labeling. Dr. Hausner indicated that the pharmacology/toxicology review is still in progress.

There was some discussion on pharmacogenomics. Dr. Pacanowski stated that he had not identified any major issues, but that his review was still ongoing.

Topic 2: *Feedback on the Division's review of the analyses of regional treatment interactions in PLATO (North American data).*

Discussion at the meeting:

There was lengthy discussion regarding the US results. Dr. Fiorentino commented that his review is still ongoing and that although the apparent ASA interaction seems to offer, at present, an explanation for the regional differences, FDA is looking at other possibilities. In particular, the review team wants to ensure that the derived ASA doses within the dataset are accurate. Further, FDA stated that they will continue to perform analyses of the ASA data to explore the robustness

of the ASA interaction as an explanation for the US results. There was some further discussion on how the ASA interaction was analyzed and how to move forward with additional analyses to provide more clarity. Dr. Stockbridge asked if the sponsor was aware of any external data which might support the ASA hypothesis. The sponsor advised that the CURRENT OASIS-7 trial which suggested no additional benefit of higher dose aspirin was the most relevant recent development. The sponsor related that in the course of their analysis they have consulted with outside experts to explore the ASA hypothesis. During the meeting both the FDA and sponsor expressed how they had been unable to identify alternate explanations, independent of the ASA interaction, for the disparate outcome in the US. Dr. Fiorentino noted that the US subjects were different than non-US subjects on some baseline factors, as well as index event and treatment characteristics.

Dr. Fiorentino commented that the sponsor seemed to be implying that the ASA interaction is real (b) (4)

Dr. Hung asked the sponsor to comment on any analysis that they may have done on the possibility of play of chance explaining the US results. The sponsor commented that they had looked at it and given the number of countries and relatively low percentage of the study population in each, chance is a plausible explanation. The sponsor asked if the Division believed it could be due to the play of chance. Dr. Zhang conceded that chance is always a possibility but that after plotting the hazard ratio over time in the US, the steadiness of the progression suggests to her something other than chance. Dr. Stockbridge commented that he was not sure what a 'chance' plot like that would look like – that it is possible that the early introduction of unfavorable outcomes occurring by chance might not be able to be overcome by more favorable outcomes as the study progressed. Dr. Fiorentino noted that the comparatively small confidence interval around the US results compared to other countries with HR>1.0, as well as the US being a clear outlier on the "funnel plots," made it uncomfortable to attribute the results purely to chance alone.

Topic 3: *Planning for the Advisory Committee Meeting and the key topics.*

Discussion at the meeting:

The sponsor offered that they may be able to provide a draft version of their briefing package in the near future and requested a follow-up teleconference afterwards to address any of the Division's concerns prior to the submission of the final briefing package at the end of the month. The sponsor asked if the Division could share any questions they might be considering. Dr. Stockbridge commented that the Division was not at that point yet, but that the Division would be open to discussion as the AC drew closer. The sponsor asked if the Division had any other guidance to offer in preparation for the AC. Dr. Stockbridge commented that the Division would share any new issues that might come up in the intervening time and that the sponsor should not be surprised by anything at the AC.

Topic 4: *Feedback on the proposed indication.*

Discussion at the meeting:

The sponsor asked if the Division had any preliminary comments on the proposed indication, particularly statements (b) (4) (b) (4)

[Redacted]

Signature, Meeting Chair: *{See appended electronic signature page}*
Norman Stockbridge, M.D., Ph.D.

Reviewed:

MMonteleone	06 JUN 10; (Finalized - 11 JUN 10)
EHausner	08 JUN 10
PHarlow	08 JUN 10
MPacanowski	08 JUN 10
RMadabushi	08 JUN 10
JZhang	09 JUN 10
JHung	09 JUN 10
MBlank	09 JUN 10
RFiorentino	09 JUN 10
TMarciniak	10 JUN 10
NStockbridge	10 JUN 10

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22433	GI-1	ASTRAZENECA LP	AZD6140

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

/s/

NORMAN L STOCKBRIDGE
06/11/2010



NDA 022433

MEETING REQUEST GRANTED

AstraZeneca LP
Attention: Emery Gigger
Regulatory Affairs Director
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803

Dear Mr. Gigger:

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

We also refer to your April 27, 2010, correspondence requesting a meeting to discuss your pending NDA 022433. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a Type C meeting.

The meeting is scheduled as follows:

Date: June 7, 2010
Time: 3:30-5 PM
Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 22
Silver Spring, Maryland 20903

Expected CDER participants:

Norman Stockbridge, MD, PhD	Division Director
Thomas Marciniak, MD	Medical Team Leader
Robert Fiorentino, MD	Medical Officer
Melanie Blank, MD	Medical Officer
Jim Hung, PhD	Biometrics Team Leader
Jialu Zhang, PhD	Biometrics
Raj Madabushi, PhD	Clinical Pharmacology, Team Leader
Younis Islam, PhD	Clinical Pharmacology
Kevin Krudys, PhD	Pharmacometrics
Patricia Harlow, PhD	Pharmacology Team Leader
Elizabeth Hausner, PhD	Pharmacology
Kasturi Srinivasachar, PhD	Chemistry Team Leader
Chhagan Tele, PhD	Chemistry

Thomas Wong, PhD
Edward Fromm, RAC RPh
Michael Monteleone, MS

Chemistry
Chief, Project Management
Project Management

Please e-mail me any updates to your attendees at michael.monteleone@fda.hhs.gov, 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 defined as any non-U.S. citizen or dual citizen who does not have 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.

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: Michael Monteleone (x61952) or Khin Zaw (x61037).

If you have any questions, please call me at (301) 796-1952.

Sincerely,

{See appended electronic signature page}

Michael Monteleone, MS
Regulatory Project Manager
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
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	AstraZeneca
MEETING START DATE AND TIME	June 7, 2010 3:30 PM
MEETING ENDING DATE AND TIME	June 7, 2010 5:00 PM
PURPOSE OF MEETING	Discuss NDA 022433
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	Building 22, Room 1311
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	No
HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number)	Michael Monteleone Regulatory Project Manager Building 22, Room 4169, (x61952)
ESCORT INFORMATION (If different from Hosting Official)	Same as hosting official

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22433

GI-1

ASTRAZENECA LP AZD6140

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

/s/

MICHAEL V MONTELEONE
05/10/2010



NDA 22-433

INFORMATION REQUEST

AstraZeneca
Attention: Emery Gigger, Director, Regulatory Affairs
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Mr. Gigger:

Please refer to your November 13, 2009 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ticagrelor tablets.

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

Drug Substance:

1. Final (b) (4) are manufactured at several locations in (b) (4) and then presumably shipped to AstraZeneca, Sweden or (b) (4). Include an identification test in the acceptance criteria for these (b) (4).
2. (b) (4)
3. In 3.2.S.3.1, you stated that it was not possible to (b) (4) whereas the stereochemistry discussed in 3.2.S.3.2 was apparently based on exactly this technique. Clarify on this apparent inconsistency.
4. Include acceptance criteria for the (b) (4) in the drug substance specification.
5. Include method numbers in the drug substance specification table for the test methods used for the release and stability of the drug substance.
6. Provide the quantitation limit (QL) of the HPLC method for (b) (4) impurity.
7. Regarding polymorphic form:
 - a. The XRPD method is used to confirm the presence of Polymorphic (b) (4) in the drug substance specification. Provide data to support the capability of the XRPD method for the quantification of other polymorphic forms (b) (4) which could potentially be present.
 - b. Provide the experimental data used to justify the design space for ticagrelor crystallization. Include all relevant process inputs (e.g., concentrations, temperature, initial purity, scale, process time), the measured responses (e.g., purity, polymorphic percent), and any statistical analysis.

- c. [REDACTED] (b) (4)
Provide data, if available.
- d. It is noted in Section 7.5.1 in S.2.6 that a [REDACTED] (b) (4)
[REDACTED]
- e. Provide information about solubility of polymorph [REDACTED] (b) (4)
8. Provide stability commitment to include commercial batches manufactured at [REDACTED] (b) (4) site and Sodertalje, Sweden site.

Drug Product:

9. Provide the following data to support your proposed design space:

[REDACTED] (b) (4)

- c. The method that you used to determine the absence of Polymorph [REDACTED] (b) (4) during the tablet manufacturing process and the sensitivity of the method.
- d. Batch analysis data on validation batch(es) manufactured with the proposed commercial batch size and equipment when results are available.
10. Modify your process description in Section P.3.3 as follows:

[REDACTED] (b) (4)

11. Upon evaluation of the data provided, the Agency is in concurrence [REDACTED] (b) (4)
[REDACTED]
This test should be listed below the specification table (not within the table) and clearly labeled. Provide a testing frequency for this test and supporting rationale for the suggested frequency.

