CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 22-433/S015

Trade Name: Brilinta®

Generic Name: ticagrelor

Sponsor: AstraZeneca Pharmaceuticals LP

Approval Date: 9/03/2015

Indication: BRILINTA is a $P2Y_{12}$ platelet inhibitor indicated to reduce the rate of cardiovascular death, myocardial infarction, and stroke in patients with acute coronary syndrome (ACS) or a history of myocardial infarction (MI). For at least the first 12 months following ACS, it is superior to clopidogrel. BRILINTA also reduces the rate of stent thrombosis in patients who have been stented for treatment of ACS.

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APPLICATION NUMBER:

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-433/S015

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22433-S015

SUPPLEMENT APPROVAL

AstraZeneca LP
ATTENTION: Robert Griffin
Director, Regulatory Affairs
One MedImmune Way
Gaithersburg, MD 20878

Dear Mr. Griffin:

Please refer to your Supplemental New Drug Application (sNDA) dated March 6, 2015, received March 6, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for BRILINTA (ticagrelor) 60 & 90 mg Tablets.

We acknowledge receipt of your amendments dated March 23 and 30, April 7, 10, 17, and 27, May 1, 8, 14, 19, 27, and 29, June 3, 9, 12, 16, 18, 22, and 30, July 1, 16, 23 (two), 28, and 31, and August 7, 2015.

This Prior Approval efficacy supplemental new drug application provides for the inclusion of data from the PEGASUS trial entitled, "A Randomized, Double-Blind, Placebo Controlled, Parallel Group, Multinational Trial, to Assess the Prevention of Thrombotic Events with Ticagrelor Compared to Placebo on a Background of Acetyl Salicylic Acid (ASA) Therapy in Patients with History of Myocardial Infarction".

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate container labels, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 22433/S-015**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

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

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable because acute coronary syndromes rarely occur in the pediatric population. Furthermore, the pathophysiology of acute coronary syndromes in children is generally different from its adult counterpart.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above, by fax to 301-847-8444, or electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call:

Alison Blaus, RAC
Senior Regulatory Project Manager
(301) 796-1138

Sincerely,

{See appended electronic signature page}

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

ENCLOSURES:
Content of Labeling
Carton and Container Labeling

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
09/03/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BRILINTA safely and effectively. See full prescribing information for BRILINTA.

BRILINTA® (ticagrelor) tablets, for oral use
Initial U.S. Approval: 2011

WARNING: (A) BLEEDING RISK, and (B) ASPIRIN DOSE AND BRILINTA EFFECTIVENESS

See full prescribing information for complete boxed warning.

BLEEDING RISK

- **BRILINTA, like other antiplatelet agents, can cause significant, sometimes fatal bleeding (5.1, 6.1).**
- **Do not use BRILINTA in patients with active pathological bleeding or a history of intracranial hemorrhage (4.1, 4.2).**
- **Do not start BRILINTA in patients undergoing urgent coronary artery bypass graft surgery (CABG) (5.1, 6.1).**
- **If possible, manage bleeding without discontinuing BRILINTA. Stopping BRILINTA increases the risk of subsequent cardiovascular events (5.4).**

ASPIRIN DOSE AND BRILINTA EFFECTIVENESS

- **Maintenance doses of aspirin above 100 mg reduce the effectiveness of BRILINTA and should be avoided (2.1, 5.2, 14.1).**

---------- RECENT MAJOR CHANGES ----------

Indications and Usage (1)	09/2015
Dosage and Administration (2)	09/2015
Contraindications (4)	09/2015
Warnings and Precautions (5)	09/2015

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

BRILINTA is a $P2Y_{12}$ platelet inhibitor indicated to reduce the rate of cardiovascular death, myocardial infarction, and stroke in patients with acute coronary syndrome (ACS) or a history of myocardial infarction (MI). For at least the first 12 months following ACS, it is superior to clopidogrel. BRILINTA also reduces the rate of stent thrombosis in patients who have been stented for treatment of ACS. (1)

---------- DOSAGE AND ADMINISTRATION ----------

Initiate treatment with 180 mg oral loading dose following an ACS event. Continue treatment with 90 mg twice daily during the first year after an ACS event. After one year, administer 60 mg twice daily. (2.1)
Use BRILINTA with a daily maintenance dose of aspirin of 75-100 mg. (2.1, 5.2)

---------- DOSAGE FORMS AND STRENGTHS ----------

- 60 mg and 90 mg tablets (3)

---------- CONTRAINDICATIONS ----------

- History of intracranial hemorrhage (4.1)
- Active pathological bleeding (4.2)
- Hypersensitivity to ticagrelor or any component of the product (4.3)

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

- Dyspnea was reported more frequently with BRILINTA than with control agents in clinical trials. Dyspnea resulting from BRILINTA is self-limiting. (5.3)
- Severe Hepatic Impairment: Likely increase in exposure to ticagrelor. (5.5)

---------- ADVERSE REACTIONS ----------

Most common adverse reactions are bleeding 12% and dyspnea 14%. (5.1, 5.3, 6.1)
To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

---------- DRUG INTERACTIONS ----------

- Avoid use with strong CYP3A inhibitors or CYP3A inducers. (7.1, 7.2)
- Patients receiving more than 40 mg per day of simvastatin or lovastatin may be at increased risk of statin-related adverse effects. (7.4)
- Monitor digoxin levels with initiation of or any change in BRILINTA. (7.5)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 09/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

Reference ID: 3815277

WARNING: (A) BLEEDING RISK, (B) ASPIRIN DOSE AND BRILINTA EFFECTIVENESS

A. BLEEDING RISK

- **BRILINTA, like other antiplatelet agents, can cause significant, sometimes fatal bleeding (5.1, 6.1).**
- **Do not use BRILINTA in patients with active pathological bleeding or a history of intracranial hemorrhage (4.1, 4.2).**
- **Do not start BRILINTA in patients undergoing urgent coronary artery bypass graft surgery (CABG) (5.1, 6.1).**
- **If possible, manage bleeding without discontinuing BRILINTA. Stopping BRILINTA increases the risk of subsequent cardiovascular events (5.4).**

B. ASPIRIN DOSE AND BRILINTA EFFECTIVENESS

- **Maintenance doses of aspirin above 100 mg reduce the effectiveness of BRILINTA and should be avoided (2.1, 5.2, 14.1).**

1 INDICATIONS AND USAGE

BRILINTA is indicated to reduce the rate of cardiovascular death, myocardial infarction, and stroke in patients with acute coronary syndrome (ACS) or a history of myocardial infarction (MI). For at least the first 12 months following ACS, it is superior to clopidogrel.

BRILINTA also reduces the rate of stent thrombosis in patients who have been stented for treatment of ACS *[see Clinical Studies (14.1)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing

In the management of ACS, initiate BRILINTA treatment with a 180 mg loading dose. Administer 90 mg twice daily during the first year after an ACS event. After one year administer 60 mg twice daily.

Do not administer BRILINTA with another oral P2Y12 platelet inhibitor.

Use BRILINTA with a daily maintenance dose of aspirin of 75-100 mg *[see Warnings (5.2) and Clinical Studies (14.1)]*. A patient who misses a dose of BRILINTA should take one tablet (their next dose) at its scheduled time.

2.2 Administration

For patients who are unable to swallow tablets whole, BRILINTA tablets can be crushed, mixed with water and drunk. The mixture can also be administered via a nasogastric tube (CH8 or greater) *[see Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

BRILINTA (ticagrelor) 90 mg is supplied as a round, biconvex, yellow, film-coated tablet marked with a “90” above “T” on one side.

BRILINTA (ticagrelor) 60 mg is supplied as a round, biconvex, pink, film-coated tablet marked with “60” above “T” on one side.

4 CONTRAINDICATIONS

4.1 History of Intracranial Hemorrhage

BRILINTA is contraindicated in patients with a history of intracranial hemorrhage (ICH) because of a high risk of recurrent ICH in this population *[see Clinical Studies (14.1)]*.

4.2 Active Bleeding

BRILINTA is contraindicated in patients with active pathological bleeding such as peptic ulcer or intracranial hemorrhage *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*.

4.3 Hypersensitivity

BRILINTA is contraindicated in patients with hypersensitivity (e.g., angioedema) to ticagrelor or any component of the product.

5 WARNINGS AND PRECAUTIONS

5.1 General Risk of Bleeding

Drugs that inhibit platelet function including BRILINTA increase the risk of bleeding *[see Adverse Reactions (6.1)]*.

If possible, manage bleeding without discontinuing BRILINTA. Stopping BRILINTA increases the risk of subsequent cardiovascular events *[see Warnings and Precautions (5.4) and Adverse Reactions (6.1)]*.

5.2 Concomitant Aspirin Maintenance Dose

In PLATO the use of BRILINTA with maintenance doses of aspirin above 100 mg decreased the effectiveness of BRILINTA. Therefore, after the initial loading dose of aspirin, use BRILINTA with a maintenance dose of aspirin of 75-100 mg *[see Dosage and Administration (2.1) and Clinical Studies (14.1)]*.

5.3 Dyspnea

In clinical trials, about 14% of patients treated with BRILINTA developed dyspnea. Dyspnea was usually mild to moderate in intensity and often resolved during continued treatment, but led to study drug discontinuation in 0.9% of BRILINTA and 0.1% of clopidogrel patients in PLATO and 4.3% of BRILINTA 60 mg and 0.7% on aspirin alone patients in PEGASUS.

In a substudy of PLATO, 199 subjects underwent pulmonary function testing irrespective of whether they reported dyspnea. There was no indication of an adverse effect on pulmonary function assessed after one month or after at least 6 months of chronic treatment.

If a patient develops new, prolonged, or worsened dyspnea that is determined to be related to BRILINTA, no specific treatment is required; continue BRILINTA without interruption if possible. In the case of intolerable dyspnea requiring discontinuation of BRILINTA, consider prescribing another antiplatelet agent.

5.4 Discontinuation of BRILINTA

Discontinuation of BRILINTA will increase the risk of myocardial infarction, stroke, and death. If BRILINTA must be temporarily discontinued (e.g., to treat bleeding or for significant surgery), restart it as soon as possible. When possible, interrupt therapy with BRILINTA for five days prior to surgery that has a major risk of bleeding. Resume BRILINTA as soon as hemostasis is achieved.

5.5 Severe Hepatic Impairment

Avoid use of BRILINTA in patients with severe hepatic impairment. Severe hepatic impairment is likely to increase serum concentration of ticagrelor. There are no studies of BRILINTA patients with severe hepatic impairment *[see Clinical Pharmacology (12.3)]*.

6 ADVERSE REACTIONS

The following adverse reactions are also discussed elsewhere in the labeling:

- Bleeding *[see Warnings and Precautions (5.1)]*
- Dyspnea *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

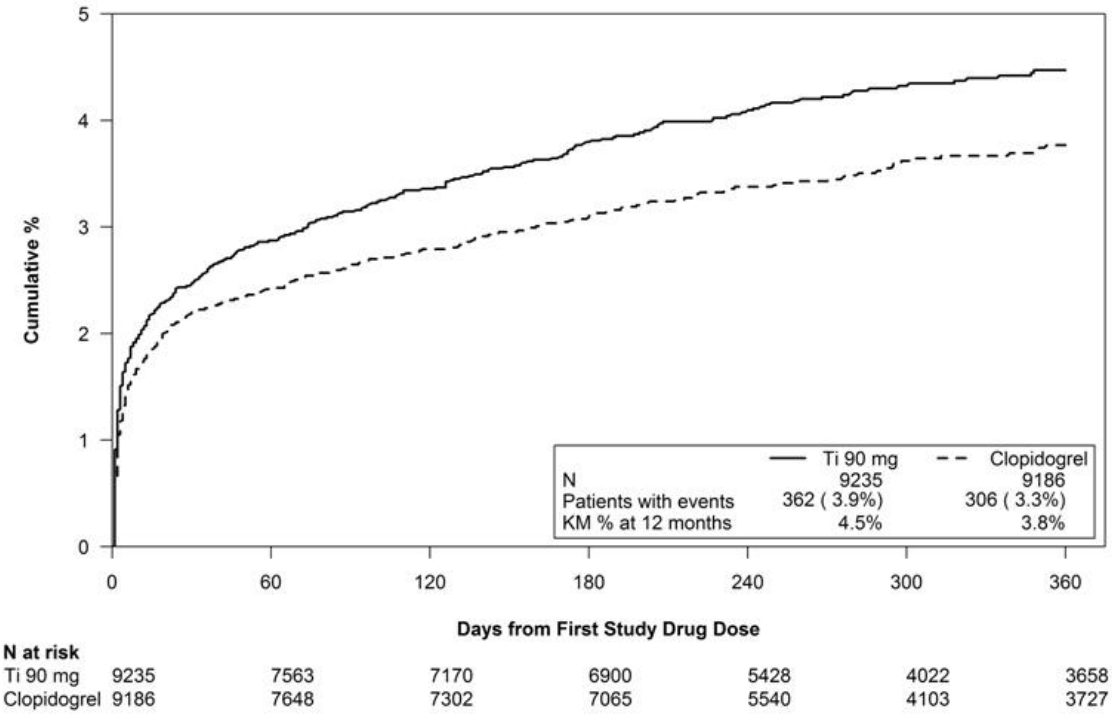
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

BRILINTA has been evaluated for safety in more than 27000 patients, including more than 13000 patients treated for at least 1 year.

Bleeding in PLATO (Reduction in risk of thrombotic events in ACS)

Figure 1 is a plot of time to the first non-CABG major bleeding event.

Figure 1 - Kaplan-Meier estimate of time to first non-CABG PLATO-defined major bleeding event (PLATO)



Frequency of bleeding in PLATO is summarized in Tables 1 and 2. About half of the Non-CABG major bleeding events were in the first 30 days .

Table 1 – Non-CABG related bleeds (PLATO)

	BRILINTA* **N=9235**	**Clopidogrel N=9186**
	n (%) patients with event	**n (%) patients with event**
PLATO Major + Minor	713 (7.7)	567 (6.2)
Major	362 (3.9)	306 (3.3)
Fatal/Life-threatening	171 (1.9)	151 (1.6)
Fatal	15 (0.2)	16 (0.2)
Intracranial hemorrhage (Fatal/Life-threatening)	26 (0.3)	15 (0.2)

90 mg BID

PLATO Minor bleed: requires medical intervention to stop or treat bleeding.

PLATO Major bleed: any one of the following: fatal; intracranial; intrapericardial with cardiac tamponade; hypovolemic shock or severe hypotension requiring intervention; significantly disabling (e.g., intraocular with permanent vision loss); associated with a decrease in Hb of at least 3 g/dL (or a fall in hematocrit (Hct) of at least 9%); transfusion of 2 or more units.