12. We acknowledge that the proposed in vitro dissolution acceptance criteria are based on demonstrated in vivo performance. However, the acceptance criteria for dissolution are generally set at Q [REDACTED] (b) (4) for an immediate release product; this criteria ensures that most of

the drug product will dissolve. The Agency recommends that the proposed dissolution specification be revised from (b) (4). Furthermore, C (b) (4) is consistent with the provided data for the 41 clinical batches and the 10 commercial batches, showing that the dissolution values at 45 minutes (b) (4) within a reasonable range of variability. This revision will reduce the probability of releasing lots that are bioequivalent due to incomplete release of drug.

13. In order to support your proposal (b) (4)

(b) (4)

14. In the footnote "a" of the drug product specification (b) (4)

(b) (4)

15. Specify which are the primary and alternative analytical methods used for testing of identification, assay and degradation products of the drug product.

16. For NIR method validation:

(b) (4)

18. Provide the specifications of the container closure systems in a tabular format. The information should include the description of the bottles (e.g. sizes and wall thickness, description of the closure, description of the blisters and the thickness of the (b) (4) the aluminum lidding foil, and the (b) (4)

19. Confirm that your design space for drug substance and drug product does not include a change in manufacturing site, to one not listed in the application. Note that at this time the agency does not have any mechanism to allow for site changes supported by a firm's Change Management Protocol.

If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22433	ORIG-1	ASTRAZENECA LP	AZD6140

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

/s/

RAMESH K SOOD
05/13/2010

Memo of TCON

Application: NDA 022433
Sponsor: Astra-Zeneca
Drug: ticagrelor
Type of Meeting: TCON
Date of Meeting: May 11, 2010

List of FDA Meeting Participants:

Rob Fiorentino, MD	Medical Officer
Patricia Harlow, PhD	Pharmacology Acting Team Leader
Elizabeth Hausner, DVM	Pharmacology
Chhagan Tele, PhD	CMC
Mike Monteleone	Project Management

List of Sponsor Attendees:

Alex Gold	Development Brand Leader
Mark Hindle	Senior Project Scientist, Development
Jay Horrow	Exec Dir Med Science, Clinical
Mike O'Donovan	Director of Genetic Toxicology
Charles Humfrey	Preclinical Scientist
Scott Boyer	Chief Scientist and Head, Comp Tox Global Safety Assessment
Maria Edebrink	Team manager, Development
David Stong	Preclinical Scientist
Emery Gigger	Regulatory Affairs Director
Mary Whealy	Global Regulatory Lead
Judith Prosser	Regulatory Affairs Manager

Background: The Division requested an informal TCON with the sponsor of NDA 022433 ticagrelor to discuss the specification limits for impurity (b) (4) which came up positive in the computational genotoxicity databases. The sponsor sent a brief outline of their position via email prior to the meeting (attached).

Discussion: Dr. Hausner outlined that because the sponsor had no experimental data on (b) (4) the Division submitted it for a computational genotoxicity analysis. This analysis was positive with two alerts, one for bacterial mutagenicity and one for mouse lymphoma. The sponsor argued that because the impurity was structurally similar to ticagrelor, which, though positive in computational genotox analysis, had been shown to be negative through genotoxicity assays, AZ had concluded that alerts for (b) (4) were also false. Dr. Hausner responded that the basis for the SAR work is that small changes in structural details can profoundly affect activity and properties and that absent experimental data on (b) (4) the information in hand suggests genotoxicity.

The sponsor proposed that the Division submit both ticagrelor and (b) (4) for another computational analysis. After the meeting Dr. Hausner submitted ticagrelor only for analysis to avoid introducing bias in its analysis. After the meeting the Division requested the sponsor provide us with calculations of exposure in the toxicology studies as the content of (b) (4) is typically listed as (b) (4)

Reviewed

MMonteleone	17 May 2010
EHausner	18 May 2010
PHarlow	18 May 2010

Attachment: Sponsor background for TCON sent via email 5/10/2010

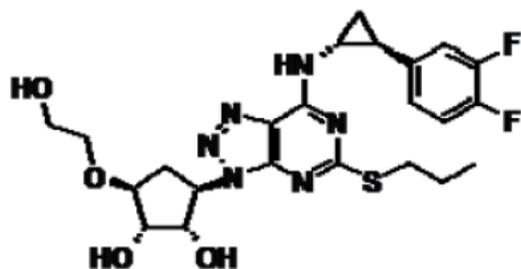
NDA 22-433 Ticagrelor Tablets
Background Information for May 11, 2010 Teleconference
May 10, 2010 – Page 1 of 1

AstraZeneca wishes to provide further information in advance of the teleconference requested by the Agency on May 11, 2010 to discuss the impurity (b) (4) in ticagrelor drug substance.

- Ticagrelor has been shown to be negative in the Ames, mouse lymphoma and rat micronucleus assays.
- (b) (4) has not been tested in any genotoxicity assays.
- Ticagrelor has been found to be negative in genotoxicity assays although it showed an alert for (b) (4) in AstraZeneca's initial QSAR MCASE analysis (2006) but not DEREK.
- The structure of (b) (4) is similar to that of ticagrelor and showed a similar alert (b) (4) in the initial AstraZeneca QSAR MCASE analysis but not in the currently used versions of DEREK and MCASE. The structures are provided below.
- The addition of the (b) (4) does not raise any unique concerns for genotoxicity compared to the (b) (4) alone.
- Given the structural similarity to ticagrelor for the impurity and the lack of any genotoxicity signal for ticagrelor, AstraZeneca concludes that the initial alert for (b) (4) was shown to be false.

Can the Agency clarify which database highlighted the concern for (b) (4) and can they indicate the result that was obtained for ticagrelor in the same database?

Structures of ticagrelor and (b) (4)



Ticagrelor



Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22433	ORIG-1	ASTRAZENECA LP	AZD6140

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

/s/

MICHAEL V MONTELEONE
05/18/2010

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO:
CDER-DDMAC-RPM

FROM: (Name/Title, Office/Division/Phone number of requestor)
Mike Monteleone, RPM DCRP x61952

REQUEST DATE
4-19-2010

IND NO.

NDA/BLA NO.
022433

TYPE OF DOCUMENTS
(PLEASE CHECK OFF BELOW)

NAME OF DRUG

Brilinta (b) (4)

PRIORITY CONSIDERATION

Standard

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE
(Generally 1 week before the wrap-up meeting)

July 28, 2010

NAME OF FIRM:

AstraZeneca

PDUFA Date: September 16, 2010

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:

(Check all that apply)

- PACKAGE INSERT (PI)
- PATIENT PACKAGE INSERT (PPI)
- CARTON/CONTAINER LABELING
- MEDICATION GUIDE
- INSTRUCTIONS FOR USE (IFU)

TYPE OF APPLICATION/SUBMISSION

- ORIGINAL NDA/BLA
- IND
- EFFICACY SUPPLEMENT
- SAFETY SUPPLEMENT
- LABELING SUPPLEMENT
- PLR CONVERSION

REASON FOR LABELING CONSULT

- INITIAL PROPOSED LABELING
- LABELING REVISION

EDR link to submission:

Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.

COMMENTS/SPECIAL INSTRUCTIONS:

Mid-Cycle Meeting: [April 14, 2010]

Wrap-Up Meeting: [August 4, 2010]

SIGNATURE OF REQUESTER
Michael Monteleone

SIGNATURE OF RECEIVER

METHOD OF DELIVERY (Check one)

- eMAIL
- DARRTS
- HAND

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22433	ORIG-1	ASTRAZENECA LP	AZD6140

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

/s/

MICHAEL V MONTELEONE
04/19/2010



NDA 022433

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

AstraZeneca LP
1800 Concord Pike
P.O. Box 8355
Wilmington, Delaware 19803

ATTENTION: Emery Gigger
Director, Regulatory Affairs

Dear Mr. Gigger:

Please refer to your New Drug Application (NDA) dated November 13, 2009, received November 16, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ticagrelor Tablets 90 mg.

We also refer to your November 20, 2009, correspondence, received November 20, 2009, requesting review of your proposed proprietary name, Brilinta. We have completed our review of the proposed proprietary name, Brilinta and have concluded that it is acceptable.

The proposed proprietary name, Brilinta, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your November 20, 2009 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nina Ton, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at 301-796-1648. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Michael Monteleone at 301-796-1952.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22433	ORIG-1	ASTRAZENECA LP	AZD6140

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

/s/

CAROL A HOLQUIST
02/18/2010



NDA 22-433

INFORMATION REQUEST

AstraZeneca
Attention: Emery Gigger, Director, Regulatory Affairs
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Mr. Gigger:

Please refer to your November 13, 2009 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ticagrelor tablets.

We reviewed your dissolution data and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Provide the complete dissolution raw data, lot/batch number, the dissolution conditions used (apparatus, media, pH, rotation speed, volume), individual and average values of % of drug dissolved at each time point, f2 values (when making profile comparisons), and the manufacturing parameters ((b) (4)) used for the tested products.

The dissolution data should include, but not limited to the following categories:

- a. The data collected during formulation development.
- b. The data for the formulations used in Phases 1 and 2.
- c. The data for the Phase 3 and commercial formulations.
- d. The data for the formulations used in study 55 (the crossover 5-arm biostudy).
- e. The data for the formulation used in DoE's (Note that in some tables, the dissolution values at 45 minutes were reported. However, in this case, the data should include the values at the early time points also).
- f. The dissolution data for pilot batches and commercial batches so far.

The data should be tabulated in SAS transport file format.

If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22433	ORIG-1	ASTRAZENECA LP	AZD6140

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

/s/

RAMESH K SOOD
01/26/2010



NDA 022433

FILING COMMUNICATION

AstraZeneca LP
Attention: Emery Gigger
Regulatory Affairs Director
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803

Dear Mr. Gigger:

Please refer to your new drug application (NDA) dated November 13, 2009, received November 16, 2009, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, for Brilinta, (ticagrelor) 90 mg tablets.

We also refer to your submissions dated November 20, 24, 25 and December 8, 16, 18 (2), 22 and 24, 2009.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed January 15, 2010, 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Standard**. Therefore, the user fee goal date is September 16, 2010.

We acknowledge your request for a priority review but have determined not to grant your request for the following reasons:

A priority review is assigned if "Preliminary estimates indicate that the drug product, if approved, has the potential to provide, in the treatment, prevention, or diagnosis of a disease, one of the following: (1) safe and effective therapy where no satisfactory alternative therapy exists; or (2) a significant improvement compared to marketed products (approved, if approval is required), including *nondrug* products or therapies." The proposed labeling for ticagrelor states that it "as compared to clopidogrel has been shown to decrease the rate of a combined endpoint of cardiovascular death, MI or stroke. The difference between treatments was driven predominantly by CV death and MI with no difference on strokes." While decreasing CV death may be viewed as a significant improvement justifying a priority review, three factors support assignment of a standard review: (1) Nominal superiority of ticagrelor to clopidogrel was not evident in the U.S. subpopulation. The submission provides evidence of a possible treatment interaction with higher doses of aspirin used in the U.S. population, suggesting that ticagrelor could be inferior to clopidogrel when given on a background of higher dose aspirin. Potential confounders in the U.S. subpopulation and higher-dose aspirin subgroups need further

exploration. (2) Ticagrelor also appears to be associated with additional adverse effects compared to clopidogrel, including dyspnea and ventricular pauses. Given these efficacy and safety issues, our preliminary estimates suggest that ticagrelor may not be a significant improvement over clopidogrel when used with higher doses of aspirin. (3) There exists an adequate alternative therapy: The superiority of ticagrelor to prasugrel, another thienopyridine also approved for ACS indication, has not been demonstrated.

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 commitment requests by July 30, 2010.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

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 indications in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, please call Michael Monteleone, Regulatory Project Manager, at (301) 796-1952.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, MD, PhD
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- NDA-22433	----- ORIG-1	----- ASTRAZENECA LP	----- AZD6140

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

/s/

NORMAN L STOCKBRIDGE
01/05/2010



NDA 022433

NDA ACKNOWLEDGMENT

AstraZeneca LP
Attention: Emery V. Gigger
Director, Regulatory Affairs
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Mr. Gigger:

We have received your new drug application (NDA) submitted section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Brilinta (ticagrelor) Tablets

Date of Application: November 13, 2009

Date of Receipt: November 16, 2009

Our Reference Number: NDA 022433

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 January 15, 2010 in accordance with 21 CFR 314.101(a).

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 Cardiovascular and Renal Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for

review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/cder/ddms/binders.htm>.

If you have any questions, please contact:

Mr. Michael Monteleone, M.S.
Regulatory Health Project Manager
(301) 796-1952

Sincerely,

{See appended electronic signature page}

Edward Fromm, R.Ph., RAC
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22433

ORIG-1

ASTRAZENECA LP AZD6140

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

/s/

EDWARD J FROMM
11/24/2009

**DIVISION OF CARDIOVASCULAR & RENAL PRODUCTS
FOOD AND DRUG ADMINISTRATION**



US Mail address:
CDER, DCRDP (HFD-110)
10903 New Hampshire Ave.,
Silver Spring, MD 20993-0002

FDA
10903 New Hampshire Ave
Silver Spring, MD 20993-00025600

This document is intended only for the use of the party to whom it is addressed and may contain information that is privileged, confidential, and protected from disclosure under applicable law. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to: CDER, DCRDP (HFD-110); 10903 New Hampshire Ave., Silver Spring, MD 20993-0002

Transmitted via email to: Emery.Gigger@astrazeneca.com

Attention: Emery Gigger

Company Name: AstraZeneca

Phone: 302.886.4048

Subject: **IND 65,808 PLATO Results
Meeting Minutes**

Date: 8 September 2009

Pages including this sheet: 39

From: Alison Blaus

Phone: 301-796-1138

Fax: 301-796-9838

*******PLEASE LET ME KNOW YOU RECEIVED THIS. THANKS!**

Meeting Minutes

Date: 5 August 2009
Application: IND 65,808
Drug: Ticagrelor (AZD6140)
Sponsor: AstraZeneca
Meeting Purpose: Phase 3 Results
Meeting Type: Type C

FDA Participants:

Robert Temple, M.D.	Director, Office of Drug Evaluation I
Ellis Unger, M.D.	Deputy Director, Office of Drug Evaluation I
Norman Stockbridge, M.D., Ph.D.	Director, Division of Cardio-Renal Drug Products
Mary Ross Southworth, Pharm.D.	Safety Deputy Director, Division of Cardio-Renal Drug Products
Stephen Grant, M.D.	Team Leader, Medical Officer
Shari Targum, M.D.	Team Leader, Medical Officer
Thomas Marciniak, M.D.	Team Leader, Medical Officer
Abraham Karkowsky, M.D., Ph.D.	Team Leader, Medical Officer
Nancy Xu, M.D.	Medical Officer
James Hung, Ph.D.	Director, Division of Biometrics I
John Lawrence, Ph.D.	Mathematical Statistician
Raj Madabushi, Ph.D.	Team Leader, Clinical Pharmacology
Islam Younis, Ph.D.	Clinical Pharmacology
Alison Blaus	Regulatory Health Project Manager

AstraZeneca Participants:

Elisabeth Björk, M.D., Ph.D.	Vice President, Late Phase Clinical Development Director CVGI TA
James Blasetto, M.D., MPH	Vice President, US Strategic Development
Kristen Buck, M.D.	Director of Clinical Research
Richard Caplan, Ph.D.	Director of Statistical Science
Simon Clowes, Bsc (Hons)	Global Product Vice President
Jonathan Fox, MD, PhD,	Vice President of Clinical Development CVGI TA
Emery Gigger	Regulatory Affairs Director
Jay Horrow, M.D., MS	Executive Director, Medical Science
Jim McDermott, Ph.D.	Executive Director, Clinical Development
Judith Prosser	Regulatory Affairs Manager
Mary Whealy	Global Regulatory Affairs Director

Consultants

(b) (4)

Background:

Ticagrelor (formerly known as AZD6140) is an oral, reversible ADP receptor antagonist acting via the P2Y₁₂-receptor, which is aimed to block ADP-mediated platelet activation and aggregation. The indication being pursued by the sponsor is (b) (4) thrombotic events in patients with acute coronary syndromes (ACS). Ticagrelor is a conventional, immediate-release, film-coated tablet for oral use, available

in (b) (4) 90 (b) (4) mg strengths. The IND for AZD6140 (IND 65,808) was initially submitted to the Division on 28 April 2003. The clinical program to date has consisted of 28 Phase 1 studies in healthy volunteers, two Phase 2 studies conducted in patients (one submitted as a Special Protocol Assessment on 14 December 2007), and one Phase 3 study, PLATO.