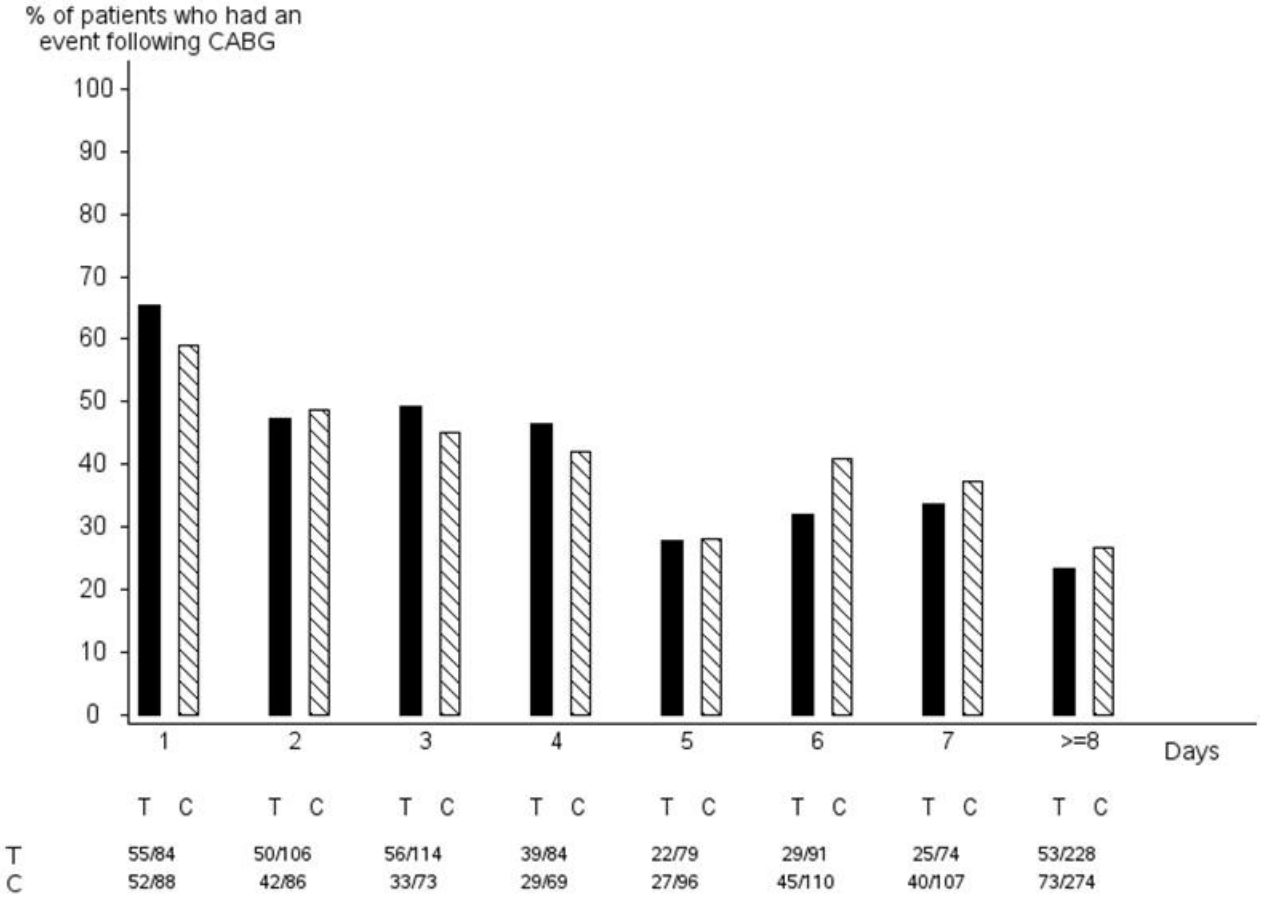
PLATO Major bleed, fatal/life-threatening: any major bleed as described above and associated with a decrease in Hb of more than 5 g/dL (or a fall in hematocrit (Hct) of at least 15%); transfusion of 4 or more units.

Fatal: A bleeding event that directly led to death within 7 days.

No baseline demographic factor altered the relative risk of bleeding with BRILINTA compared to clopidogrel.

In PLATO, 1584 patients underwent CABG surgery. The percentages of those patients who bled are shown in Figure 2 and Table 2.

Figure 2 – 'Major fatal/life-threatening' CABG-related bleeding by days from last dose of study drug to CABG procedure (PLATO)



X-axis is days from last dose of study drug prior to CABG.
The PLATO protocol recommended a procedure for withholding study drug prior to CABG or other major surgery without unblinding. If surgery was elective or non-urgent, study drug was interrupted temporarily, as follows: If local practice was to allow antiplatelet effects to dissipate before surgery, capsules (blinded clopidogrel) were withheld 5 days before surgery and tablets (blinded ticagrelor) were withheld for a minimum of 24 hours and a maximum of 72 hours before surgery. If local practice was to perform surgery without waiting for dissipation of antiplatelet effects capsules and tablets were withheld 24 hours prior to surgery and use of aprotinin or other haemostatic agents was allowed. If local practice was to use IPA monitoring to determine when surgery could be performed both the capsules and tablets were withheld at the same time and the usual monitoring procedures followed.
T Ticagrelor; C Clopidogrel.

Table – 2 CABG-related bleeding (PLATO)

	BRILINTA* N=770	**Clopidogrel N=814**
	n (%) patients with event	**n (%) patients with event**
PLATO Total Major	626 (81.3)	666 (81.8)
Fatal/Life-threatening	337 (43.8)	350 (43.0)
Fatal	6 (0.8)	7 (0.9)

* 90 mg BID

PLATO Major bleed: any one of the following: fatal; intracranial; intrapericardial with cardiac tamponade; hypovolemic shock or severe hypotension requiring intervention; significantly disabling (e.g., intraocular with permanent vision loss); associated with a decrease in Hb of at least 3 g/dL (or a fall in hematocrit (Hct) of at least 9%); transfusion of 2 or more units.

PLATO Major bleed, fatal/life-threatening: any major bleed as described above and associated with a decrease in Hb of more than 5 g/dL (or a fall in hematocrit (Hct) of at least 15%); transfusion of 4 or more units.

When antiplatelet therapy was stopped 5 days before CABG, major bleeding occurred in 75% of BRILINTA treated patients and 79% on clopidogrel.

Other Adverse Reactions in PLATO

Adverse reactions that occurred at a rate of 4% or more in PLATO are shown in Table 3.

Table 3 – Percentage of patients reporting non-hemorrhagic adverse reactions at least 4% or more in either group and more frequently on BRILINTA (PLATO)

	BRILINTA* N=9235	Clopidogrel N=9186
Dyspnea	13.8	7.8
Dizziness	4.5	3.9
Nausea	4.3	3.8

* 90 mg BID

Bleeding in PEGASUS (Secondary Prevention in Patients with a History of Myocardial Infarction)

Overall outcome of bleeding events in the PEGASUS study are shown in Table 4.

Table 4 – Bleeding events (PEGASUS)

	BRILINTA* + Aspirin N=6958		Aspirin Alone N=6996	
	n (%) patients with event	Events / 100 pt yrs	n (%) patients with event	Events / 100 pt yrs
TIMI Major	115 (1.7)	0.78	54 (0.8)	0.34
Fatal	11 (0.2)	0.08	12 (0.2)	0.08
Intracranial hemorrhage	28 (0.4)	0.19	23 (0.3)	0.14
TIMI Major or Minor	168 (2.4)	1.15	72 (1.0)	0.45

* 60 mg BID
TIMI Major: Fatal bleeding, OR any intracranial bleeding, OR clinically overt signs of hemorrhage associated with a drop in hemoglobin (Hgb) of ≥5 g/dL, or a fall in hematocrit (Hct) of 15%.
Fatal: A bleeding event that directly led to death within 7 days.
TIMI Minor: Clinically apparent with 3-5 g/dL decrease in hemoglobin.

The bleeding profile of BRILINTA 60 mg compared to aspirin alone was consistent across multiple pre-defined subgroups (e.g., by age, gender, weight, race, geographic region, concurrent conditions, concomitant therapy, stent, and medical history) for TIMI Major and TIMI Major or Minor bleeding events.

Other Adverse Reactions in PEGASUS

Adverse reactions that occurred in PEGASUS at rates of 3% or more are shown in Table 5.

Table 5 – Non-hemorrhagic adverse reactions reported in >3.0% of patients in the ticagrelor 60 mg treatment group (PEGASUS)

	BRILINTA* + Aspirin N=6958	Aspirin Alone N=6996
Dyspnea	14.2	5.5
Dizziness	4.5	4.1
Diarrhea	3.3	2.5

60 mg BID

Bradycardia

In a Holter substudy of about 3000 patients in PLATO, more patients had ventricular pauses with BRILINTA (6.0%) than with clopidogrel (3.5%) in the acute phase; rates were 2.2% and 1.6% respectively after 1 month. PLATO and PEGASUS excluded patients at increased risk of bradycardic events (e.g., patients who have sick sinus syndrome, 2nd or 3rd degree AV block, or bradycardic-related syncope and not protected with a pacemaker). In PLATO, syncope, pre-syncope and loss of consciousness were reported by 1.7% and 1.5% of BRILINTA 90 mg and clopidogrel patients, respectively. In PEGASUS, syncope was reported by 1.2% and 0.9% of patients on BRILINTA 60 mg and aspirin alone, respectively.

Lab abnormalities

Serum Uric Acid:

In PLATO, serum uric acid levels increased approximately 0.6 mg/dL from baseline on BRILINTA 90 mg and approximately 0.2 mg/dL on clopidogrel. The difference disappeared within 30 days of discontinuing treatment. Reports of gout did not differ between treatment groups in PLATO (0.6% in each group).

In PEGASUS, serum uric acid levels increased approximately 0.2 mg/dL from baseline on BRILINTA 60 mg and no elevation was observed on aspirin alone. Gout occurred more commonly in patients on BRILINTA than in patients on aspirin alone (1.5%,1.1%). Mean serum uric acid concentrations decreased after treatment was stopped.

Serum Creatinine:

In PLATO, a >50% increase in serum creatinine levels was observed in 7.4% of patients receiving BRILINTA 90 mg compared to 5.9% of patients receiving clopidogrel. The increases typically did not progress with ongoing treatment and often decreased with continued therapy. Evidence of reversibility upon discontinuation was observed even in those with the greatest on treatment increases. Treatment groups in PLATO did not differ for renal-related serious adverse events such as acute renal failure, chronic renal failure, toxic nephropathy, or oliguria.

In PEGASUS, serum creatinine concentration increased by >50% in approximately 4% of patients receiving BRILINTA 60 mg, similar to aspirin alone. The frequency of renal related adverse events was similar for ticagrelor and aspirin alone regardless of age and baseline renal function.

7 DRUG INTERACTIONS

7.1 Strong CYP3A Inhibitors

Strong CYP3A inhibitors substantially increase ticagrelor exposure and so increase the risk of dyspnea, bleeding, and other adverse events. Avoid use of strong inhibitors of CYP3A (e.g., ketoconazole, itraconazole, voriconazole, clarithromycin, nefazodone, ritonavir, saquinavir, nelfinavir, indinavir, atazanavir and telithromycin) *[see Clinical Pharmacology (12.3)]*.

7.2 Strong CYP3A Inducers

Strong CYP3A inducers substantially reduce ticagrelor exposure and so decrease the efficacy of ticagrelor. Avoid use with strong inducers of CYP3A (e.g., rifampin, phenytoin, carbamazepine and phenobarbital) *[see Clinical Pharmacology (12.3)]*.

7.3 Aspirin

Use of BRILINTA with aspirin maintenance doses above 100 mg reduced the effectiveness of BRILINTA *[see Warnings and Precautions (5.2) and Clinical Studies (14.1)]*.

7.4 Simvastatin, Lovastatin

BRILINTA increases serum concentrations of simvastatin and lovastatin because these drugs are metabolized by CYP3A4. Avoid simvastatin and lovastatin doses greater than 40 mg *[see Clinical Pharmacology (12.3)]*.

7.5 Digoxin

BRILINTA inhibits the P-glycoprotein transporter; monitor digoxin levels with initiation of or change in BRILINTA therapy *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C:

There are no adequate and well-controlled studies of BRILINTA use in pregnant women. In animal studies, ticagrelor caused structural abnormalities at maternal doses about 5 to 7 times the maximum recommended human dose (MRHD) based on body surface area. BRILINTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In reproductive toxicology studies, pregnant rats received ticagrelor during organogenesis at doses from 20 to 300 mg/kg/day. 20 mg/kg/day is approximately the same as the MRHD of 90 mg twice daily for a 60 kg human on a mg/m^2 basis. Adverse outcomes in offspring occurred at doses of 300 mg/kg/day (16.5 times the MRHD on a mg/m^2 basis) and included supernumerary liver lobe and ribs, incomplete ossification of sternebrae, displaced articulation of pelvis, and misshapen/misaligned sternebrae. At the mid-dose of 100 mg/kg/day, delayed development of liver and skeleton was seen. When pregnant rabbits received ticagrelor during organogenesis at doses from 21 to 63 mg/kg/day, fetuses exposed to the highest maternal dose of 63 mg/kg/day (6.8 times the MRHD on a mg/m^2 basis) had delayed gall bladder development and incomplete ossification of the hyoid, pubis and sternebrae occurred.

In a prenatal/postnatal study, pregnant rats received ticagrelor at doses of 10 to 180 mg/kg/day during late gestation and lactation. Pup death and effects on pup growth were observed at 180 mg/kg/day (approximately 10 times the MRHD on a mg/m^2 basis). Relatively minor effects such as delays in pinna unfolding and eye opening occurred at doses of 10 and 60 mg/kg (approximately one-half and 3.2 times the MRHD on a mg/m^2 basis).

8.3 Nursing Mothers

It is not known whether ticagrelor or its active metabolites are excreted in human milk. Ticagrelor is excreted in rat milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from BRILINTA, a decision should be made whether to discontinue nursing or to discontinue BRILINTA.

8.4 Pediatric Use

The safety and effectiveness of BRILINTA in pediatric patients have not been established.

8.5 Geriatric Use

In PLATO and PEGASUS, about half of patients in each study were ≥65 years of age and about 15% were ≥75 years of age. No overall differences in safety or effectiveness were observed between elderly and younger patients.

8.6 Hepatic Impairment

Ticagrelor is metabolized by the liver and impaired hepatic function can increase risks for bleeding and other adverse events. Avoid use of BRILINTA in patients with severe hepatic impairment. There is limited experience with BRILINTA in patients with moderate hepatic impairment; consider the risks and benefits of treatment, noting the probable increase in exposure to ticagrelor. No dosage adjustment is needed in patients with mild hepatic impairment *[see Contraindications (4), Warnings and Precautions (5.5) and Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

No dosage adjustment is needed in patients with renal impairment. Patients receiving dialysis have not been studied *[see Clinical Pharmacology (12.3)]*.

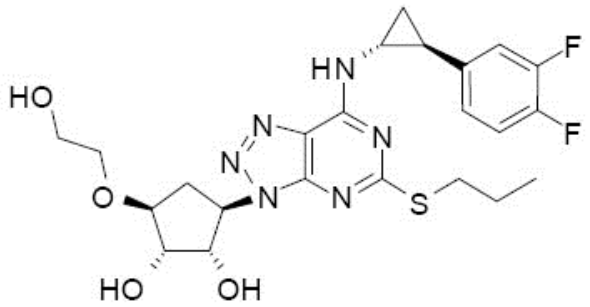
10 OVERDOSAGE

There is currently no known treatment to reverse the effects of BRILINTA, and ticagrelor is not expected to be dialyzable. Treatment of overdose should follow local standard medical practice. Bleeding is the expected pharmacologic effect of overdosing. If bleeding occurs, appropriate supportive measures should be taken.

Other effects of overdose may include gastrointestinal effects (nausea, vomiting, diarrhea) or ventricular pauses. Monitor the ECG.

11 DESCRIPTION

BRILINTA contains ticagrelor, a cyclopentyltriazolopyrimidine, inhibitor of platelet activation and aggregation mediated by the $P2Y_{12}$ ADP-receptor. Chemically it is (1*S*,2*S*,3*R*,5*S*)-3-[7-{[(1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl]amino}-5-(propylthio)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-3-yl]-5-(2-hydroxyethoxy)cyclopentane-1,2-diol. The empirical formula of ticagrelor is $C_{23}H_{28}F_2N_6O_4S$ and its molecular weight is 522.57. The chemical structure of ticagrelor is:



Ticagrelor is a crystalline powder with an aqueous solubility of approximately 10 µg/mL at room temperature.

BRILINTA 90 mg tablets for oral administration contain 90 mg of ticagrelor and the following ingredients: mannitol, dibasic calcium phosphate, sodium starch glycolate, hydroxypropyl cellulose, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, talc, polyethylene glycol 400, and ferric oxide yellow.

BRILINTA 60 mg tablets for oral administration contain 60 mg of ticagrelor and the following ingredients: mannitol, dibasic calcium phosphate, sodium starch glycolate, hydroxypropyl cellulose, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol 400, ferric oxide black, and ferric oxide red.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ticagrelor and its major metabolite reversibly interact with the platelet $P2Y_{12}$ ADP-receptor to prevent signal transduction and platelet activation. Ticagrelor and its active metabolite are approximately equipotent.

12.2 Pharmacodynamics

The inhibition of platelet aggregation (IPA) by ticagrelor and clopidogrel was compared in a 6 week study examining both acute and chronic platelet inhibition effects in response to 20 μM ADP as the platelet aggregation agonist.

The onset of IPA was evaluated on Day 1 of the study following loading doses of 180 mg ticagrelor or 600 mg clopidogrel. As shown in Figure 3, IPA was higher in the ticagrelor group at all time points. The maximum IPA effect of ticagrelor was reached at around 2 hours, and was maintained for at least 8 hours.
The offset of IPA was examined after 6 weeks on ticagrelor 90 mg twice daily or clopidogrel 75 mg daily, again in response to 20 μM ADP.