AstraZeneca plans to submit a NDA for ticagrelor during the second half of 2009 for the following indication: Ticagrelor is indicated for (b) (4) thrombotic events (CV death, MI, or stroke) in patients with Acute Coronary Syndromes (unstable angina, non-ST elevation Myocardial Infarction [NSTEMI] or ST-elevation Myocardial Infarction [STEMI] (b) (4). The goal for this meeting was for the sponsor to provide preliminary results from the Phase 3 PLATO study and to obtain the Division' initial impressions of the data. The slides presented at this meeting appear as an Appendix to these minutes.

Discussion During Meeting:

PLATO Study Design

- The sponsor confirmed that the dose for the Phase 3 protocol was based on the DISPERSE 2 trial data.
- Dr. Temple asked why the duration of exposure to study drugs in PLATO ranged from 6-12 months (on slide 4, located in the Appendix of these minutes). When the last patient enrolled completed 6 months of treatment, the trial was terminated so all subjects completed a minimum of 6 months of treatment and most subjects were treated for 12 months.
- Dr. Madabushi confirmed with the sponsor that patients were randomized and received treatment as early as possible and before any procedure, such as PCI.

Primary and Secondary Efficacy Endpoints

- After considering slide 6, FDA asked AstraZeneca to analyze and present the results for the subgroups of subjects with NSTEMI ACS and STEMI. AstraZeneca agreed to do this.
- The sponsor explained that the nominal p-value was 0.0003 for all cause mortality was not considered statistically significant because the p-value for the secondary endpoint above it in the hierarchical analysis, reduction in stroke, was not less than 0.05. CV mortality, however, was significant. FDA noted that this would be considered further.
- The consistency of treatment effect from 1-30 and 31-360 days was explored. AstraZeneca agreed to explore other time periods in the NDA submission.

Bleeding results

AstraZeneca presented slides 11-18, which examined the bleeding results from PLATO. AstraZeneca explained that bleeding in PLATO was adjudicated and included both CABG and non-CABG bleeds. Overall, more bleeding was observed in subjects randomized to ticagrelor than clopidogrel, although the difference was not significant. The most striking difference was in fatal and life-threatening intracranial hemorrhage. The sponsor will examine the total bleeding burden and intracranial bleeding.

Safety Results

- AstraZeneca explained that dose dependent bradycardia was observed in Phase 2 but not in PLATO. AstraZeneca added that bradycardia did not appear to be due to a drug-drug interaction. An increase in frequency in bradycardic episodes was observed in overweight patients as well as at night.
- A mild increase in uric acid was also observed in slightly more subjects randomized to ticagrelor than clopidogrel. AstraZeneca noted that after stopping ticagrelor, uric acid levels decrease but do not normalize. No other markers for kidney injury were explored. The sponsor suggested that it is likely due

to inhibition of organic anion transporter(s), but the only transporter-interaction study they have performed was with digoxin (P-glycoprotein transport substrate).

- As shown on slide 29, AstraZeneca stated that no potential Hy's law cases were observed in PLATO. Two subjects' lab tests on Day 1 of treatment met criteria for a potential Hy's law case but both had readily identifiable reasons for the lab abnormalities.

Subgroup Efficacy Results

AstraZeneca indicated that the results in the subgroup of subjects enrolled in North America (NA) were notably different from the rest of the world, favoring clopidogrel on the primary endpoint (20 fewer MIs/strokes/CV deaths, with no one component predominating). AstraZeneca indicated they had extensively reviewed the data for an explanation. There did not seem to be major differences in the standard of care between North America and the rest of the world. One difference found was that in NA the dose of aspirin tended to be 325 mg while the dose in the rest of the world was less. Dr. Temple observed that the evidence for dose-response for aspirin indicated that dose of aspirin does not appear to have much dose related effect on MACE outcomes. AstraZeneca agreed to explore possible interactions with aspirin/ticagrelor.

Other Items of Discussion

AstraZeneca inquired whether the ticagrelor NDA would be granted a priority review. Dr. Stockbridge noted that the difference between a priority and standard lies with the indication sought. The sponsor plans to submit their proposed indication prior to submission of the NDA to gain Division feedback.

Meeting recorder: _____
Alison Blaus

Meeting concurrence: _____
Robert Temple, M.D.

Draft: ab 11Aug09
Final: ab 8Sep09

RD:
Lawrence 11Aug09
Hung 12Aug09
Younis 13Aug09
Madabushi 14Aug09
Xu 8/17/09
Grant 18Aug2009
Marciniak 24Aug09
Targum 31Aug09
Southworth 31Aug09
Stockbridge 31Aug09
Temple 8Sep09

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-65808	GI-1	ASTRAZENECA LP	AZD6140
IND-65808	GI-1	ASTRAZENECA LP	AZD6140

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

/s/

ALISON L BLAUS
09/08/2009

ROBERT TEMPLE
09/08/2009

**DIVISION OF CARDIOVASCULAR & RENAL PRODUCTS
FOOD AND DRUG ADMINISTRATION**



US Mail address:
CDER, DCRDP (HFD-110)
10903 New Hampshire Ave.,
Silver Spring, MD 20993-0002

FDA
10903 New Hampshire Ave
Silver Spring, MD 20993-00025600

This document is intended only for the use of the party to whom it is addressed and may contain information that is privileged, confidential, and protected from disclosure under applicable law. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to: CDER, DCRDP (HFD-110); 10903 New Hampshire Ave., Silver Spring, MD 20993-0002

Transmitted via email to: Emery.Gigger@astrazeneca.com

Attention: Emery Gigger

Company Name: AstraZeneca

Phone: 302.886.4048

Subject: IND 65,808 Pre-NDA Meeting
Meeting Minutes

Date: 14 May 2009

Pages including this sheet: 19

From: Alison Blaus
Phone: 301-796-1138
Fax: 301-796-9838

*******PLEASE LET ME KNOW YOU RECEIVED THIS. THANKS!**

Meeting Minutes

Date: 20 April 2009
Application: IND 65,808
Drug: Ticagrelor (AZD6140)
Sponsor: AstraZeneca
Meeting Purpose: Pre-NDA
Meeting Type: Type B

FDA Participants:

Norman Stockbridge, M.D., Ph.D.	Director, Division of Cardio-Renal Drug Products
Ellis Unger, M.D.	Deputy Director, Division of Cardio-Renal Drug Products
Shari Targum, M.D.	Team Leader, Medical Officer
Stephen Grant, M.D.	Team Leader, Medical Officer
Nancy Xu, M.D.	Medical Officer
James Hung, Ph.D.	Director, Division of Biometrics I
John Lawrence, Ph.D.	Mathematical Statistician
Elizabeth A Hausner, D.V.M.	Pharmacologist
Elena Mishina, Ph. D	Clinical Pharmacology
Michael Pacanowski, Pharm.D.	Pharmacogenomics
Kasturi Srinivasachar, Ph.D.	Pharmaceutical Assessment Lead, ONDQA
Alison Blaus	Regulatory Health Project Manager
Russell Fortney	Regulatory Health Project Manager

AstraZeneca Participants:

Anders Sveno	Team Manager Process Chemistry
Malin Vägerö, BSc	Lead Analytical Chemistry
David Stong, Ph.D.	Director, Preclinical Team Leader
Jay Horrow, M.D.	Director, Medical Science
Richard Caplan, Ph.D.	Director, Statistical Science
Kathleen Butler, M.D.	Director, Clinical Research
Renli Teng, Ph.D.	Senior Director, Clinical Pharmacology
Judith Prosser	Regulatory Affairs Manager
Mary Whealy	Global Director, Regulatory Affairs
Emery Gigger	Director, Regulatory Affairs
Laurence Huang	Regulatory Affairs observer
Jim McDermott, Ph.D.	Executive Director, Clinical Development
Sandy Fitt	Director, Information Science
Frank Senk	Principle Programmer

Background:

Ticagrelor (formerly known as AZD6140) is an oral, reversible ADP receptor antagonist acting via the P2Y₁₂-receptor, which is aimed to fully block ADP-mediated platelet activation and aggregation. The indication being pursued by the sponsor is (b) (4) thrombotic events in patients with acute coronary syndromes (ACS). Ticagrelor is a conventional, immediate-release, film-coated tablet for oral use, available in (b) (4) 90 (b) (4) mg strengths. The IND for AZD6140 (IND 65,808) was initially submitted to the Division on 28 April 2003. The clinical program to date has consisted of 28 Phase 1 studies in healthy

volunteers, two Phase 2 studies conducted in patients (one submitted as a Special Protocol Assessment on 14 December 2007), and one Phase 3 study, PLATO.