As shown in Figure 4, mean maximum IPA following the last dose of ticagrelor was 88% and 62% for clopidogrel. The insert in Figure 4 shows that after 24 hours, IPA in the ticagrelor group (58%) was similar to IPA in clopidogrel group (52%), indicating that patients who miss a dose of ticagrelor would still maintain IPA similar to the trough IPA of patients treated with clopidogrel. After 5 days, IPA in the ticagrelor group was similar to IPA in the placebo group. It is not known how either bleeding risk or thrombotic risk track with IPA, for either ticagrelor or clopidogrel.

Figure 3 – Mean inhibition of platelet aggregation (±SE) following single oral doses of placebo, 180 mg ticagrelor or 600 mg clopidogrel

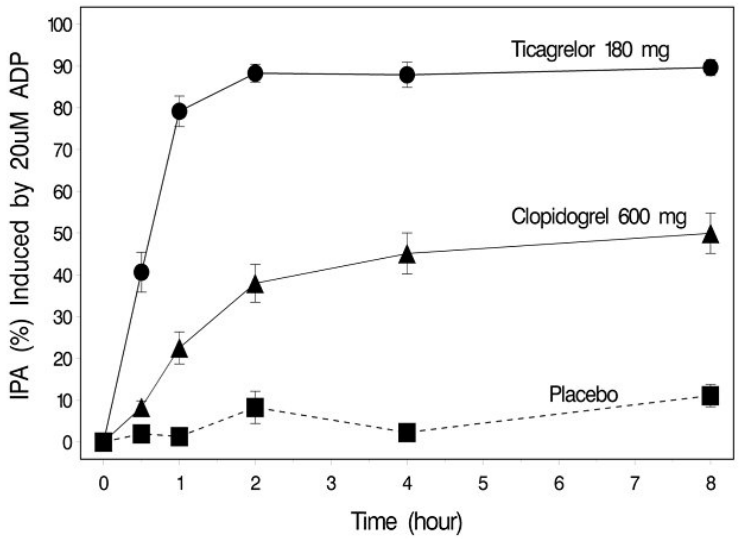
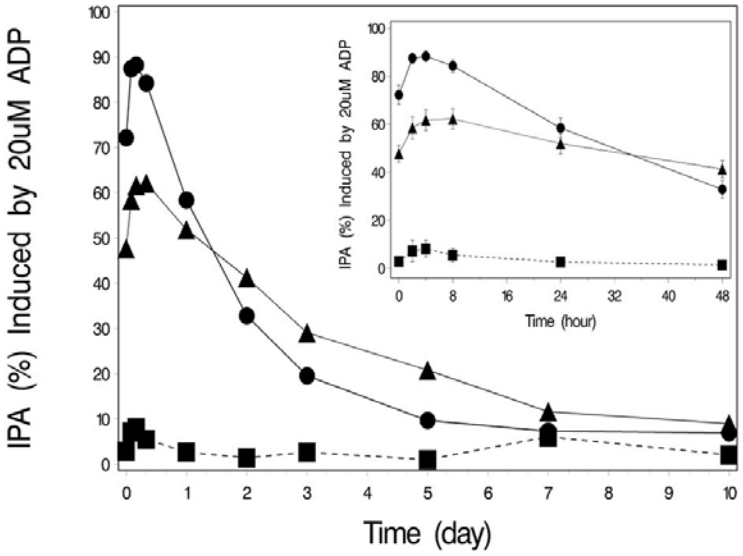


Figure 4 – Mean inhibition of platelet aggregation (IPA) following 6 weeks on placebo, ticagrelor 90 mg twice daily, or clopidogrel 75 mg daily



● Ticagrelor ▲Clopidogrel ■ Placebo

Transitioning from clopidogrel to BRILINTA resulted in an absolute IPA increase of 26.4% and from BRILINTA to clopidogrel resulted in an absolute IPA decrease of 24.5%. Patients can be transitioned from clopidogrel to BRILINTA without interruption of antiplatelet effect *[see Dosage and Administration (2)]*.

12.3 Pharmacokinetics

Ticagrelor demonstrates dose proportional pharmacokinetics, which are similar in patients and healthy volunteers.

Absorption

BRILINTA can be taken with or without food. Absorption of ticagrelor occurs with a median t_{max} of 1.5 h (range 1.0–4.0). The formation of the major circulating metabolite AR-C124910XX (active) from ticagrelor occurs with a median t_{max} of 2.5 h (range 1.5-5.0).

The mean absolute bioavailability of ticagrelor is about 36% (range 30%-42%). Ingestion of a high-fat meal had no effect on ticagrelor C_{max}, but resulted in a 21% increase in AUC. The C_{max} of its major metabolite was decreased by 22% with no change in AUC.

BRILINTA as crushed tablets mixed in water, given orally or administered through a nasogastric tube into the stomach, is bioequivalent to whole tablets (AUC and C_{max} within 80-125% for ticagrelor and AR-C124910XX) with a median t_{max} of 1.0 hour (range 1.0 – 4.0) for ticagrelor and 2.0 hours (range 1.0 –8.0) for AR-C124910XX.

Distribution

The steady state volume of distribution of ticagrelor is 88 L. Ticagrelor and the active metabolite are extensively bound to human plasma proteins (>99%).

Metabolism

CYP3A4 is the major enzyme responsible for ticagrelor metabolism and the formation of its major active metabolite. Ticagrelor and its major active metabolite are weak P-glycoprotein substrates and inhibitors. The systemic exposure to the active metabolite is approximately 30-40% of the exposure of ticagrelor.

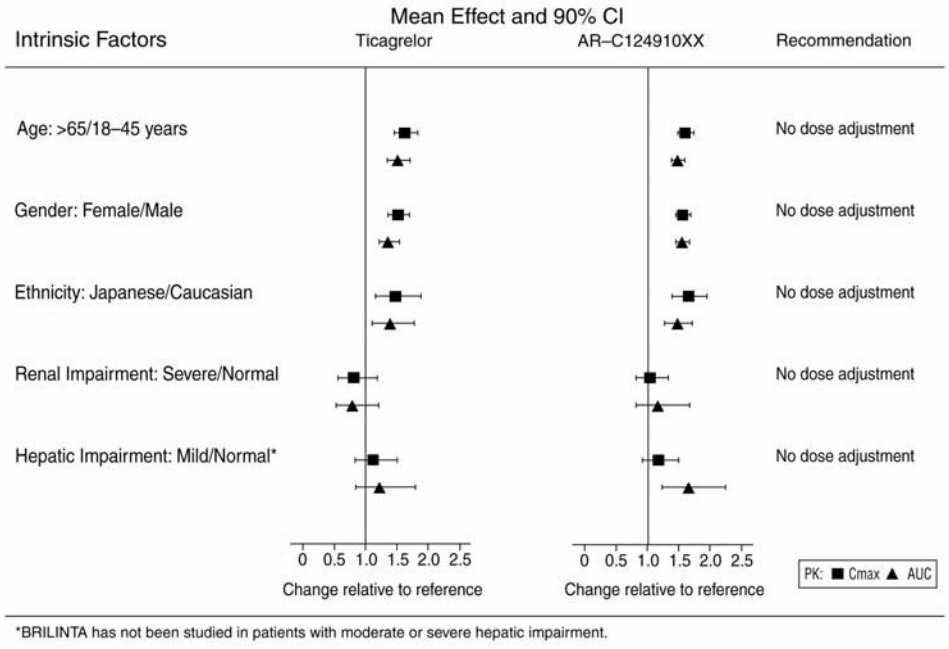
Excretion

The primary route of ticagrelor elimination is hepatic metabolism. When radiolabeled ticagrelor is administered, the mean recovery of radioactivity is approximately 84% (58% in feces, 26% in urine). Recoveries of ticagrelor and the active metabolite in urine were both less than 1% of the dose. The primary route of elimination for the major metabolite of ticagrelor is most likely to be biliary secretion. The mean $t_{1/2}$ is approximately 7 hours for ticagrelor and 9 hours for the active metabolite.

Specific Populations

The effects of age, gender, ethnicity, renal impairment and mild hepatic impairment on the pharmacokinetics of ticagrelor are presented in Figure 5. Effects are modest and do not require dose adjustment.

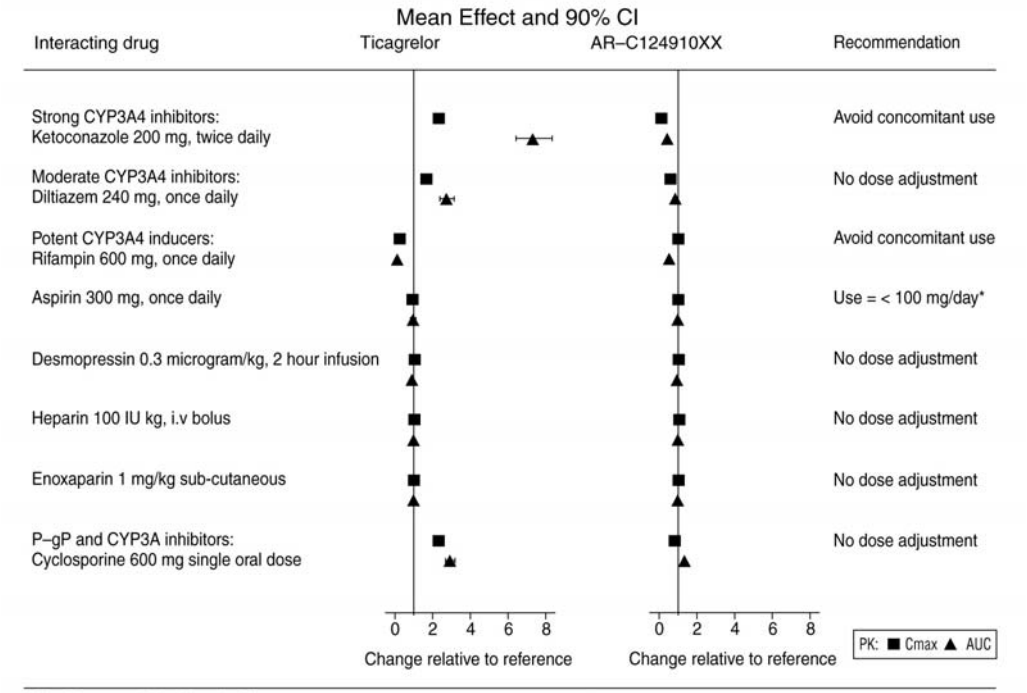
Figure 5 – Impact of intrinsic factors on the pharmacokinetics of ticagrelor



Effects of Other Drugs on BRILINTA

CYP3A4 is the major enzyme responsible for ticagrelor metabolism and the formation of its major active metabolite. The effects of other drugs on the pharmacokinetics of ticagrelor are presented in Figure 6 as change relative to ticagrelor given alone (test/reference). Strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, and clarithromycin) substantially increase ticagrelor exposure. Moderate CYP3A inhibitors have lesser effects (e.g., diltiazem). CYP3A inducers (e.g., rifampin) substantially reduce ticagrelor blood levels. P-gp inhibitors (e.g., cyclosporine) increase ticagrelor exposure.

Figure 6 – Effect of co-administered drugs on the pharmacokinetics of ticagrelor

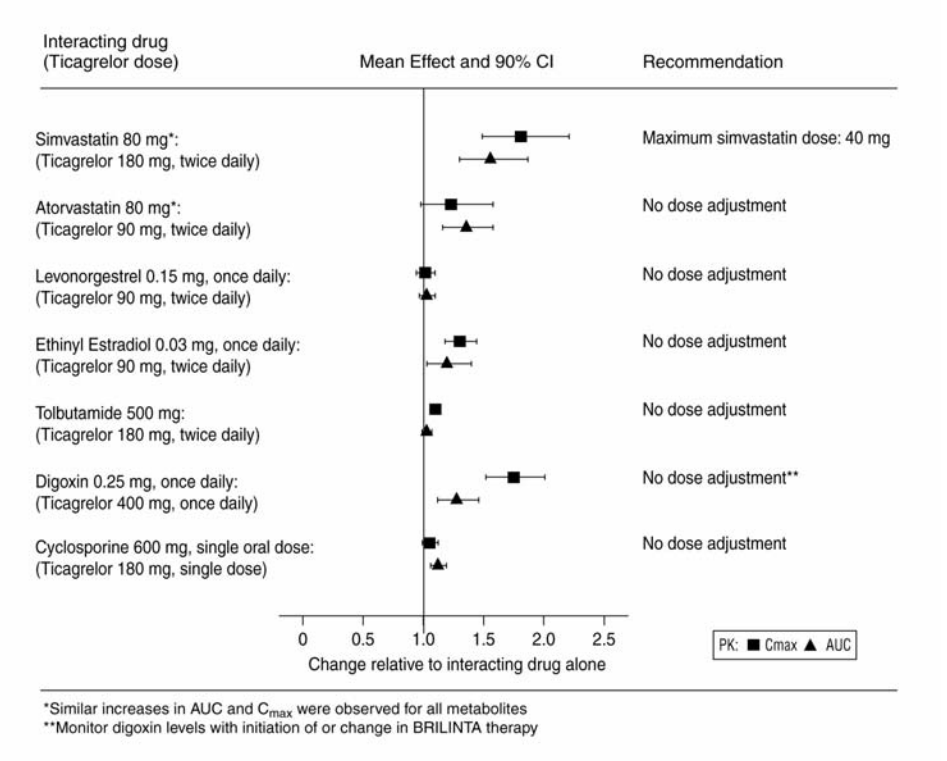


*See *Dosage and Administration (2).*

Effects of BRILINTA on Other Drugs

In vitro metabolism studies demonstrate that ticagrelor and its major active metabolite are weak inhibitors of CYP3A4, potential activators of CYP3A5 and inhibitors of the P-gp transporter. Ticagrelor and AR-C124910XX were shown to have no inhibitory effect on human CYP1A2, CYP2C19, and CYP2E1 activity. For specific *in vivo* effects on the pharmacokinetics of simvastatin, atorvastatin, ethinyl estradiol, levonorgesterol, tolbutamide, digoxin and cyclosporine, see Figure 7.

Figure 7 – Impact of BRILINTA on the pharmacokinetics of co-administered drugs



12.5 Pharmacogenetics

In a genetic substudy cohort of PLATO, the rate of thrombotic CV events in the BRILINTA arm did not depend on CYP2C19 loss of function status.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Ticagrelor was not carcinogenic in the mouse at doses up to 250 mg/kg/day or in the male rat at doses up to 120 mg/kg/day (19 and 15 times the MRHD of 90 mg twice daily on the basis of AUC, respectively). Uterine carcinomas, uterine adenocarcinomas and hepatocellular adenomas were seen in female rats at doses of 180 mg/kg/day (29-fold the maximally recommended dose of 90 mg twice daily on the basis of AUC), whereas 60 mg/kg/day (8-fold the MRHD based on AUC) was not carcinogenic in female rats.

Mutagenesis

Ticagrelor did not demonstrate genotoxicity when tested in the Ames bacterial mutagenicity test, mouse lymphoma assay and the rat micronucleus test. The active O-demethylated metabolite did not demonstrate genotoxicity in the Ames assay and mouse lymphoma assay.

Impairment of Fertility

Ticagrelor had no effect on male fertility at doses up to 180 mg/kg/day or on female fertility at doses up to 200 mg/kg/day (>15-fold the MRHD on the basis of AUC). Doses of ≥10 mg/kg/day given to female rats caused an increased incidence of irregular duration estrus cycles (1.5-fold the MRHD based on AUC).

14 CLINICAL STUDIES

14.1 Acute Coronary Syndromes and Secondary Prevention after Myocardial Infarction

PLATO

PLATO was a randomized double-blind study comparing BRILINTA (N=9333) to clopidogrel (N=9291), both given in combination with aspirin and other standard therapy, in patients with acute coronary syndromes (ACS), who presented within 24 hours of onset of the most recent episode of chest pain or symptoms. The study's primary endpoint was the composite of first occurrence of cardiovascular death, non-fatal MI (excluding silent MI), or non-fatal stroke.

Patients who had already been treated with clopidogrel could be enrolled and randomized to either study treatment. Patients with previous intracranial hemorrhage, gastrointestinal bleeding within the past 6 months, or with known bleeding diathesis or coagulation disorder were excluded. Patients taking anticoagulants were excluded from participating and patients who developed an indication for anticoagulation during the trial were discontinued from study drug. Patients could be included whether there was intent to manage the ACS medically or invasively, but patient randomization was not stratified by this intent.