AstraZeneca plans to submit a NDA for ticagrelor during the second half of 2009 for the following indication: Ticagrelor is indicated for (b) (4) thrombotic events (CV death, MI, or stroke) in patients with Acute Coronary Syndromes (unstable angina, non-ST elevation Myocardial Infarction [NSTEMI] or ST-elevation Myocardial Infarction [STEMI]) (b) (4)

(b) (4) The goal of the sponsor for this pre-NDA meeting is to gain agreement with the Division regarding the proposed format, data, and analyses planned to be included in the NDA to support the approval of ticagrelor.

Questions for the Division:

Chemistry, manufacturing and controls

1. The Sponsor presents a risk assessment process, including the use of structural similarity arguments, which define the control strategy for potential genotoxic impurities in ticagrelor. Does the Division find the risk assessment process acceptable?

Preliminary Response:

We agree with your approach to risk assessment for genotoxic impurities but cannot comment on the adequacy of the process at this time. It is expected that complete information about your control strategy as well as supporting data for all potential genotoxic impurities will be submitted to the NDA for review. Your risk assessment should also take into account the limitations of (b) (4) as documented for (b) (4). Is it possible that the genotoxicity of (b) (4) is a result of trace amounts of (b) (4) such as (b) (4) carried over during its synthesis?

Additional Discussion During Meeting:

The sponsor presented a number of possible genotoxic impurities, as shown in Attachment I to these minutes. After the presentation, Dr. Srinivasachar asked whether impurities with multiple structural alert features, like those identified for (b) (4) could result in a positive Ames result. The sponsor thought this unlikely, and added that they believe the reactivity would not change much. Per slide 5, the sponsor noted that, in conclusion, they are comfortable with their non-genotoxic assessment. Dr. Srinivasachar noted that the spiking experiments were carried out on laboratory scales and the sponsor should explain why the results would also be valid for production scale batches. The risk assessment in the NDA is expected to address the limitations of (b) (4) and the possibility that other genotoxic impurities, such as (b) (4) could be present.

Non-clinical

2. Does the Division agree to the Sponsor's proposal for non-clinical datasets in the NDA?

Preliminary Response:

Yes.

Additional Discussion During Meeting:

No further discussion.

Clinical

3. Does the Division agree with the Sponsor's proposal not to pool safety data from the Phase I clinical pharmacology program?

Preliminary Response:

Yes.

Additional Discussion During Meeting:

No further discussion.

4. Does the Division agree with the proposal to pool safety data from the Phase II studies only, and present the integrated dataset in Module 5, Section 5.3.5.3, with pooling not to include Phase III safety data?

Preliminary Response:

Yes, you can pool phase II trials, as long as the data are not from special populations.

Additional Discussion During Meeting:

No further discussion.

5. Does the Division agree with the Sponsor's proposal for the presentation of bleeding data in the Summary of Clinical Safety?

Preliminary Response:

We recommend that you analyze the following:

- Both time to major and time to major plus minor bleeding (latter indicated in the original protocol).
- Total number of the bleeding events over treatment in addition to time to first major bleed.

In addition, please submit complete data from the adjudication committee.

Additional Discussion During Meeting:

The Division reiterated that in order to evaluate the bleeding burden, the sponsor should also explore the total number of bleeding events, not simply total patients with major or minor bleeding. The sponsor agreed to the Division's bleeding data presentation suggestions for the Summary of Clinical Safety section to be included in the NDA. They noted that they will detail all PLATO-defined bleeding as well as TIMI- and GUSTO-defined bleeding, and will compare the data in tabular format. Bleeding will be assessed by the investigators and then by the adjudication committee. Finally, the Division asked whether there were any bleeding events that the investigators were instructed not to report. The sponsor replied that there were none, and that all bleeds, even minor, were to be reported to the adjudication committee.

6. Does the Division agree that the proposed analysis will provide relevant information regarding the clustering of cardiovascular events following cessation of antiplatelet therapy?

Preliminary Response:

Yes.

Additional Discussion During Meeting:

No further discussion.

7. Does the Division agree with the Sponsor's plan not to submit the PLATO collaborative substudy reports as part of the NDA?

Preliminary Response:

We currently do not have sufficient information to advise you. Please enumerate all substudies for our review to order for us to advise you. In general, you should submit the PLATO collaborative substudy reports as part of the NDA, particularly if there are safety signals that have emerged in your analyses.

Please submit SAS datasets for all data from the pulmonary function substudy.

Lastly, for your ECG analysis from the Holter, please also evaluate sinus node pauses ≥ 5 seconds and (if known) symptomatic pauses.

Additional Discussion During Meeting:

The sponsor presented a table detailing all of the substudies planned for PLATO (see Attachment II to these minutes) and stated that the safety information from the Holter Monitoring and Pulmonary Function substudies will be provided as attachments to their respective CSRs in the NDA. This will include sinus node pauses ≥ 5 and ≥ 3 seconds in the Holter study. The sponsor stated that the six other substudies largely evaluate exploratory biomarkers in addition to information already included in the safety dataset. For example, in the Platelet Function substudy, the sponsor is collecting additional samples to test for flow cytometrics, potentially new proteins of expression, and novel markers for new work in the area. The Division asked for submission of the descriptions of all substudies to be included in the NDA. The sponsor agreed.

8. Does the Division agree to the proposed content and format of the patient safety narratives?

Preliminary Response:

Your narratives appear to be based only on the data in the case report forms. We expect narratives to be based on all available information including narratives and hospital documents submitted by investigators. Please also submit case report forms as required by FDA regulations. Case report forms include all clinical information communicated from investigators to you or your contractors regardless of whether a document is labeled a “case report form”—e.g., a “serious adverse event worksheet” or a Medwatch form is a case report form. Endpoint adjudication packages should also be included with the case report forms.

Additional Discussion During Meeting:

AstraZeneca explained that they were to provide the narratives of about 5000 patients, which included all deaths, subjects with serious adverse events (SAEs), and all discontinuations. Case Report Forms (CRFs) would also be provided for deaths and SAEs. The Division also requested that if a patient’s treatment assignment was unblinded, the sponsor should differentiate which information on the narrative was received before and after unblinding. All narratives should be dated. The sponsor assured the Division that all information in the clinical database was the same as that on the Medwatch. The Division asked to be provided with source documentation from the site. The Division noted that this information would not be used for page by page review but rather as a reference if needed. Per the Agency’s request, the sponsor also agreed to follow-up on the feasibility of providing the classifications of cases from the adjudication committee as pdf files. Finally, the sponsor asked whether the CSRs could be separate from the clinical data and placed in Module 5, given that they were submitted globally. The Division agreed.

9. Does the Division agree to the Sponsor’s proposal for the Summary of Clinical Efficacy section of the submission, and the proposal to include requirements for the Integrated Summary of Efficacy within that Section?

Preliminary Response: We agree. Please see the list of variables we would like in our analysis dataset.

Additional Discussion During Meeting:

Dr. Unger asked the sponsor whether it was possible to provide a list of all those patients who failed randomization (screen failures) and why. The sponsor noted that they did not capture that information in the database and would not be able to provide it as part of the NDA. The sponsor did agree to provide the Division with a by-subject listing whether patients were unblinded, the date of unblinding, reason for unblinding, whether included in the safety population (Y/N), and whether included in the efficacy population (Y/N). AstraZeneca noted that they will also provide a list of all patients on proton pump inhibitors (PPIs) or H2 blockers. Dr. Unger said that he will discuss with the sponsor an effective way to capture these data based on the different ways usage could be defined.

10. Does the Division agree that for purpose of analysis administration of two 300 mg clopidogrel doses within 4 hours can be classified as a 600 mg loading dose?

Preliminary Response:

Yes.

Additional Discussion During Meeting:

No further discussion.

11. Does the Division agree that the early PCI subgroup is medically relevant and inclusion in the label should be considered under the conditions described?

Preliminary Response:

If the safety and efficacy profiles for your pre-specified first secondary objective (the intent for invasive management group) and your explorative secondary endpoint (those who actually undergo PCI within 24 hours following randomization) are similar, we will then *consider* whether the data from both subgroups should appear in the label.

Additional Discussion During Meeting:

No further discussion.

12. Does the Division agree that the results of the combined efficacy and safety analysis, placed in the Summary of Clinical Efficacy, provides information that is medically relevant to guide physicians in prescribing ticagrelor, and thus might appear in the label?

Preliminary Response:

We agree with the concept of net clinical benefit; however, specific labeling decisions cannot be made until the data have been reviewed. We have the following comments:

- The definition of net clinical benefit should be pre-specified.
- For net clinical benefit: death should include all death, not only vascular death.
- We can discuss in our meeting approaches to incorporate and weigh bleeding endpoints in the “combined efficacy and safety composite.” The approach should be based on compelling evidence and reflect what is clinically meaningful.
- While you can present and analyze the ICAC adjudicated bleeding data, we may also review bleeding data unadjudicated for the attribution of CABG.
- Bleeding endpoints should also be included separately in the safety analysis section.