All patients randomized to BRILINTA received a loading dose of 180 mg followed by a maintenance dose of 90 mg twice daily. Patients in the clopidogrel arm were treated with an initial loading dose of clopidogrel 300 mg, if clopidogrel therapy had not already been given. Patients undergoing PCI could receive an additional 300 mg of clopidogrel at investigator discretion. A daily maintenance dose of aspirin 75-100 mg was recommended, but higher maintenance doses of aspirin were allowed according to local judgment. Patients were treated for at least 6 months and for up to 12 months.

PLATO patients were predominantly male (72%) and Caucasian (92%). About 43% of patients were >65 years and 15% were >75 years. Median exposure to study drug was 277 days. About half of the patients received pre-study clopidogrel and about 99% of the patients received aspirin at some time during PLATO. About 35% of patients were receiving a statin at baseline and 93% received a statin sometime during PLATO.

Table 6 shows the study results for the primary composite endpoint and the contribution of each component to the primary endpoint. Separate secondary endpoint analyses are shown for the overall occurrence of CV death, MI, and stroke and overall mortality.

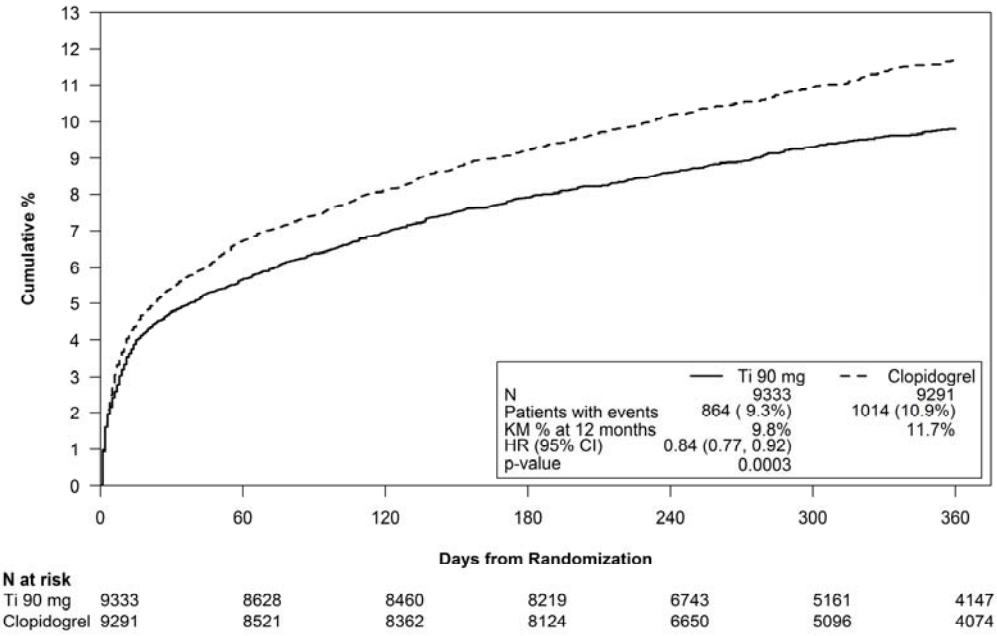
Table 6 – Patients with outcome events (KM%)(PLATO)

	BRILINTA[1] N=9333	Clopidogrel N=9291	Hazard Ratio (95% CI)	*p*-value
Composite of CV death, MI, or stroke	9.8	11.7	0.84 (0.77, 0.92)	0.0003
CV death	2.9	4.0	0.74	
Non-fatal MI	5.8	6.9	0.84	
Non-fatal stroke	1.4	1.1	1.24	
Secondary endpoints[2]				
CV death	4.0	5.1	0.79 (0.69, 0.91)	0.0013
MI[3]	5.8	6.9	0.84 (0.75, 0.95)	0.0045
Stroke[3]	1.5	1.3	1.17 (0.91, 1.52)	0.22
All-cause mortality	4.5	5.9	0.78 (0.69, 0.89)	0.0003

1. Dosed at 90 mg bid.
2. Note: rates of first events for the components CV Death, MI and Stroke are the actual rates for first events for each component and do not add up to the overall rate of events in the composite endpoint.
3. Including patients who could have had other non-fatal events or died.

The Kaplan-Meier curve (Figure 8) shows time to first occurrence of the primary composite endpoint of CV death, non-fatal MI or non-fatal stroke in the overall study.

Figure 8 – Time to first occurrence of CV death, MI, or stroke (PLATO)



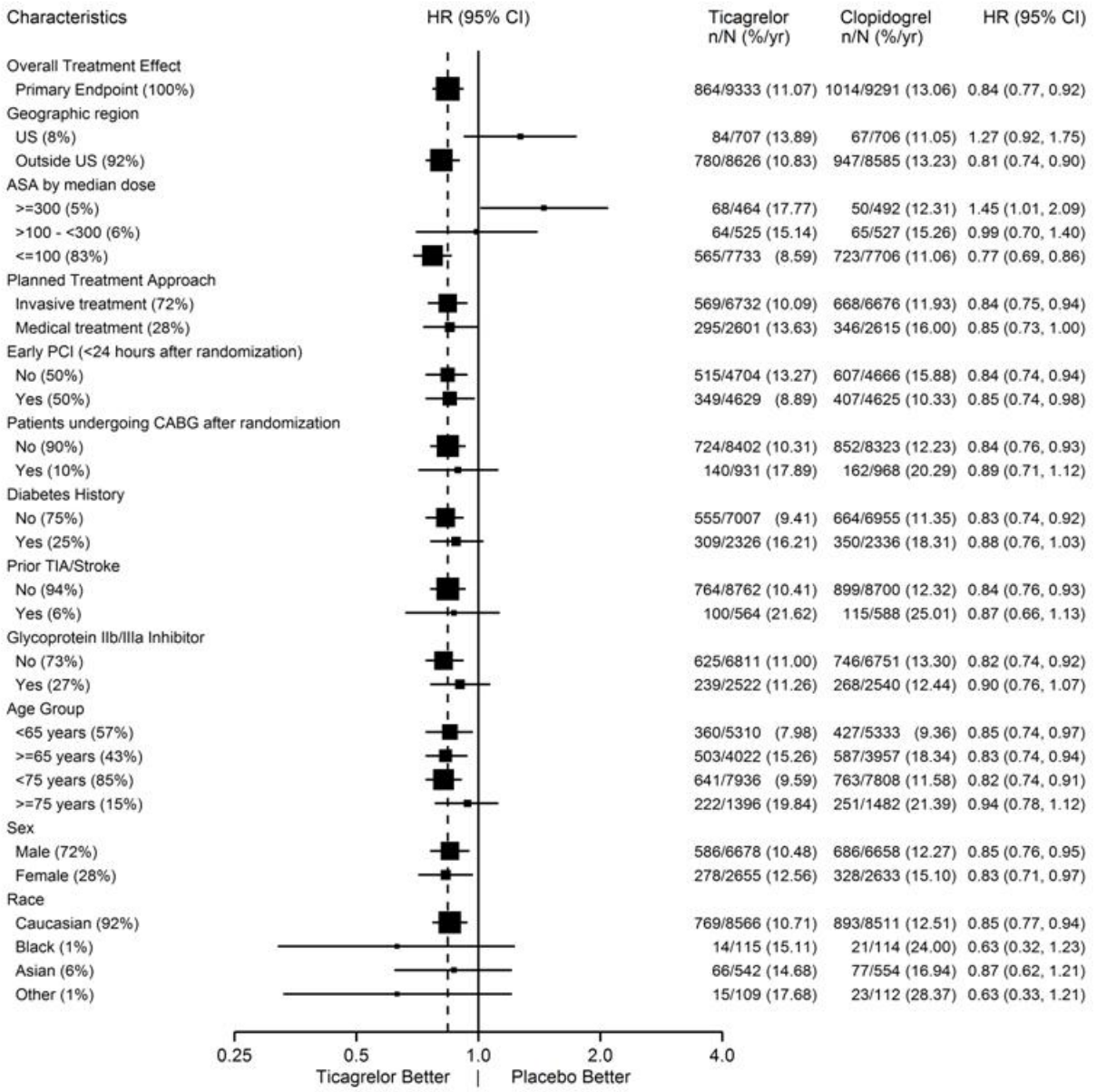
The curves separate by 30 days [relative risk reduction (RRR) 12%] and continue to diverge throughout the 12 month treatment period (RRR 16%).

Among 11289 patients with PCI receiving any stent during PLATO, there was a lower risk of stent thrombosis (1.3% for adjudicated "definite") than with clopidogrel (1.9%) (HR 0.67, 95% CI 0.50-0.91; *p*=0.009). The results were similar for drug-eluting and bare metal stents.

A wide range of demographic, concurrent baseline medications, and other treatment differences were examined for their influence on outcome. Some of these are shown in Figure 9. Such analyses must be interpreted cautiously, as differences can reflect the play of chance among a large number of analyses. Most of the analyses show effects consistent with the overall results, but there are two exceptions: a finding of heterogeneity by region and a strong influence of the maintenance dose of aspirin. These are considered further below.

Most of the characteristics shown are baseline characteristics, but some reflect post-randomization determinations (e.g., aspirin maintenance dose, use of PCI).

Figure 9 – Subgroup analyses of (PLATO)



Note: The figure above presents effects in various subgroups most of which are baseline characteristics and most of which were pre-specified. The 95% confidence limits that are shown do not take into account how many comparisons were made, nor do they reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

Regional Differences

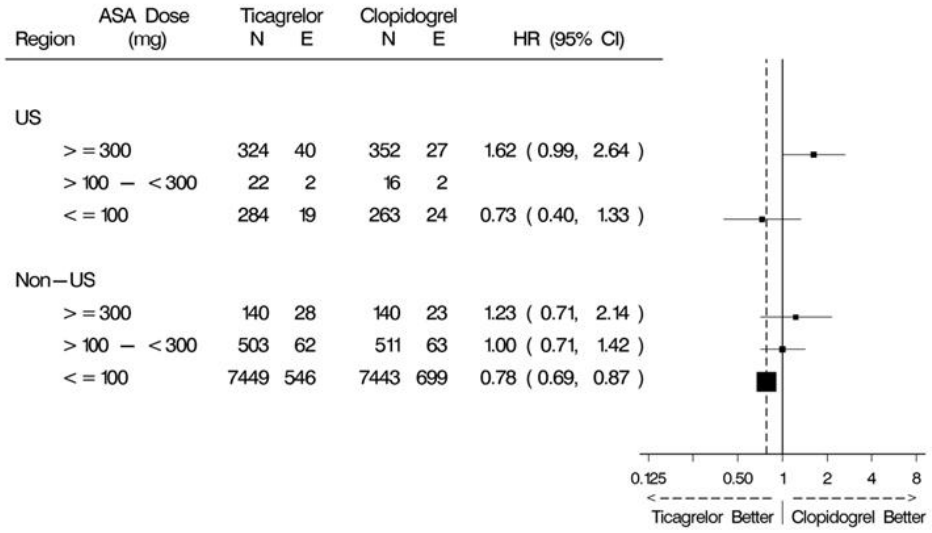
Results in the rest of the world compared to effects in North America (US and Canada) show a smaller effect in North America, numerically inferior to the control and driven by the US subset. The statistical test for the US/non-US comparison is statistically significant (p=0.009), and the same trend is present for both CV death and non-fatal MI. The individual results and nominal p-values, like all subset analyses, need cautious interpretation, and they could represent chance findings. The consistency of the differences in both the CV mortality and non-fatal MI components, however, supports the possibility that the finding is reliable.

A wide variety of baseline and procedural differences between the US and non-US (including intended invasive *vs.* planned medical management, use of GPIIb/IIIa inhibitors, use of drug eluting vs. bare-metal stents) were examined to see if they could account for regional differences, but with one exception, aspirin maintenance dose, these differences did not appear to lead to differences in outcome.

Aspirin Dose

The PLATO protocol left the choice of aspirin maintenance dose up to the investigator and use patterns were different in US sites from sites outside of the US. About 8% of non-US investigators administered aspirin doses above 100 mg, and about 2% administered doses above 300 mg. In the US 57% of patients received doses above 100 mg and 54% received doses above 300 mg. Overall results favored BRILINTA when used with low maintenance doses (≤100 mg) of aspirin, and results analyzed by aspirin dose were similar in the US and elsewhere. Figure 10 shows overall results by median aspirin dose. Figure 10 shows results by region and dose.

Figure 10 – CV death, MI, stroke by maintenance aspirin dose in the US and outside the US (PLATO)



Like any unplanned subset analysis, especially one where the characteristic is not a true baseline characteristic (but may be determined by usual investigator practice), the above analyses must be treated with caution. It is notable, however, that aspirin dose predicts outcome in both regions with a similar pattern, and that the pattern is similar for the two major components of the primary endpoint, CV death and non-fatal MI.

Despite the need to treat such results cautiously, there appears to be good reason to restrict aspirin maintenance dosage accompanying ticagrelor to 100 mg. Higher doses do not have an established benefit in the ACS setting, and there is a strong suggestion that use of such doses reduces the effectiveness of BRILINTA.

PEGASUS

The PEGASUS TIMI-54 study was a 21162-patient, randomized, double-blind, placebo-controlled, parallel-group study. Two doses of ticagrelor, either 90 mg twice daily or 60 mg twice daily, co-administered with 75-150 mg of aspirin, were compared to aspirin therapy alone in patients with history of MI. The primary endpoint was the composite of first occurrence of CV death, non-fatal MI and non-fatal stroke. CV death and all-cause mortality were assessed as secondary endpoints.

Patients were eligible to participate if they were ≥50 years old, with a history of MI 1 to 3 years prior to randomization, and had at least one of the following risk factors for thrombotic cardiovascular events: age ≥65 years, diabetes mellitus

requiring medication, at least one other prior MI, evidence of multivessel coronary artery disease, or creatinine clearance <60 mL/min. Patients could be randomized regardless of their prior ADP receptor blocker therapy or a lapse in therapy. Patients requiring or who were expected to require renal dialysis during the study were excluded. Patients with any previous intracranial hemorrhage, gastrointestinal bleeding within the past 6 months, or with known bleeding diathesis or coagulation disorder were excluded. Patients taking anticoagulants were excluded from participating and patients who developed an indication for anticoagulation during the trial were discontinued from study drug. A small number of patients with a history of stroke were included. Based on information external to PEGASUS, 102 patients with a history of stroke (90 of whom received study drug) were terminated early and no further such patients were enrolled.

Patients were treated for at least 12 months and up to 48 months with a median follow up time of 33 months.

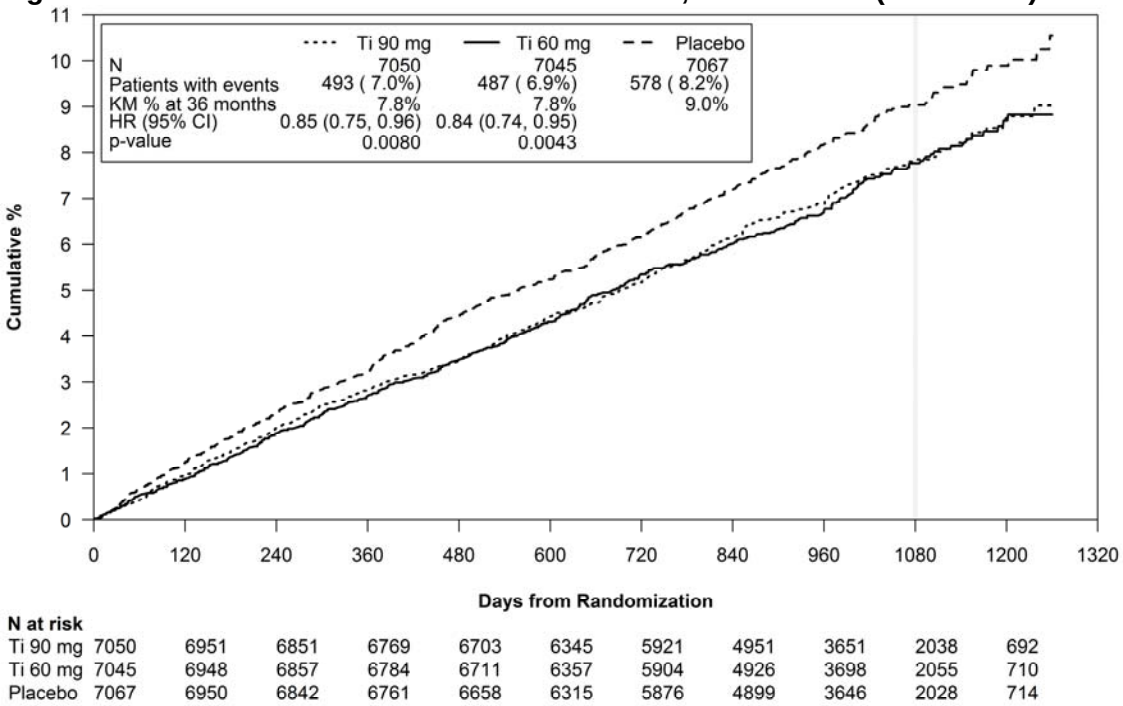
Patients were predominantly male (76%) Caucasian (87%) with a mean age 65 years, and 99.8% of patients received prior Aspirin therapy. See Table 7 for key baseline features.

Table 7 – Baseline features (PEGASUS)

Demographic	% Patients
<65 years	45%
Diabetes	32%
Multivessel disease	59%
History of >1 MI	17%
Chronic non-end stage renal disease	19%
Stent	80%
Prior P2Y12 platelet inhibitor therapy	89%
Lipid lowering therapy	94%

The Kaplan-Meier curve (Figure 11) shows time to first occurrence of the primary composite endpoint of CV death, non-fatal MI or non-fatal stroke.

Figure 11 – Time to First Occurrence of CV death, MI or Stroke (PEGASUS)



N at risk

Ti 90 mg	7050	6951	6851	6769	6703	6345	5921	4951	3651	2038	692
Ti 60 mg	7045	6948	6857	6784	6711	6357	5904	4926	3698	2055	710
Placebo	7067	6950	6842	6761	6658	6315	5876	4899	3646	2028	714

Ti = Ticagrelor BID, CI = Confidence interval; HR = Hazard ratio; KM = Kaplan-Meier; N = Number of patients.

Both the 60 mg and 90 mg regimens of BRILINTA in combination with aspirin were superior to aspirin alone in reducing the incidence of CV death, MI or stroke. The absolute risk reductions for BRILINTA plus aspirin *vs.* aspirin alone were 1.27% and 1.19% for the 60 and 90 mg regimens, respectively. Although the efficacy profiles of the two regimens were similar, the lower dose had lower risks of bleeding and dyspnea.

Table 8 shows the results for the 60 mg plus aspirin regimen *vs.* aspirin alone.

Table 8 – Incidences of the primary composite endpoint, primary composite endpoint components, and secondary endpoints (PEGASUS)

	BRILINTA* + Aspirin N=7045		Aspirin Alone N=7067		HR (95% CI)	*p*-value
	n (patients with event)	KM%	n (patients with event)	KM%		
Time to first CV death, MI, or stroke*	487	7.8	578	9.0	0.84 (0.74, 0.95)	0.0043
CV Death[a]	116		128			
Myocardial infarction[a]	283		336			
Stroke[a]	88		114			
Subjects with events at any time CV Death [b] **	174	2.9	210	3.4	0.83 (0.68, 1.01)	
Myocardial infarction[b]	285	4.5	338	5.2	0.84 (0.72, 0.98)	
Stroke[b]	91	1.5	122	1.9	0.75 (0.57, 0.98)	
All-cause mortality**	289	4.7	326	5.2	0.89 (0.76, 1.04)	

* 60 mg BID

CI = Confidence interval; CV = Cardiovascular; HR = Hazard ratio; KM = Kaplan-Meier percentage calculated at 36 months; MI = Myocardial infarction; N = Number of patients; *Primary endpoint; **Secondary endpoints.

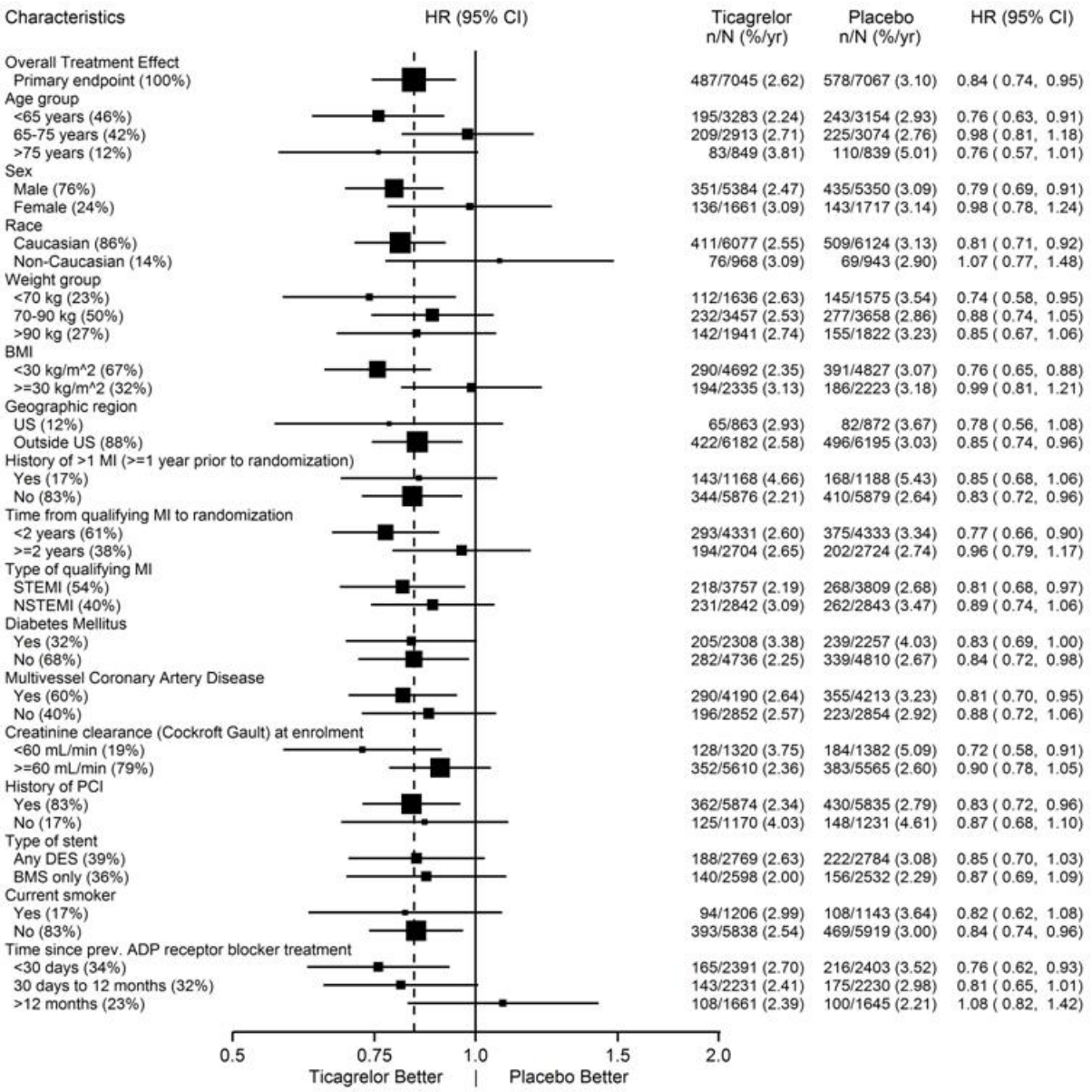
[a] For the components, the first-occurring component of the composite is included.

[b] The number of first events for the components CV Death, MI and Stroke are the actual number of first events for each component and do not add up to the number of events in the composite endpoint.

In PEGASUS, the RRR for the composite endpoint from 1 to 360 days (17% RRR) and from 361 days and onwards (16% RRR) were similar.

The treatment effect of BRILINTA 60 mg over aspirin appeared similar across most pre-defined subgroups, see Figure 12.

Figure 12 – Subgroup analyses of ticagrelor 60 mg (PEGASUS)



Note: The figure above presents effects in various subgroups all of which are baseline characteristics and most of which were pre-specified. The 95% confidence limits that are shown do not take into account how many comparisons were made, nor do they reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

16 HOW SUPPLIED/STORAGE AND HANDLING

BRILINTA (ticagrelor) 90 mg is supplied as a round, biconvex, yellow, film-coated tablet with a “90” above “T” on one side:

Bottles of 14 – NDC 0186-0777-28
Bottles of 60 – NDC 0186-0777-60
100 count Hospital Unit Dose – NDC 0186-0777-39

BRILINTA (ticagrelor) 60 mg is supplied as a round, biconvex, pink, film-coated tablet with a “60” above “T” on one side;

Bottles of 60 – NDC 0186-0776-60
Blister of 14 – NDC 0186-0776-94

Storage and Handling

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP controlled room temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide)

Advise patients daily doses of aspirin should not exceed 100 mg and to avoid taking any other medications that contain aspirin.

Advise patients that they:

- Will bleed and bruise more easily
- Will take longer than usual to stop bleeding
- Should report any unanticipated, prolonged or excessive bleeding, or blood in their stool or urine.

Advise patients to contact their doctor if they experience unexpected shortness of breath, especially if severe.

Advise patients to inform physicians and dentists that they are taking BRILINTA before any surgery or dental procedure.

BRILINTA® is a trademark of the AstraZeneca group of companies.

Distributed by: AstraZeneca LP, Wilmington, DE 19850

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MEDICATION GUIDE

BRILINTA® (brih-LIN-tah)

(ticagrelor) Tablets

What is the most important information I should know about BRILINTA?

BRILINTA is used to lower your chance of having a heart attack or dying from a heart attack or stroke **but BRILINTA (and similar drugs) can cause bleeding that can be serious and sometimes lead to death.** In cases of serious bleeding, such as internal bleeding, the bleeding may result in the need for blood transfusions or surgery. While you take BRILINTA:

- you may bruise and bleed more easily
- you are more likely to have nose bleeds
- it will take longer than usual for any bleeding to stop

Call your doctor right away, if you have any of these signs or symptoms of bleeding while taking BRILINTA:

- bleeding that is severe or that you cannot control
- pink, red or brown urine
- vomiting blood or your vomit looks like “coffee grounds”
- red or black stools (looks like tar)
- coughing up blood or blood clots

Do not stop taking BRILINTA without talking to the doctor who prescribes it for you. People who are treated with a stent, and stop taking BRILINTA too soon, have a higher risk of getting a blood clot in the stent, having a heart attack, or dying. If you stop BRILINTA because of bleeding, or for other reasons, your risk of a heart attack or stroke may increase.

Your doctor may instruct you to stop taking BRILINTA 5 days before surgery. This will help to decrease your risk of bleeding with your surgery or procedure. Your doctor should tell you when to start taking BRILINTA again, as soon as possible after surgery.

Taking BRILINTA with aspirin

BRILINTA is taken with aspirin. Talk to your doctor about the dose of aspirin that you should take with BRILINTA. You should not take a dose of aspirin higher than 100 mg daily because it can affect how well BRILINTA works. Do not take doses of aspirin higher than what your doctor tells you to take. Tell your doctor if you take other medicines that contain aspirin, and do not take new over-the-counter medicines with aspirin in them.

What is BRILINTA?

BRILINTA is a prescription medicine used to treat people who:

- have had a heart attack or severe chest pain that happened because their heart was not getting enough oxygen.

BRILINTA is used with aspirin to lower your chance of having another serious problem with your heart or blood vessels, such as heart attack, stroke, or blood clots in your stent. These can be fatal.

Platelets are blood cells that help with normal blood clotting. BRILINTA helps prevent platelets from sticking together and forming a clot that can block an artery.

It is not known if BRILINTA is safe and effective in children.

Who should not take BRILINTA?

Do not take BRILINTA if you:

- have a history of bleeding in the brain
- are bleeding now
- are allergic to ticagrelor or any of the ingredients in BRILINTA. See the end of this Medication Guide for a complete list of ingredients in BRILINTA.

What should I tell my doctor before taking BRILINTA?

Before you take BRILINTA, tell your doctor if you:

- have had bleeding problems in the past
- have had any recent serious injury or surgery
- plan to have surgery or a dental procedure
- have a history of stomach ulcers or colon polyps
- have lung problems, such as COPD or asthma
- have liver problems
- have a history of stroke
- are pregnant or plan to become pregnant. It is not known if BRILINTA will harm your unborn baby. You and your doctor

should decide if you will take BRILINTA.

- are breastfeeding or plan to breastfeed. It is not known if BRILINTA passes into your breast milk. You and your doctor should decide if you will take BRILINTA or breastfeed. You should not do both without talking with your doctor.

Tell all of your doctors and dentists that you are taking BRILINTA. They should talk to the doctor who prescribed BRILINTA for you before you have any surgery or invasive procedure.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. **BRILINTA may affect the way other** medicines work, and other medicines may affect how BRILINTA works.

Especially tell your doctor if you take:

- an HIV-AIDS medicine
- medicine for heart conditions or high blood pressure
- medicine for high blood cholesterol levels
- an anti-fungal medicine by mouth
- an anti-seizure medicine
- a blood thinner medicine
- rifampin (Rifater, Rifamate, Rimactane, Rifadin)

Ask your doctor or pharmacist if you are not sure if your medicine is listed above.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I take BRILINTA?

- Take BRILINTA exactly as prescribed by your doctor.
- Your doctor will tell you how many BRILINTA tablets to take and when to take them.
- Take BRILINTA with a low dose (not more than 100 mg daily) of aspirin. You may take BRILINTA with or without food.
- Take your doses of BRILINTA around the same time every day.
- If you forget to take your scheduled dose of BRILINTA, take your next dose at its scheduled time. Do not take 2 doses at the same time unless your doctor tells you to.
- If you take too much BRILINTA or overdose, call your doctor or poison control center right away, or go to the nearest emergency room.

If you are unable to swallow the tablet(s) whole, you may crush the BRILINTA tablet(s) and mix it with water. Drink all the water right away. Refill the glass with water, stir, and drink all the water.

What are the possible side effects of BRILINTA?

BRILINTA can cause serious side effects, including:

- **See "What is the most important information I should know about BRILINTA?"**
- **Shortness of breath**. Call your doctor if you have new or unexpected shortness of breath when you are at rest, at night, or when you are doing any activity. Your doctor can decide what treatment is needed.

These are not all of the possible side effects of BRILINTA. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store BRILINTA?

- Store BRILINTA at room temperature between 68°F to 77°F (20°C to 25°C).

Keep BRILINTA and all medicines out of the reach of children.

General information about BRILINTA

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use BRILINTA for a condition for which it was not prescribed. Do not give BRILINTA to other people, even if they have the same symptoms you have. It may harm them. You can ask your pharmacist or doctor for information about BRILINTA that is written for health professionals.

What are the ingredients in BRILINTA?

Active ingredient: ticagrelor

90 mg tablets:

Inactive ingredients: mannitol, dibasic calcium phosphate, sodium starch glycolate, hydroxypropyl cellulose, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, talc, polyethylene glycol 400, and ferric oxide yellow.

60 mg tablets:

Inactive ingredients: mannitol, dibasic calcium phosphate, sodium starch glycolate, hydroxypropyl cellulose, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol 400, ferric oxide black and ferric oxide red.

Distributed by: AstraZeneca LP, Wilmington, DE 19850

For more information call 1-800-236-9933 or go to www.Brilinta.com.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 09/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-433/S015

SUMMARY REVIEW

DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Regulatory Project Manager Review

sNDA:	22433-S015
Drug:	BRILINTA (ticagrelor) 60 & 90mg Tablets
Class:	$P2Y_{12}$ Inhibitor
Applicant:	AstraZeneca

Proposed Indication:
(New Indication is 1.2)

(b) (4)

(b) (4)

(b) (4)

FINAL Indication:

BRILINTA is indicated to reduce the rate of cardiovascular death, myocardial infarction, and stroke in patients with acute coronary syndrome (ACS) or a history of myocardial infarction (MI). For at least the first 12 months following ACS, it is superior to clopidogrel. BRILINTA also reduces the rate of stent thrombosis in patients who have been stented for treatment of ACS [see Clinical Studies (14.1)].