Additional Discussion During Meeting:

Dr. Stockbridge said that the net clinical benefit analysis should always be prespecified. As this is not the case here, the above analyses should be treated as exploratory and there is a divergence of opinion on whether conducting them is helpful. Nonetheless, he added that the sponsor should explore as many different ways as possible to define and weigh benefits and risks. What and how the results of these exploratory analyses should be translated into the label will be discussed at the time of labeling discussions. For example, the Division suggested a time-to-event weighted analysis might be of interest to the Division at the time of the NDA. Dr. Stockbridge did not think that it would be wise to add anything more to the Statistical Analysis Plan at this point.

13. Does the Division agree with the proposed format of the study reports?

Preliminary Response:

Yes.

Additional Discussion During Meeting:

No further discussion.

14. Does the Division agree to the Sponsor's proposal for published references cited within the NDA?

Preliminary Response:

Yes.

Additional Discussion During Meeting:

No further discussion.

15. Does the Division agree with the proposal to include only listings and analysis datasets and not individual patient profiles in the NDA?

Preliminary Response:

Yes.

Additional Discussion During Meeting:

No further discussion.

16. Does the Division agree to the format for submitting study data in electronic format?

Preliminary Response:

- a. We expect study data in electronic format will include all data entered from the case report forms. Please provide annotated case report forms showing the variables for all CRF fields and define.pdf files indentifying the raw variables and the derivations of any derived variables.
- b. Please provide a dataset documenting the audit trail for any values amended from the investigator's initial data entry.
- c. SAS codes for generating analysis data from the raw data and for statistical analyses need to be submitted in electronic format.
- d. Do not split dataset that are greater than >100 MB
- e. Please also see our responses for questions 7 and 8.
- f. Please also see additional comments, clinical, #6.

Additional Discussion During Meeting:

The sponsor agreed to all of the specifications detailed above in a through f, but wanted to discuss comment b further. The Division explained that they would like to see how the data evolved (through reviewing the audit trail) and that this would help the Division put the data in context. The Division reiterated their request for the audit trail to be able to detail what was changed and when. The original and final/cleaned data should be linked and fully queryable.

17. Does the Division agree that a Pediatric Waiver for ticagrelor is appropriate for the proposed indication?

Preliminary Response:

Your request for a waiver will be reviewed by the Pediatric Review Committee (PeRC) once your NDA is submitted, but the Division agrees that a waiver would be appropriate.

Additional Discussion During Meeting:

No further discussion.

Additional Comments:

Clinical

1. Submit copies of the original versions of all protocols, statistical analysis plans, DSMB and adjudication committee charters, and all amendments.

Additional Discussion During Meeting:

The sponsor agreed.

2. Submit copies of minutes of all investigator, DSMB, and adjudication committee meetings.

Additional Discussion During Meeting:

The sponsor will provide presentation materials from the investigator meetings and the DSMB minutes (provided to the sponsor after database lock). The adjudication committee actions will be provided (as part of the clinical database) but there are no minutes from these meetings to provide. The sponsor added that they have a list of the information that was provided to the committee in the database and who performed the adjudication, but not how each member voted. The Agency noted that this is useful for congruency.

3. If investigator instructions were produced in addition to the protocol and investigator brochure, please submit copies of all such instructions.

Additional Discussion During Meeting:

The sponsor said that these would be provided and were produced if there were any changes to the protocol during the trial.

4. Submit copies (in SAS transport format) of randomization lists and, if used, IVRS datasets.

Additional Discussion During Meeting:

The sponsor agreed.

5. Submit copies (in SAS transport format) of all datasets used to track adjudications.

Additional Discussion During Meeting:

See Additional Clinical Comment #2.

6. For PLATO, we would appreciate receiving a combined analysis dataset (SAS Transport file), including one record per subject screened, that includes the following variables:

Study Information:

Subject ID, subject enrolled (Y/N), subject in efficacy population (Y/N), subject in safety population (Y/N), date/time of randomization. Please provide a variable for enrollment by study half, i.e., find the median date of study enrollment and characterize enrolled subjects as those enrolled in the first or second half (1 or 2).

Demographics:

Sex, race/ethnicity, age, weight, BMI, weight <60 kg (Y/N), weight quintile, weight quintile for males, weight quintile for females, location U.S. (Y/N), region (i.e., North America, Eastern Europe, Western Europe, etc.).

Study Medications:

Treatment assignment (for efficacy analyses), treatment designation for safety analyses (“as treated”), date/time of initial dose, date/time of last dose, total days of treatment, total dose received. In addition, please provide the study medication lot numbers for the loading dose, as well as the initial lot used for the maintenance dose, if available.

Index Event:

Please provide variables specific to the patient population, i.e., presentation (STEMI, NSTEMI, UA), anterior MI location (Y/N/unknown), date/time of symptom onset, date/time of coronary arteriogram, and date/time of PCI. Please characterize subjects into quintiles based on symptom to PCI time, and symptom to time of study drug loading dose. Please provide a variable for stent type (bare metal, drug eluting, none).

Baseline Disease Characteristics:

Please provide (Y/N): prior MI, prior stroke, prior TIA, hypertension, diabetes, metabolic syndrome, congestive heart failure, prior CABG, hepatic impairment, and renal impairment (none, moderate, severe, or unknown, by estimated GFR). If you have obtained genetic information on metabolic status for some or all subjects, please include an appropriate variable(s).

Key Concomitant Medication Use:

Use of proton pump inhibitors throughout first three study days (Y/N), use of proton pump inhibitors at any time during first three study days (Y/N), aspirin dose (in quintiles), GPIIb/IIIa inhibitors (Y/N), thrombolytic agents (alteplase, tenecteplase, other), antithrombin therapies, and tobacco use (current, former, never).

Outcomes:

Please provide the censors and time-to variables for: primary efficacy endpoint, individual components of the primary endpoint, stent thrombosis, first PLATO Major bleeding event, first PLATO (Major or Minor) bleeding event. In addition, please categorize non-fatal myocardial infarctions as those detected solely by elevations in enzymatic biomarkers, versus those detected as a result of a combination of factors (presumably clinical presentation and electrocardiographic change(s), in addition to enzyme elevations). For the latter characterization (i.e., myocardial infarctions detected by clinical presentation and electrocardiographic changes, in addition to enzyme increases), please provide the censors and time-to variables for the primary efficacy endpoint, as well as the censoring and time to variables for the non-fatal myocardial infarctions.

Other:

Please provide a Y/N variable for potential conflict of interest, i.e., subjects enrolled at sites where an investigator or member of DSMB have reported a potential conflict of interest(s) should receive a "yes" flag.

Clinical Pharmacology

1. We would like to inform you that the Office of Clinical Pharmacology is currently developing a new format for the clinical pharmacology/biopharmaceutics information to be included in the overall summary of NDA submissions. The new format includes the clinical pharmacology/ biopharmaceutics key-questions and it is expected that the response to each one of these questions will be linked to the corresponding study(ies), data, and labeling statements (as appropriate). This new summary-format is intended to facilitate and expedite our review process. Therefore, we would like that you use this new format for your NDA to-be-submitted. We will give you a copy of the document during our meeting on April 20th or shortly thereafter.

Please note that both summaries (i.e., standard format and new format) can also be included in your NDA submission.

2. We encourage you to perform a study to evaluate the pharmacodynamic interaction between Ticagrelor and one of the proton pump inhibitors and one of the H2 inhibitors.
3. Please include all PK and PD raw data in the submission in .xpt format.
4. Please include all raw genotype data from PK, PD, and efficacy studies in the submission in .xpt format.

Additional Discussion During Meeting:

Dr. Mishina informed the sponsor that the Clinical Pharmacology template will be available soon and hopefully will be part of the final pre-NDA meeting minutes. The sponsor asked for more detail behind request number 2. Dr. Mishina said that she wanted a clearer picture on the ticagrelor interaction (if any) with 2C19 and H2 blockers. The sponsor explained that in previous data from approximately 6300 subjects, the compound did not interact with 2C19. Dr. Mishina added that if the data in the NDA support this finding, a DDI study for this purpose is not needed.

Regarding comment #4, the sponsor said that there were no raw data available. The sponsor, however, noted that they will have raw data (platelet aggregation) on early responders/non-responders to clopidogrel (approximately 90 subjects). Dr. Pacanowski agreed to review what the sponsor could provide. The sponsor also agreed to provide genotype information on increased dyspnea and increased serum uric acid.