Date of Submission:	6 March 2015
Approval date:	3 September 2015
PDUFA date:	6 September 2015

❖ REVIEW TEAM

- Office of New Drugs, Office of Drug Evaluation I (ODE I)
  - Division of Cardiovascular & Renal Products (DCRP)
    - Norman Stockbridge, M.D., Ph.D. (Division Director)
    - Martin Rose, M.D., JD (Cross-Discipline Team Leader - CDTL)
    - Preston Dunnmon, M.D. (Clinical Reviewer - Efficacy)
    - Melanie Blank, M.D. (Clinical Reviewer - Safety)
    - Alison Blaus, RAC (Senior Regulatory Health Project Manager)
- Office of Clinical Pharmacology
  - Sreedharan Sabarinath, Ph.D.
- Office of Biostatistics, Division of Biometrics I
  - Steven Bai, Ph.D.
- Office of New Drug Quality Assessment (ONDQA)
  - Kris Raman, Ph.D. (Drug Substance / Drug Product)
  - Banu Zolnik, Ph.D. (Biopharmaceutics)
- Office of Surveillance and Epidemiology
  - Tingting Gao (DMEPA)
- Office of Medical Policy
  - Office of Prescription Drug Promotion (OPDP)
    - Zarna Patel
  - Patient Labeling
    - Shawna Hutchins (Medication Guide)

❖ BACKGROUND

BRILINTA (ticagrelor) is an oral, reversible blocker of the platelet $P2Y_{12}$ receptor, an action which blocks ADP-mediated platelet activation and aggregation. Ticagrelor was approved for marketing in the USA in 2011 for reduction of the rate of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) (unstable angina, non-ST elevation myocardial infarction, or ST elevation myocardial infarction) based on the results from the trial PLATO.

AstraZeneca (AZ) conducted a second trial entitled, "*A Randomized, Double-Blind, Placebo Controlled, Parallel Group, Multinational Trial, to Assess the Prevention of Thrombotic Events with Ticagrelor Compared to Placebo on a Background of Acetyl Salicylic Acid (ASA) Therapy in Patients with History of Myocardial Infarction* ("**PEGASUS**")" aimed to support the indication for patients with a history of MI.

PEGASUS was an event-driven trial in which about 21,000 subjects with previous MI (1 to 3 years prior to enrollment) and at least one additional risk factor (age ≥65 years, diabetes, a second prior MI, evidence of multi-vessel coronary artery disease, or chronic non-end-stage renal dysfunction) were randomized 1:1:1 to ticagrelor 90 mg or 60 mg BID or placebo. The primary endpoint was a composite of cardiovascular (CV) death, myocardial infarction (MI), and stroke. The topline results were discussed on 11 February 2015 (minutes dated 19 March 2015) and the sNDA was subsequently submitted on 6 March 2015.

❖ REGULATORY TIMELINE and GENERAL APPLICATION MILESTONES

This section will cover a number of clinical development and general application milestones (pre- and post-NDA submission). The review of this application proceeded relatively smoothly, with approximately 25 information requests since 6 March 2015.

- NDA Approved for ACS: 20 July 2011
- End of Phase 2 Meeting (PEGASUS): None
- SPA No-Agreement Letter: 13 November 2009
- SPA Resubmission No-Agreement Letter: 18 February 2010
- SPA Teleconference: 1 July 2010 (minutes dated 19 July 2015)
- Pre-sNDA Meeting: 8Apr14 (WRO) (clarifications dated 10 September 2014)
- PEGASUS Top-Line Meeting: 11 February 2015 (minutes dated 19 March 2015)
- sNDA Submission Received: 6 March 2015
- Filing Meeting: 9 April 2015
- Priority Designation Letter (No 74-day Issues Identified): 24 April 2015
- Mid-cycle Meeting: 2 June 2015
- PDUFA Date: 6 September 2015
- **Approval Letter Date**: 3 September 2015

User Fee

The user fee for this application was paid in full on 5 February 2015, prior to the submission of the application (ID 3014864).

Pediatric Review Committee (PeRC)

The PeRC meeting to discuss this application was held on 3 June 2015. The applicant proposed a full waiver because necessary studies are impossible or highly impracticable because acute coronary syndromes rarely occur in the pediatric population. Furthermore, the pathophysiology of acute coronary syndromes in children is generally different from its adult counterpart. The PeRC and the Division agreed with this rationale. Therefore, a full pediatric waiver was granted for this application.

Advisory Committee

It was decided at the filing meeting and through internal discussions with various individuals within the Agency that an Advisory Committee (ADCOM) would not be needed for this efficacy supplement as there were no review issues identified that warranted public discussion or input from outside experts.

Review Status

Due to the Phase 3 trial results from PEGASUS, the applicant requested and was granted a priority review. Please see the Clinical Filing Review for the rationale.

❖ LABELING REVIEW

Labeling negotiations began on 12 August 2015 and were concluded on 3 September 2015 after four official rounds of editing (there were edits requested via email in between rounds of labeling exchanges). Please see the Division Director's memo for the indication changes rationale and see the final label appended to the approval letter.

❖ DISCIPLINE REVIEWS

Below are the conclusions reached by the PEGASUS Team CDTL and the Division Director. Please refer to the individual discipline reviews for the primary reviewer's conclusions.

Divisional Memorandum (14 August 2015)
Dr. Stockbridge drafted and finalized a review on 14 August 2015 concurring with the primary clinical reviewers recommending approval. He noted in his review, however, that although the applicant split ACS (approved in 2011) and the new indication (secondary prevention of MI) into two distinct indications, this is in fact one indication that starts when someone declares the severity of their coronary artery disease by having a myocardial infarction and continues indefinitely. (b) (4)

Further, Dr. Stockbridge noted in his review that PLATO showed ticagrelor superior to clopidogrel on the MACE end point with $p<0.001$, on cardiovascular death with $p=0.001$, and on all-cause mortality with $p<0.001$, ordinarily robust enough to have earned an explicit superiority claim, even as a single study. In 2011, however, BRILINTA did not get such a claim, perhaps a reflection of residual uncertainty regarding the interpretation of US-vs-non-US findings in PLATO, Dr. Stockbridge states; this issue was not addressed in Dr. Temple's decisional memo. Dr. Stockbridge noted that in PEGASUS, conducted solely with a background of low-dose aspirin, no discrepant US results were seen, so he concluded that either the original observation was unreliable or the low-dose aspirin resolved the discrepancy, but in any event, residual concern about the comparison with clopidogrel is alleviated. As a result, he added this explicit claim to the Indications section: for at least the first 12 months following myocardial infarction, BRILINTA is superior to clopidogrel.

Cross-Discipline Team Leader - CDTL (11 August 2015)
Dr. Rose concurred with the primary reviewers on this efficacy supplement and recommended approval of BRILINTA for the secondary prevention of MI (an expansion of the existing 2011 indication for ACS).

❖ CONSULT REVIEWS

Please see the following consults that were requested during the NDA review and the corresponding date they were finalized:

- DMEPA (Carton-Container Labeling): 16 June 2015
- Patient Labeling (Medication Guide): 20 August 2015
- Office of Prescription Drug Promotion (OPDP): 24 August 2015

❖ CONCLUSION

After taking into consideration all of the primary reviews, consults, and the applicant's additional analyses, the Division issued an approval letter for NDA 22433-S015 on 3 September 2015. This approval letter was signed by Norman Stockbridge, MD, PhD (Division of Cardiovascular & Renal Products Director).

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
09/03/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-433/S015

OFFICER/EMPLOYEE LIST

Officer/Employee List
Application: NDA 22433-S015
Product: BRILINTA (ticagrelor)

The following officers or employees of FDA participated in the decision to approve this application and consented to be identified:

Norman Stockbridge
Martin Rose
Preston Dunnmon
Mary Ross Southworth
Michael Monteleone
Edward Fromm
Alison Blaus
Steven Bai
Raj Madabushi
Sreedharan Sabarinath
Zedong Dong
Banu Zolnik
George Greeley
Tingting Gao
Marcia Britt Williams
Shawna Hutchins

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-433/S015

OFFICE DIRECTOR MEMO

DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Divisional Memo

NDA: 22433 Ticagrelor (Brilinta) for reduction of cardiovascular events in patients one year from myocardial infarction.

Sponsor: Astra Zeneca

Review date: 14 August 2015

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

Distribution: NDA 22433

This memo conveys the Division's decision to approve this application, pending resolution of labeling.

Ticagrelor is a concentration-dependent P2Y12 inhibitor, distinguished from clopidogrel and prasugrel, both of which have effects that last the lifetime of platelets.

This supplement extends the 2011 approval of Brilinta for use beginning with ACS to use beginning more remote from myocardial infarction. There are reviews of CMC (Raman, 10 August 2015), biopharmaceutics (Zolnik, 6 August 2015), clinical pharmacology (Sabarinath, 22 July 2015), clinical (Dunnmon and Blank, 11 August 2015), and biometrics (Bai, 2 July 2015). There is a comprehensive CDTL memo (Rose, 11 August 2015) with which I am largely in agreement. I comment on a few issues here.

The 60-mg dose would be new. There are no issues with approval, based upon product quality or biopharmaceutics. Facility inspections have completed without an issue.

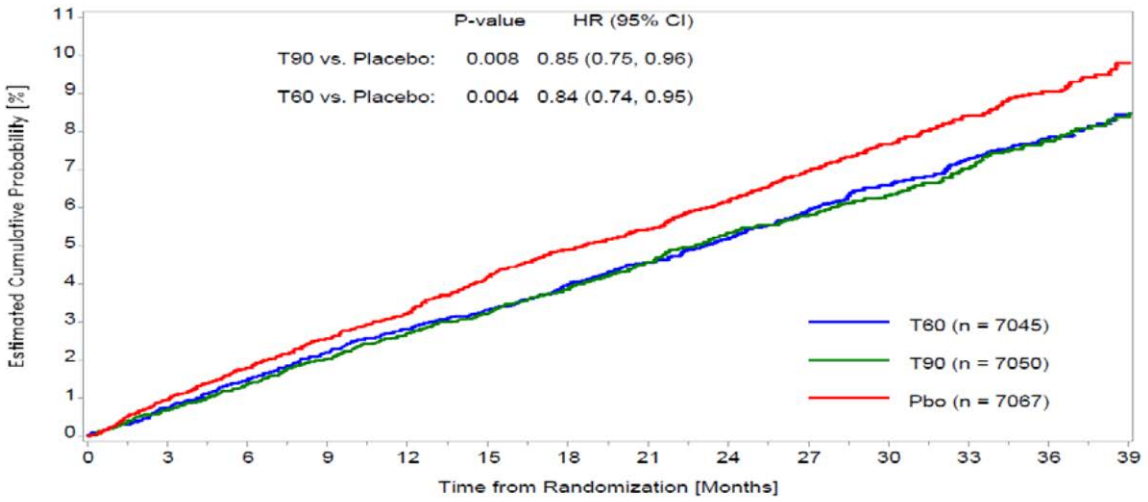
All other disciplines have also recommended approval, although, as Dr. Rose describes, we have had considerable discussion regarding generalization of PEGASUS results.

The extended indication, which the sponsor proposed as a distinct, disjoint indication from the use in ACS, is supported by the 21000-subject PEGASUS trial, comparing rates of recurrent thrombotic events in patients with a history of myocardial infarction 1-3 years ago, plus another cardiovascular risk factor, randomized to placebo, ticagrelor 60 mg, and ticagrelor 90 mg (the approved dose in ACS), all on a background of aspirin but not other anticoagulant or antiplatelet therapy.

The applicant did well to study more than one dose, in particular some dose lower than was approved in the higher-risk ACS setting. The PEGASUS statistical analysis plan allocated alpha to each dose, with alpha-splitting according to Dunnett's procedure, which is only slightly more efficient than is Bonferoni. Then CV death, a component of the primary end point, was tested with each dose, then all-cause mortality. From my perspective, these choices were inefficient. The sponsor might reasonably have allocated alpha to one dose or pooled two doses as close as these. There is not universal agreement on this, but I think they ought not to have allocated alpha to the components of the composite primary end point, nor do I recommend formal testing of all-cause mortality, because there is no conceivable basis for granting a claim for all-cause mortality; all-cause mortality merely shows that net benefit was reliably preserved after considering adverse effects of treatment; in this case, that is apt principally to be bleeding.

The statistical reviewer's analysis of the primary composite end point (CV death, MI, stroke) reveals no hint of difference between the 60- and 90-mg arms.

Reference ID: 3806556

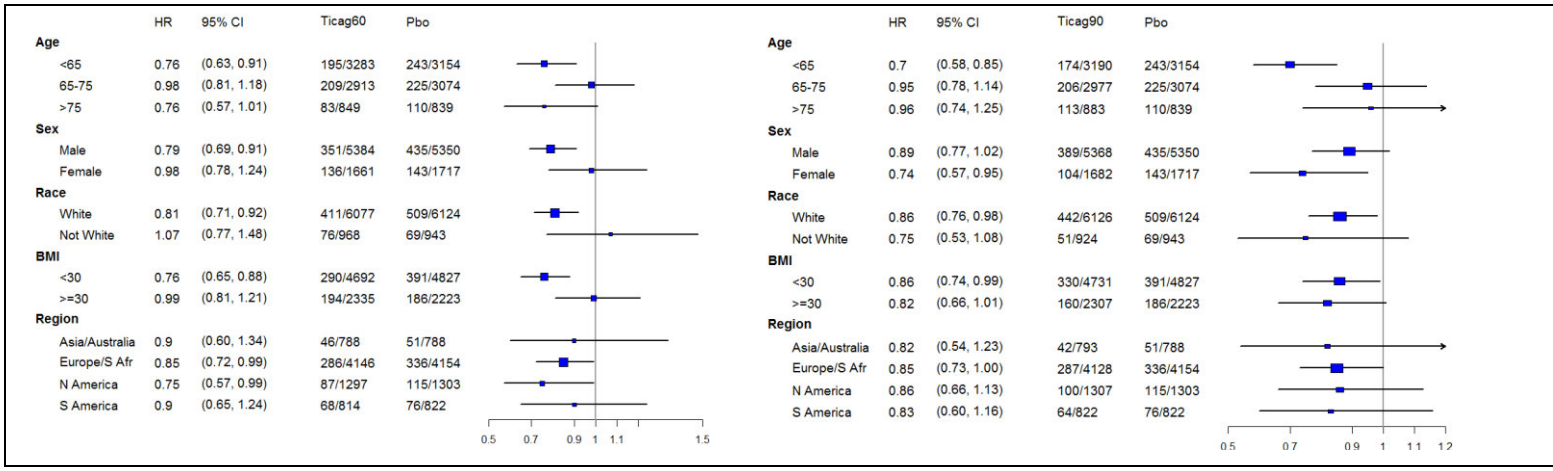


No. at risk														
Placebo	7067	6977	6891	6822	6760	6678	6503	6235	5851	5143	4328	3355	2025	986
T60	7045	6968	6903	6841	6783	6732	6555	6269	5893	5210	4410	3390	2053	998
T90	7050	6972	6897	6826	6768	6718	6547	6271	5909	5230	4383	3367	2035	1004

The review team believes the overall results for effectiveness are similar for the two doses (and I agree) and that the safety results reveal, more reliably, more bleeding on the higher dose (and I agree). (b) (4) .

All of the components of the primary end point favor ticagrelor in both doses. The review team concludes that all components contribute to the effectiveness, and I agree.

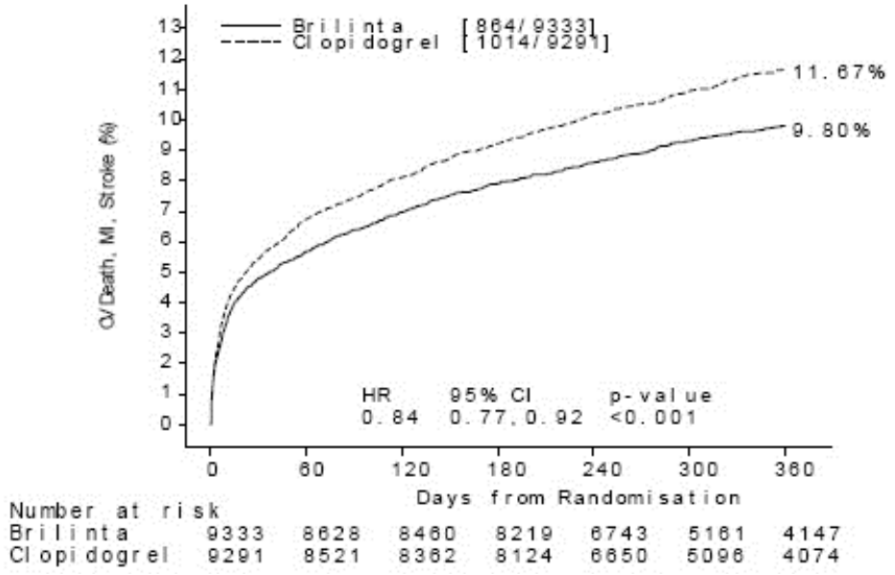
However, I note numerous oddities in subgroup analyses:



Note that men appear to do better at 60 mg (left) and women do better at 90 mg (right). Caucasians do better on 60 mg and worse on 90 mg. Low BMI does better at 60 mg, not so well on 90 mg. None of these is likely to be a reliable inference. It is not entirely clear how this needs to be exposed in the label; choices include (a) showing results in both doses, (b) showing only the subgroups for the 60-mg dose and supplementing usual language about its interpretation, (c) showing overall, pooled results for the two doses, and (d) omitting the subgroup analyses.

Ticagrelor was approved on the basis of effects on thrombotic cardiovascular events in ACS patients (mostly MI) in the 18000-subject, clopidogrel-controlled PLATO study. Treatment effects seen in PLATO continued for the one year of follow-up, as shown below:

Reference ID: 3806556



Relatively little of the experience in PLATO was with patients presenting with unstable angina, and the results in that subgroup are not particularly encouraging:

(b) (4)

The team is not in agreement on whether the results of PEGASUS apply across the risk spectrum represented therein, but I am persuaded by Dr. McDowell's analyses[1] demonstrating some differences in benefit as a function of risk, but net benefit across a large spectrum. It is about one irreversible cardiovascular morbidity/mortality event per major hemorrhage in the lowest risk population, and it is progressively better than that for patients at higher baseline risk. We will label for use regardless of other risk factors.

Dr. Rose notes that patients who entered the study with a long event-free gap off any antiplatelet therapy other than aspirin did not show benefit on ticagrelor. I believe that this observation is consistent with the idea that, other risk factors notwithstanding, such patients were at somewhat less risk than those with shorter gaps (Dr. Rose's Tables 6 and 7), but mostly I would describe the results as being non-persuasive of any relationship, because few of the subgroups for either dose are able to show any differentiation from placebo.

Dosing instructions will be merged accordingly. PLATO was conducted with a loading dose, followed by 90 mg daily. This will be preserved, with instructions to drop the dose to 60 mg after a year.

The sponsor curtailed enrollment of patients in PEGASUS with a prior history of stroke on the basis of adverse findings with vorapaxar. (b) (4)

[1] *Pages 21-23 and appendix to the CDTL memo*

Reference ID: 3806556

(b) (4)

I concur.

The clinical reviewers and the CDTL recommend labeling relating to pulmonary fibrosis on the basis of the following case counts:

		Ticagrelor 90 mg N=7050	**Ticagrelor 60 mg N=7045**	**Placebo N=7067**
Pulmonary fibrosis	AE	5	5	5
	SAE	3	2	0
Interstitial lung disease	AE	3	1	6
	SAE	2	0	3

I do not see a signal in these data that warrants description in labeling. *Dyspnea* is the second most common reason for discontinuing ticagrelor (after hemorrhage), and there is really no evidence that this effect (almost certainly related to adenosine receptor activity) has long-term consequences.

PLATO showed ticagrelor superior to clopidogrel on the MACE end point with $p<0.001$, on cardiovascular death with $p=0.001$, and on all-cause mortality with $p<0.001$, ordinarily robust enough to have earned an explicit superiority claim, even as a single study. It did not get such a claim, perhaps a reflection of residual uncertainty regarding the interpretation of US-vs-non-US findings in PLATO; this issue is not addressed in Dr. Temple's decisional memo. I note that in PEGASUS, conducted solely with a background of low-dose aspirin, no discrepant US results were seen, so either the original observation was unreliable or the low-dose aspirin resolved the discrepancy, but in any event, residual concern about the comparison with clopidogrel is alleviated. As a result, I will add this explicit claim to the Indications section: for at least the first 12 months following myocardial infarction, Brilinta is superior to clopidogrel.

Reference ID: 3806556

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/s/

NORMAN L STOCKBRIDGE
08/14/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-433/S015

CROSS DISCIPLINE TEAM LEADER REVIEW

Division of Cardiovascular and Renal Products
Cross-Discipline Team Leader Review of an Efficacy Supplement

Date	11 August 2015
From	Martin Rose, MD, JD
Subject	Cross-Discipline Team Leader Review
NDA #	022433 Supp. 15 (SD-1112) -- Efficacy supp. for a new indication
Applicant	AstraZeneca Pharmaceuticals LP
Date of Submission	6 March 2015
PDUFA Goal Date	6 September 2015
Proprietary Name / Established (USAN) Name	Brilinta® / Ticagrelor
Dosage forms / Strength	Oral tablets / 60 mg
Proposed Indication	(b) (4)
Recommended:	Approval

1 Introduction[1]

Ticagrelor is a non-thienopyridine, concentration-dependent inhibitor of the platelet P2Y12 receptor, and inhibits ADP-induced platelet aggregation. It was approved in the US in 2011 to reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS). Approval was based on the results of one study, the clopidogrel-controlled, two-arm PLATO trial, conducted against a background of aspirin treatment in >18,000 patients with ACS (STEMI, NSTEMI or UA). The single experimental treatment arm in this study utilized a ticagrelor loading of dose of 180 mg (given once) and a maintenance dose of 90 mg bid. Ticagrelor was shown to reduce the rate of a combined endpoint of cardiovascular (CV) death, myocardial infarction (MI), or stroke compared to clopidogrel. The difference between treatments was driven by CV death and MI with no difference in stroke. In patients treated with PCI, it also reduced the rate of stent thrombosis. The recommended dose in labeling for the ACS indication is the same as used in PLATO.

The instant application is an efficacy supplement for a new indication: (b) (4)

Issues raised by the various components of the review team are:

1. CMC/Biopharmaceutics: The CMC review indicates that the supplement is approvable from the CMC perspective. The Biopharmaceutics team recommends approval.

2. Pharmacology/Toxicology: No data were submitted, and no issues affect approval.

3. Clinical Pharmacology/Biopharmaceutics: The OCP review indicates that the supplement is acceptable and may be approved is from a clinical pharmacology standpoint. They recommend no Phase 3 commitments.

4. Clinical: The Clinical team has no issues affecting approval, which is supported by a favorable balance of benefits and risks across a broad range of patients. There are modeled data that predicts a favorable benefit-risk profile in low risk subjects who were not studied. However, there are several a number of labeling issues, and one of these is contentious. These include:
   (1) Drs. Stockbridge and Grant have indicated that they favor combining the current ACS indication with the proposed secondary prevention indication. The revised indication they have proposed is "…to reduce the rate of cardiovascular death, myocardial infarction, and stroke in patients with acute coronary syndrome (b) (4) and in patients with a prior history of myocardial infarction (MI)." The clinical members of the review team do not disagree.
   (2) There is disagreement within the clinical review team about the scope of the secondary prevention indication. The PEGASUS trial, which is the basis of this supplement, included only individuals with a prior MI and one or more of 5

[1] This is a review of an efficacy supplement and it follows the old CDTL format. A discussion of benefit-risk follows the safety section (Sec. 7.3.5). These data show that the benefit-risk balance favors ticagrelor across a broad range of patients who would fall under the Applicant's proposed indication.

specified, additional risk factors. Dr. Dunnmon strongly asserts that should be language in labeling indicating that this drug should be indicated for continued treatment along with aspirin only for those at high risk of having a CV event after the end of one year of DAPT following an MI. Dr. Blank believes that the available data showing that the benefits of treatment outweigh the risks can be extrapolated to all low-risk individuals with a history of MI. My view is closer to Dr. Blank's, but I believe that the study data indicate that some enrolled patients – those who enrolled more than a year after they discontinued use of ADP receptor antagonist (ADPRB) therapy for their index MI -- did not benefit from ticagrelor.

(3) (b) (4) [redacted] .

5. Statistical: The review from OB indicates that the Biometrics team has no issues with the application. They agree that PEGASUS met its primary objective of demonstrating that ticagrelor at each studied dose lowered the rate of MACE compared to placebo.

I did not identify any other major issues in my review of the NDA. Accordingly, this review will focus primarily on the clinical topics described above.

2 Background

2.1 Secondary prevention after an MI

Patients with a history of MI remain at an increased risk of thrombotic CV events for an extended period and perhaps indefinitely following their infarctions, and several drugs have been approved for the prevention of such events. Drugs that are recommended for use in secondary prevention in labeling or in the 2011 ACC/AHA secondary prevention treatment guidelines (1), sometimes referred to here as "the guidelines," are described below. The list below does not include drugs that are indicated to treat patients acutely with an MI and then are continued for no more than one year.

Note that guideline recommendations usually refer to drug classes, while labeling refers to individual molecular entities.[2] Guideline recommendations described below are those that have a "Level of Evidence" (LOE) of A or B. An LOE of A indicates a recommendation based on multiple RCTs or a meta-analysis, while an LOE of B means that the supporting evidence is based on at least one RCT or multiple non-randomized studies.

Readers who are familiar with current therapy for cardiovascular secondary prevention can skip to the end of this discussion on page 8.

[2] It should be noted that the guidelines do not differentiate between patients with a prior MI and other patients with well documented coronary artery disease.

- **Aspirin:**
    - Aspirin is indicated in the US to reduce the combined risk of death and nonfatal MI in patients with a previous MI or unstable angina pectoris (UA) at a dose of 75 to 325 mg daily, to be continued indefinitely. The Code of Federal Regulations provision establishing this labeling (21 CFR Part 343.80) indicates that 6 placebo-controlled RCTs were conducted in patients with a prior MI and one such trial was conducted in patients with UA. In the combined prior MI studies (all in men only), there was a ~ 20% reduction in the composite endpoint of "subsequent death and/or reinfarction," although event rates were not provided. However, event rate data are available from a meta-analysis published in 2002 involving 12 RCTs of the use of aspirin in patients with a prior MI including 20,000 patients.(2) In those studies, the incidence of vascular death, MI or stroke over a mean of 27 months of treatment was 13.5% with aspirin vs. 17.0% with control (not specified), with a 25% reduction in the OR for this endpoint in the aspirin group. Note that ticagrelor labeling in the US indicates that there is reduced efficacy for the ACS indication when ticagrelor is used with aspirin doses greater than 100 mg. In the EU, labeling for the ticagrelor ACS indication recommends use with aspirin 75 – 150 mg daily.
    - The 2011 AHA/ACC secondary prevention guidelines recommend aspirin 75 to 162 mg daily as first-line therapy for secondary prevention in patients with CAD.

- **Clopidogrel:**
    - Based on the results of the aspirin-controlled CAPRIE study, clopidogrel is indicated for use in patients with "[r]ecent MI, recent stroke, or established peripheral arterial disease. Plavix has been shown to reduce the combined endpoint of new ischemic stroke, new MI, and other vascular death." However, in Section 14, it states that results for the primary endpoint of vascular death, ischemic stroke or MI were heterogeneous over the 3 populations named in the indication, and that, "In patients who were enrolled in the trial on the sole basis of a recent myocardial infarction, Plavix was not numerically superior to aspirin."
    - In the guidelines, clopidogrel is recommended for patients with CAD as second-line therapy "as an alternative for patients who are intolerant of or allergic to aspirin."

- **Beta-blockers:**

  Class members with labelled secondary prevention claims include:
    - Carvedilol "is indicated to reduce cardiovascular mortality in clinically stable patients who have survived the acute phase of a myocardial infarction and have a left ventricular ejection fraction of ≤40% (with or without symptomatic heart failure)." The duration of use is indefinite.
    - Metoprolol is "indicated in the treatment of hemodynamically stable patients with definite or suspected acute myocardial infarction to reduce cardiovascular mortality." The recommended duration of use is unclear but indefinite use seems consistent with the text describing use in patients with an MI.
    - Propranolol is "indicated to reduce cardiovascular mortality in patients who have survived the acute phase of myocardial infarction and are clinically stable." The duration of use is indefinite.
    - Timolol "is indicated in patients who have survived the acute phase of myocardial infarction, and are clinically stable, to reduce cardiovascular mortality and the risk of reinfarction."

Use of beta blockers is recommended in the guidelines as follows:

- Use in all patients with left ventricular systolic dysfunction (ejection fraction ≤ 40%) with heart failure or prior myocardial infarction, unless contraindicated. (Use should be limited to carvedilol, metoprolol succinate, or bisoprolol, which have been shown to reduce mortality.) (Class I, LOE A)
- It is reasonable to continue beta-blockers beyond 3 years as chronic therapy in all patients with normal left ventricular function who have had myocardial infarction or ACS. (Class IIa, LOE B)

- **ACE inhibitors (ACEIs):**

ACEIs with secondary prevention claims include:

- Lisinopril is indicated for "the treatment of hemodynamically stable patients within 24 hours of acute myocardial infarction, to improve survival." This indication is based on the results of the GISSI 3 trial, which had a 6 week survival endpoint. The effects of longer term treatment are not clear.
- Ramipril is indicated "in patients 55 years or older at high risk of developing a major cardiovascular event because of a history of coronary artery disease, stroke, peripheral vascular disease, or diabetes that is accompanied by at least one other cardiovascular risk factor (hypertension, elevated total cholesterol levels, low HDL levels, cigarette smoking, or documented microalbuminuria), to reduce the risk of myocardial infarction, stroke, or death from cardiovascular causes. " Treatment duration is indefinite.
- Captopril is indicated "to improve survival following myocardial infarction in clinically stable patients with left ventricular dysfunction manifested as an ejection fraction ≤40% and to reduce the incidence of overt heart failure and subsequent hospitalizations for congestive heart failure in these patients." Treatment duration is indefinite.
- Perindopril is indicated "for treatment of patients with stable coronary artery disease to reduce the risk of cardiovascular mortality or nonfatal myocardial infarction." This indication is based on the result of EUROPA, which included patients with an MI at least 3 months prior to screening, as well patients without an MI who had other evidence of CAD. Treatment duration is indefinite.
- Trandolapril "is indicated in stable patients who have evidence of left-ventricular systolic dysfunction (identified by wall motion abnormalities) or who are symptomatic from congestive heart failure within the first few days after sustaining acute myocardial infarction. Administration of trandolapril to Caucasian patients has been shown to decrease the risk of death (principally cardiovascular death) and to decrease the risk of heart failure-related hospitalization

Recommendations in the guidelines include:

- Use of ACEIs in patients with an MI and ejection fraction ≤ 40% and in those with hypertension, diabetes, or CKD, unless contraindicated (Class I, LOE A). Use indefinitely.
- It is reasonable to use ACEIs in all other patients with ASCVD. Use indefinitely. (Class IIa, LOE B).

- **Angiotensin receptor blockers (ARBs):**

Members of this class with post-MI secondary prevention claims include:

- Valsartan is indicated to "reduce cardiovascular mortality" in "clinically stable patients with left ventricular failure or left ventricular dysfunction following myocardial infarction." The duration of treatment is indefinite.

- Telmisartan "is indicated for reduction of the risk of myocardial infarction, stroke, or death from cardiovascular causes in patients 55 years of age or older at high risk of developing major cardiovascular events who are unable to take ACE inhibitors." The target patient population includes those with a prior MI. The duration of treatment is indefinite.

Guideline recommendations are as follows:

- The use of ARBs is recommended in patients who have heart failure or who have had a myocardial infarction with left ventricular ejection fraction ≤ 40% and who are ACE-inhibitor intolerant (Class I, LOE A)
- It is reasonable to use ARBs in other patients who are ACE-inhibitor intolerant. (Class IIa, LOE B)

- **Vorapaxar:**
  Vorapaxar is a first-in-class antiplatelet agent that is an antagonist of the protease-activated receptor-1 (PAR-1), which is expressed on platelets and activated by thrombin. It was approved in 2014 "for the reduction of thrombotic cardiovascular events in patients with a history of myocardial infarction (MI) or with peripheral arterial disease (PAD). ZONTIVITY has been shown to reduce the rate of a combined endpoint of cardiovascular death, MI, stroke, and urgent coronary revascularization (UCR)." In the TRA°2P study that supported this approval, vorapaxar was started between 2 weeks and 12 months after an MI. The duration of treatment is indefinite. Vorapaxar should be used with aspirin and/or clopidogrel. Vorapaxar is not mentioned in the 2011 secondary prevention guidelines, which were drafted prior to the completion of TRA°2P and approval of the drug.