ACTION ITEMS

- Dr. Srinivasachar agreed to follow-up with the sponsor to clarify what details CMC would like to see in the NDA regarding the risk assessment of genotoxic impurities (Question number 1).
- The sponsor agreed to follow-up on the feasibility of providing the classifications of cases from the adjudication committee as a pdf in the NDA (Question number 8).
- Dr. Unger to discuss with the sponsor an effective way to capture PPI/H2 concomitant use data (Question 9).
- Dr. Mishina is planning to provide the sponsor with the Clinical Pharmacology template by the end of May 2009.

Meeting recorder: _____
Alison Blaus

Meeting concurrence: _____
Norman Stockbridge, M.D., Ph.D.

Draft: ab 29Apr09
Final: ab 14May09

RD:

Fortney 4May09
Srinivasachar 5May09
Hausner 7May09
Resnick 7May09
Lawrence 8May09
Hung 8May09
Mishina 10May09
Dorantes 11May09
Xu 12May09
Grant 12May09
Targum 13May09
Unger 13May09
Stockbridge 14May09

Linked Applications

Sponsor Name

Drug Name / Subject

IND 65808

ASTRAZENECA LP

AZD6140

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

/s/

ALISON L BLAUS

05/14/2009

NORMAN L STOCKBRIDGE

05/15/2009

Minutes of a Meeting

Meeting Date: December 8, 2005
Application: IND 65,808
AZD 6140

Sponsor: AstraZeneca
Type of Meeting: Type B
End of Phase 2

Date requested: October 12, 2005
Date Confirmed: October 18, 2005
Date Package Received: November 12, 2005

Meeting Chair: Robert Temple, M.D.
Meeting Recorder: Meg Pease-Fye, M.S.

FDA Participants:

Robert Temple, M.D., Director, Office of Drug Evaluation I
Norman Stockbridge, M.D., Ph.D., Acting Director, Division of Cardiovascular and Renal Products
Ellis Unger, M.D., Deputy Director, Division of Cardiovascular and Renal Products
Thomas Marciniak, M.D., Team Leader, Medical Officers
Salma Lemtouni, M.D., M.P.H., Medical Officer, Division of Cardiovascular and Renal Products
Mehul Desai, M.D., Medical Officer, Division of Cardiovascular and Renal Products
Elena Mishina, Ph.D., Reviewer, Clinical Pharmacology and Biopharmaceutics
Elizabeth Hausner, D.V.M., Reviewer, Pharmacology
James Hung, Ph.D., Director, Office of Biometrics I
John Lawrence, Ph.D., Team Leader, Office of Biometrics I
Ququan Liu, M.D., M.S., Reviewer, Office of Biometrics I
Edward Fromm, RPh., Chief, Project Management Staff
Meg Pease-Fye, M.S., Regulatory Health Project Manager

AstraZeneca Participants:

Scott Allendar, M.D., Drug Safety Physician
Scott Berkowitz, M.D., Senior Director, Clinical Research
Darshan Bhatt, M.D., Global Safety Physician
Kathleen Butler, M.D., Director, Clinical Pharmacology
Simon Clowes, B.Sc., Global Product Director
Philip de Vane, M.D., Executive Director, Development Brand Leader
Emery Gigger, Director, Regulatory Affairs
Jamie Huston, M.S., Associate Director, Regulatory Affairs
Howard Hutchinson, M.D., Vice President, Cardiovascular Clinical Development
James Li, Associate Director, Clinical Pharmacokinetics
Patrick Mitchell, M.A., Principle Statistician
Gary Peters, M.D., Executive Director, Medical Science
Anthony Rogers, Vice President, U.S., Regulatory
David Stong, Ph.D., Toxicology Team Leader
Mary Whealey, Global Regulatory Affairs Director
Mark Wickens, Ph.D., Global Statistical Scientist

Consultant:

(b) (4)

Background:

An original IND was submitted to the Division on June 29, 2003. A preIND meeting was held on December 5, 2002. AZD6140 is an oral ADP receptor antagonist intended to block ADP-mediated platelet activation and aggregation. This drug is being developed for the treatment of acute coronary syndrome, and secondary event prevention following a stroke or transient ischemic attack. In their briefing package, AZ submitted a draft Phase 3 protocol, draft statistical analysis plan, and a draft label. The Phase 3 study, PLATO, is a randomized, double-blind, parallel study of ACS patients comparing AZD6140 (180 mg bid) and clopidogrel (75 mg qd) on time to vascular death, MI, or stroke. The planned enrollment is 16,000, but the study is event-driven (1800 events). The hypothesis is that AZD6140 is a substrate for CYP3A and P-glycoprotein.

Meeting:

After introductions, all agreed to discuss the sponsor's submitted questions.

Questions:

1. Does the Division agree that the non-clinical data presented supports the proposed dosing for the Phase 3 PLATO study?

Agency Response: The Agency agrees.

2. Does the Division agree that the PLATO plan for the concomitant use of statins is acceptable?

Agency Response: AZD6104 is a moderate inhibitor of CYP3A, so AZ proposed that concomitant therapy with either simvastatin or lovastatin at doses higher than 40-mg should be avoided. The Agency finds this reasonable.

3. Does the Division agree that the exclusion criteria and instructions for use of concomitant medications in the PLATO study plan for strong cytochrome P450 3A inhibitors and strong inducers are appropriate?

Agency Response: The Agency agrees. Ketoconazole produces a 7-fold increase in AZD6140, so strong CYP3A inhibitors (antifungals, protease inhibitors, etc...) are prohibited. The dose of CYP3A-dependent statins (simvastatin, lovastatin) is limited to 40 mg. Other narrow therapeutic index drugs metabolized by CYP3A (cyclosporine, quinidine) are prohibited.

4. Does the Division agree that the PLATO plan for the concomitant use of P-glycoprotein substrates and/or inhibitors is acceptable?

Agency Response: The Agency agrees. The effect of AZD6140 on digoxin is about a 30% increase (at trough). "Close monitoring" of digoxin is planning around times of changes in AZD6140.

5. Does the Division agree that there is no need to have dose adjustments for the administration of AZD6140 with food?

Agency Response: The Agency agrees.

6. Does the Division agree that a thorough QTc study conducted in parallel with PLATO and routine electrocardiograms as proposed in PLATO is acceptable?

Agency Response: There was some discussion as to the timing of a QT study. AZ noted that both the hERG channel assay and Purkinje cell monitoring were clean, as were digital ECGs to date, and AZ is confident there is no effect on cardiac repolarization. In terms of dose selection, AZ noted that they intend to perform another ascending dose study. Although there were few events of cardiac pauses and ventricular rhythm abnormalities observed, they noted no increase in arrhythmias. They acknowledge that the numbers were small, particularly for syncope and bradycardic events, and they believe that a large outcome study is appropriate at this point to clarify the cardiac effects of AZD6140.

Dr. Marciniak asked about other receptor or ion channel activity in any of the screens performed. AZ noted there was some adenosine A3 receptor activity.

7. Does the Division agree that the emerging safety profile is acceptable for continuing into Phase 3?

Agency Response: Dr. Stockbridge asked if the dyspnea-like events related to the underlying respiratory problems might affect patients with COPD or asthma. AZ noted that the numbers in the completed studies were small, but they currently had no plans to exclude these patients from their trial.

The Division asked about CNS effects, specifically the safety pharmacology finding of respiratory effects, interactions with GABA receptors, and decreased threshold for seizures. AZ responded that distribution studies showed little effect on the brain, but perhaps some carotid or chemoreceptor activity. The Division noted that we are not convinced that these are not treatment-related. AZ acknowledged that these events are being investigated further and they will continue to watch as they move toward Phase 3.

8. Does the Division agree that clopidogrel provides an appropriate comparator for patients suffering from acute coronary syndromes (unstable angina, non-ST elevation myocardial infarction [NSTEMI] or ST elevation myocardial infarction [STEMI])?

Agency Response: The Agency finds this acceptable. AZ believes AZD6140 may be an appropriate alternative therapy for clopidogrel-resistant patients, which they estimate to be up to 30%. Dr. Temple suggested that AZ consider performing a separate study in this resistant population.

9. Will the proposed site selection plan provide the appropriate patient population to obtain approved labeling in the United States?

Agency Response: The Agency had no comment about site selection.

10. Does the Division agree that the loading dose regimen proposed for clopidogrel is acceptable?

Agency Response: The Agency finds this acceptable. AZ noted a trend among interventional cardiologists toward using a 600-mg loading as standard practice and proposed to leave this up to investigator discretion. Further, they stated that European IRBs, in particular, will not approve an application if the comparator is used off-label. Dr. Temple argued that if there is an early effect, similar to ACS trials where most of the benefit was observed within the first two weeks, (b) (4) An effective dose should be used, particularly if early effects are expected. Also, Dr. Temple noted that AZ could make a modest case to its investigators for using the higher loading dose, and if it is not mandated, the sponsor could use stratification to enhance interpretability of the data.

11. Does the Division agree that patients on moderate CYP3A inhibitors, for over 7 days, should be dosed with AZD6140 at 90 mg bd, and if the moderate inhibitor is stopped they should return to 180 mg bd?

Agency Response: AZ noted that dosing subjects on CYP3A inhibitors at 90 mg bid will not reduce blood concentration of AZD6140, but will maintain it at approximately the same level as on 180 mg bid when not on CYP3A inhibitors. The Agency thought that was a reasonable strategy.

12. Does the Division agree that for patients who develop clinical intolerance that could be attributed to AZD6140, it is reasonable to down-titrate from 180 mg bd to 90 mg bd, and if clinical intolerance resolves the AZD6140 doses should return to 180 mg bd at the discretion of the principal investigator?

Agency Response: AZ proposed that patients determined to be clinically intolerant drop down to 90-mg, since this trial is an intent-to-treat study, other than dropping out. AZ believes this step will be a small number of patients and this will be used as a last resort, but they opined that it is better to down titrate the dose than to lose a patient. The Agency agreed.

When asked about how AZ will blind the study, they responded that this will be double-blinded, and those on a moderate CYP 3A inhibitor, such as verapamil, will start at a lower dose. When asked about a dummy capsule for the lower strength, AZ replied that they plan corresponding placebos for both the 90-mg and 180-mg strengths. Thus, patients will be un-blinded in terms of low- versus high-dose, but the study will remain blinded as to whether a subject is receiving AZD or clopidogel (double dummy).

Dr. Lemtouni asked that subpopulation analyses be performed on the over-75 age group and AZ responded that they will take a look at this.

13. Does the Division agree that the composite primary endpoint of death due to vascular causes, myocardial infarction, and stroke, is appropriate for the PLATO study?

Agency Response: The Agency agrees that this is appropriate, but there was additional discussion. When asked if AZ was considering vascular mortality as a primary endpoint as in the COMMIT trial, AZ responded that they were not. Dr. Temple noted that antiplatelet agents seem to show better effects on recurrent infarcts than on mortality.

Dr. Stockbridge stressed the importance of the secondary endpoint hierarchy, and suggested that these be considered with great care.

Patients with events will be followed until death or until the end of the trial. Primary analysis is time to first event. Dr. Temple suggested continuing to track time to a second event, when applicable.

14. Does the Division agree with the definitions provided for the primary efficacy endpoints?

Agency Response: AZ clarified that transient ischemic attacks were part of the secondary endpoint but not a part of the primary endpoint. There are four secondary composite efficacy endpoints:

- (i) The time to first occurrence of any event from the composite of death from vascular causes, MI and stroke for the subgroup of patients with intent for invasive management at randomization (planned coronary angiography with revascularization if indicated during the index event hospitalization)
- (ii) The time to first occurrence of any event from the composite of all-cause mortality, MI, and stroke
- (iii) The time to first occurrence of any event from the composite of death from vascular causes, MI, stroke, severe recurrent cardiac ischemia and other serious arterial thrombotic events
- (iv) The time to first occurrence of any event from the composite of death from vascular causes, MI, stroke, severe recurrent cardiac ischemia, recurrent cardiac ischemia, TIA, pulmonary embolism (PE), deep vein thrombosis (DVT) and other serious thrombotic events

Dr. Stockbridge noted that in terms of silent (asymptomatic) MIs, the TPT (Thrombosis Prevention Trial) suggested serial ECG evidence of AMI (Q-waves) may occasionally be transient. Dr. Stockbridge asked AZ what they intend to do concerning this type of MI. AZ stated that they did not observe this, although with a larger trial they expect to see this occasionally. They will perform an ECG at discharge, and if Q wave is seen, it will be classified as an event, and will be counted as such even if this observation is not seen at a subsequent visit.

15. Does the Division agree with the statistical analysis comparing AZD6140 therapy (no separate consideration for the 2 dose levels) to clopidogrel therapy as the primary outcome analysis?

Agency Response: AZ clarified that this is an event-driven trial which will not stop until 1800 events are observed. Further, AZ does not intend to perform a separate analysis of 90-mg versus 180-mg because they anticipate that the 90-mg cohort will be small and not powered to be useful,

and it is expected that plasma levels will be similar to the 180-mg cohort. This will be clearly described in the label. The Agency said this was acceptable.

16. Does the Division agree with the ordering of the secondary outcome variables and their use in labeling?

Agency Response: There was discussion about the significance level for secondary endpoints if the study were terminated as a result of an interim analysis. Dr. Hung stated that it is controversial whether the same α as for the primary endpoint or a standard α (e.g., $\alpha=0.05$) should be used. Using a $\alpha=0.05$ would be problematic, but it would be excessively conservative using $\alpha=0.001$. He suggested that a α between 0.05 and 0.001 may be appropriate. Dr. Temple urged that the trial be stopped early only for a mortality benefit. Stopping for other reasons limits information, especially longer term data.

17. Does the Division agree that it is appropriate to include the subgroup of patients planned for invasive management as a secondary outcome variable and that this information can be included in the label?

Agency Response: Provided this is part of a valid plan for analyses of secondary endpoints, the Agency thought this was a reasonable plan.

18. Does the Division agree that the single PLATO study as described is sufficient to support the approval of AZD6140?

Agency Response: Dr. Stockbridge stated that a single trial at $p < 0.05$ against an active comparator can be compelling evidence of effectiveness. (b) (4)

19. Does the Division agree that cardiac ischemic events should not be reported as adverse events?

Agency Response: The Agency agrees.

20. Does the Division agree that the collection of concomitant medications proposed is acceptable?

Agency Response: The Agency finds this acceptable.

21. Does the Division agree with the proposed bleeding definitions?

Agency Response: The Agency agrees.

22. Does the Division agree that the planned safety laboratory collection for a subset of 8000 patients is acceptable for the PLATO study?

Agency Response: The Agency finds this reasonable. Dr. Stockbridge asked why in clinical chemistry, differentials will not be taken. AZ responded that they have not seen any value to looking at lymphocytes since they have done this in other studies and have not seen much. The Agency agrees as long as there are enough data to address this issue.

In terms of sparse sampling for pharmacokinetic analysis in subset populations, Drs. Stockbridge and Mishina recommended more than one sample per subject. Dr. Mishina recommended that AZ submit their plan for the PK/PD data analysis for review. Also, she recommended that a sample should be taken as close as possible to the time of a serious adverse event. AZ noted that this was attempted but that frequently patients do not go to the clinical site at the time of an event, choosing emergency services at other facilities. Dr. Unger noted that for early events, when patients are still hospitalized, there should be little difficulty obtaining sera. AZ agreed to give this issue more thought.

23. Does the Division agree that the data from the pharmacodynamic effect offset study in combination with the 30-day follow-up visit in PLATO are acceptable to evaluate the potential for clinical events after withdrawal of therapy?

Agency Response: The Agency agrees.

24. Does the Division agree that the time required for platelets to return to baseline aggregation, as determined in the pharmacodynamic effect offset study, could be included in the label?

Agency Response: The Agency agrees such data are relevant, but the language would be circumspect with regard to clinical implications.

25. Does the Division agree that the bleeding event information as it relates to the time from stop of study drug to coronary artery bypass graft (CABG), for both AZD6140 and clopidogrel, could be included in the label?

Agency Response: The Agency urged caution about the nature of any comparison claim.

26. Does the Division agree that [REDACTED] ^{(b) (4)} AZD6140 compared to clopidogrel can be made based on the PLATO study design?

Agency Response: See response to Question 18.

Date Minutes Drafted: December 14, 2005
Date Minutes Finalized: January 5, 2006

Signature minutes preparer: *{See appended electronic signature page}*
Meg Pease-Fye, M.S.

Concurrence, Chair:

{See appended electronic signature page}

Robert Temple, M.D.

Reviewed:

R. Temple

N. Stockbridge 12/23/05

E. Unger 12/22/05

T. Marciniak 12/20/05

S. Lemtouni 12/20/05

E. Mishina 12/20/05

A. Defelice 12.16.05

E. Hausner 12.19.05

K. Srinivasachar 12.15.2005

J. Lawrence 12.15.05

Q. Liu 12.15.2005

E. Fromm 12.22.2005

J. Hung 12.15.2005

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

/s/

Margaret Pease-Fye
1/5/2006 02:25:42 PM

Robert Temple
1/5/2006 04:19:28 PM