- **Statins:**
  - Atorvastatin has a secondary prevention indication:
    "Prevention of Cardiovascular Disease
    In patients with clinically evident coronary heart disease [including patients with a history of MI], LIPITOR is indicated to:
    - Reduce the risk of non-fatal myocardial infarction
    - Reduce the risk of fatal and non-fatal stroke
    - Reduce the risk for revascularization procedures
    - Reduce the risk of hospitalization for CHF
    - Reduce the risk of angina"

    This indication was added to labeling in 2007. There are no specific dosing instructions in Sec. 2 for this indication, but in Sec. 14 there is a description of the TNT study (3), on which this indication was based. This RCT compared fixed doses of atorvastatin 80 mg to atorvastatin 10 mg daily in a population with "clinically evident" CAD with an LDL-C level <u>less than</u> 130 mg/dL after 8 weeks of treatment with open label atorvastatin 10 mg daily. There was a statistically significant 22% reduction in the primary composite endpoint of coronary death, non-fatal MI, resuscitated cardiac arrest, and fatal and non-fatal stroke with the higher dose. The dose of atorvastatin used in TNT, 80 mg daily, is considered "high intensity" treatment in the guidelines (see below).

  - Simvastatin is indicated for:
    "Risk of CHD Mortality and Cardiovascular Events

In patients at high risk of coronary events because of existing coronary heart disease, diabetes, peripheral vessel disease, history of stroke or other cerebrovascular disease, ZOCOR is indicated to:

- Reduce the risk of total mortality by reducing CHD deaths.
- Reduce the risk of non-fatal myocardial infarction and stroke.
- Reduce the need for coronary and non-coronary revascularization procedures."

This indication has no reference to baseline lipid levels or lipid targets. The recommended dose for this indication is 40 mg daily. This dose is "moderate intensity" treatment as described in the guidelines.

o Cholesterol treatment guidelines:
In 2013, while PEGASUS was underway, the AHA/ACC guidelines on the treatment of blood cholesterol were modified to include what is essentially a secondary prevention claim for selected statins that is silent regarding treatment of elevated lipid levels. The guidelines recommend use of "high intensity" statin treatment for adults ≤ 75 years old with clinical atherosclerotic cardiovascular disease (ASCVD),[3] including those with a prior MI, who can tolerate these drugs. "High intensity" treatment is defined as 80 mg atorvastatin daily (40 mg for those who cannot tolerate 80 mg) or 20 mg rosuvastatin daily (40 mg is a labeled dose, but there was little experience with that dose). "Moderate intensity" treatment is recommended for those over 75 with ASCVD or when there are safety concerns about use of high dose statins.[4] These recommendations are made without suggesting that treatment should be reserved for persons with an LDL level above some trigger and do not state that LDL should be reduced to some target level. The secondary prevention claim of atorvastatin, discussed above, is consistent with the guidelines.

Notably, rosuvastatin has no secondary prevention claim that is consistent with the guidelines. There is a primary prevention claim that is based on the placebo-controlled JUPITER trial (4) and is independent of lipid levels:

"Primary Prevention of Cardiovascular Disease
In individuals without clinically evident coronary heart disease but with an increased risk of cardiovascular disease based on age ≥ 50 years old in men and ≥ 60 years old in women, hsCRP ≥ 2 mg/L, and the presence of at least one additional cardiovascular disease risk factor such as hypertension, low HDL-C, smoking, or a family history of premature coronary heart disease, CRESTOR is indicated to:

- reduce the risk of stroke
- reduce the risk of myocardial infarction
- reduce the risk of arterial revascularization procedures"

[3] Clinical atherosclerotic vascular disease is defined as a history of any ACS, stable angina, coronary or other arterial revascularization procedure, stroke, TIA, or PAD presumed to be of atherosclerotic origin.
[4] Moderate intensity statin treatment includes the following regimens: atorvastatin 10-20 mg, rosuvastatin 5-10 mg, simvastatin 20–40 mg, pravastatin 40-80 mg, lovastatin 40 mg, fluvastatin XL 80 mg, fluvastatin 40 mg BID, pitavastatin 2–4 mg. Dosing is once daily unless otherwise specified.

The recommended dose for this indication is not stated in Sec. 2 of labeling, but Sec. 14 states that the dose used in JUPITER was 20 mg daily, which is "high intensity" treatment as described in the guidelines.

2.2 Other Approvals of Ticagrelor

Ticagrelor is approved for treatment of ACS in the US, EU, Canada, Australia, and elsewhere. We are not aware of any approvals for the secondary prevention indication that is the subject of this review.

3 CMC/Biopharmaceutics

The CMC review by Dr. Kris Raman is complete and recommends approval. The recommended shelf life at this point is 36 months for all presentations of the 60 mg tablet. OPF has approved the proposed facility.

Drug Substance

The drug substance is ticagrelor and is identical to the one used in the marketed 90 mg tablet.

Drug Product

A new dosage form, an immediate-release, 60 mg compressed tablet with a pink coating, is proposed to fulfill the maintenance dosing instructions proposed for the secondary prevention indication (60 mg orally bid). The currently marketed 90 mg tablet is also an immediate-release compressed tablet, but has a yellow coating. The same blend of ingredients is used to make each of the two tablet cores, and was also used to make the core of clinical trial formulation used in PEGASUS. (b) (4)

- The 60 mg tablet: The tablet core has a compression weight of 200 mg. It contains 60 mg of ticagrelor (b) (4) and the following inactive ingredients: mannitol (b) (4), dibasic calcium phosphate (b) (4), sodium starch glycolate (b) (4), hydroxypropyl cellulose (b) (4), magnesium stearate (b) (4). The coating contains hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol 400, ferric oxide black, ferric oxide red and purified water.

- The 90 mg tablet: The tablet core has a compression weight of 300 mg. It contains 90 mg of ticagrelor and the following inactive ingredients: mannitol, dibasic calcium phosphate, sodium starch glycolate, hydroxypropyl cellulose, magnesium stearate, and purified water qs. (b) (4) The coating contains hydroxypropyl methylcellulose, titanium dioxide, talc, polyethylene glycol 400, and ferric oxide yellow and purified water.

The PEGASUS clinical trial tablet has a core that is identical to the core of the proposed 60 mg tablet. The coating is white.

A biopharmaceutics review was completed and signed by Drs. Banu Zolnik and Elsbeth Chikhale. They reviewed the proposed dissolution method and acceptance criteria for the new 60 mg tablet and the data supporting bridging from the clinical trial formulation to the to-be-marketed formulation. They found that the dissolution method and acceptance criteria, which are similar to those for the marketed 90 mg tablet, were acceptable. They also found that "Based on the overlapping dissolution profiles, differences between the formulation used in the clinical studies and to-be-marketed do not impact the product performance." Their final conclusion was from the Biopharmaceutics perspective the efficacy supplement for the PEGASUS-based claim sought by the Applicant "is recommended for APPROVAL."

4 Nonclinical Pharmacology/Toxicology

There are no non-clinical pharmacology issues affecting approval. No non-clinical data was included in the Supplement, and none is required for the new indication.

5 Clinical Pharmacology

There are no clinical pharmacology issues affecting approval or indicating the need for a postmarketing commitment.

The reviewer in OCP was Dr. Sreedharan Sabarinath, and the other signatories were Drs. Jeffry Florian and Rajanikanth Madabushi. They emphasized the following points:

Their review concise and lucid review is an abbreviated question-based review that addresses the issues relevant to the supplement. Detailed information on the clinical pharmacology of ticagrelor is available in the original submission reviews for NDA 22433. [5]

They reached the following conclusions:

- A dose response was not apparent for efficacy. Primary endpoint results for the 60 mg bid and 90 mg bid arms were quite similar, and both active arms were superior to placebo. However, the expected dose response was observed for bleeding (see Section 6, Clinical, for more information).
- No changes to Section 7 or 12 of the approved label are needed.

They discussed gender-specific findings. For males in both active treatment arms and for women on the 90 mg treatment arm, there was a finding of improved efficacy relative to the control arm. However, a finding of similar efficacy for ticagrelor 60 mg and placebo was observed in women (HR: 0.98 [95 % CI 0.78-1.24]). However, PK observations from PEGASUS (~30 % higher exposure in females relative to males) cannot explain the subgroup findings in females administered 60 mg twice daily.

Further evaluation suggested to the reviewers that this finding is not exposure-related because consistent trends in efficacy and safety were not identified between doses and male/female subgroups. As noted below, the higher exposure in women relative to men in the ticagrelor 60 bid arm was associated with the expected increased risk of bleeding relative to men, even

[5] NDA 22433 Clinical Pharmacology Reviews, DARRTS dates 6/27/2010 and 8/29/2010

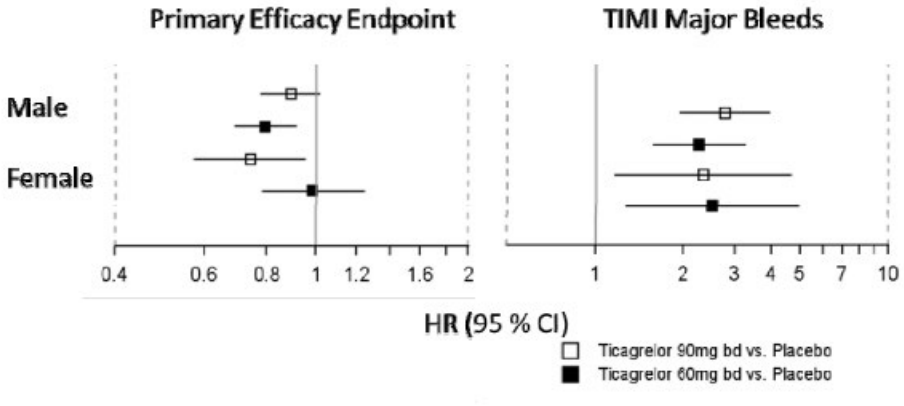
though efficacy in women was observed to be less than in men in this arm (**Table 1** and **Figure 1**). The OCP thus believed the finding of reduced efficacy in women with ticagrelor 60 mg bid was likely a chance event.

Table 1 OCP Analysis of Weight and Steady State Concentrations by Gender in PEGASUS

Characteristics/Dose Group	Males		Females	
	60 mg	90 mg	60 mg	90 mg
Median C_{ss} (nM)	796	1314	1040	1688
Mean Body Weight (kg)	87	86	76	75
Mean Age (years)	64	64	67	67

Source: Prepared by FDA, PEGASUS study PK subset

Figure 1 Primary Efficacy Endpoint and TIMI Major Bleeding in PEGASUS by Gender



6 Clinical Microbiology

Ticagrelor is an oral tablet. No microbiology data were provided in the supplement.

7 Clinical/Statistical- Efficacy

7.1 Clinical Program

The current protocol was an outgrowth of two SPA submissions for a post-MI secondary prevention study, both in 2009 and each followed by a non-agreement letter. In the second NA letter we expressed our oft-stated concerns about CYP2C19 inhibitors and poor metabolizers in connection with the planned use of clopidogrel in patients who develop an ACS during the study. We also expressed our strong preference for including more than one dose of ticagrelor in PEGASUS. There were no further SPA submissions after the second NA letter. The Applicant then submitted a revised protocol in 2010 with two doses of ticagrelor vs. placebo – 90 mg bid (the same dose as used in PLATO) and 60 mg bid. The rationale for the latter dose was that it would provide a level of platelet inhibition intermediate between that provided by 90

mg bid and clopidogrel 75 mg. The sponsor argued that a dose higher than 90 mg bid would provide minimally increased platelet inhibition, while a substantially lower dose, 45 mg bid, would have similar platelet inhibition as clopidogrel, which seemed to be of no interest to the Applicant. The Division remained concerned that the two selected doses were too close together and might not be possible to distinguish them clinically. The sponsor went forward with the study without a SPA in 2010. A SAP was submitted in 2013 after the study was underway. We found it "acceptable".

7 . 2 Design and results of the pivotal efficacy study: PEGASUS.

7.2.1 Protocol design

In support of the proposed indication, the Applicant conducted one trial, PEGASUS. This was a 21,162-patient,international, randomized, double-blind, double-dummy, event-driven, 3-arm study comparing ticagrelor 60 mg bid, ticagrelor 90 mg bid and placebo in patients age 50 and above with a history of spontaneous MI 1 to 3 years prior to enrollment, with no intervening MIs. No loading dose of ticagrelor was used. All patients were to be receiving aspirin at a dose of 75 to 150 mg daily at entry and for the course of the study.

In addition to the history of spontaneous MI, patients were required to have at least one of five additional risk factors for CV events:

- Age ≥ 65 years
- Diabetes mellitus requiring pharmacologic treatment
- Cockcroft-Gault creatinine clearance (CrCL) ≤ 60 mL/min
- One or more MIs prior to the MI that established eligibility for the trial
- Angiographic evidence of multi-vessel coronary disease.

Implications of this prognostic enrichment strategy are discussed following the efficacy results.

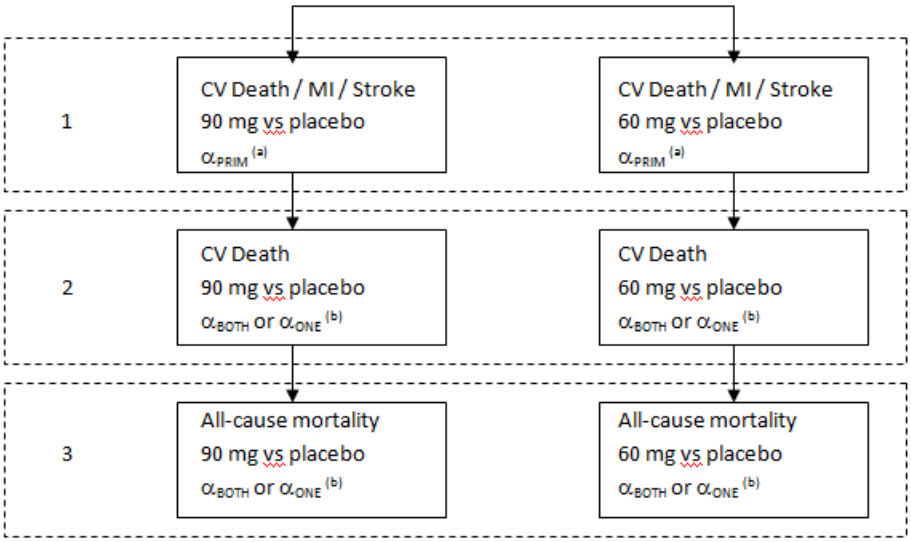
Key health-related study exclusions included:

- planned use of an ADP receptor blocker
- planned arterial revascularization, or
- use of strong CYP3A inhibitors or CYP3A substrates with narrow therapeutic indices that could not be stopped for the duration of the study
- need for chronic oral or injectable anticoagulant therapy (at venous thromboembolism treatment doses, but not at prophylaxis doses)
- An ischemic stroke within 14 days of enrollment (this exclusion was later widened in scope, see below for details)
- History of ICH or other specified risk factors for serious bleeding
- Sick sinus syndrome or 2nd or 3rd degree heart block, unless the patient has a permanent pacemaker
- Known severe liver disease (e.g., ascites or signs of coagulopathy)
- Renal failure requiring dialysis or anticipated need for dialysis (this was the only renally-based exclusion)

The primary study endpoint was time to the first event of the composite of CV death, MI or stroke (MACE), and was analyzed using a Cox model with a factor for each treatment arm. Each ticagrelor dose was tested separately against placebo. The multiplicity issue arising from testing two doses against placebo was handled with the Dunnett approach. There was a single

interim analysis when ~50% of the planned 1360 events were attained, but the DMC did not recommend stopping the study. The final alpha allotted to each treatment arm was 0.02598. Secondary endpoints were CV death and all-cause death, these were included in the planned multiple testing procedure, shown in **Figure 2**.

Figure 2 Multiple Testing Procedure



(a) The significance level for the primary analysis at the final analysis αPRIM=0.02598 was determined based on the proportion of events and the interim analysis using the Haybittle-Peto approach.
(b) If tests of both doses are significant for the endpoint at the previous level in the hierarchy, then both doses would be tested at significance level αBOTH=0.02478. If only one of the tests is significant for the previous endpoint, this dose will be tested at significance level αONE=0.02106 determined based on the proportion of events at the interim analysis.
Source: CSR Figure 5

If a patient developed an indication for dual antiplatelet therapy during the trial (e.g., ACS or PCI), the investigator was to select therapy per local standard of care. If clopidogrel was considered appropriate therapy, it was recommended that the patient be reassigned by the IVRS to either ticagrelor 90 mg + ASA (for those for either ticagrelor arm) or to clopidogrel + ASA (for placebo arm patients) in a blinded fashion. Additional tablets (ticagrelor) or capsules of active clopidogrel medication were provided for loading doses, along with placebo for the other medication. The ticagrelor loading dose was 180 mg, while the clopidogrel loading dose could be either 300 or 600 mg. This was achieved in a blinded fashion. Patients given clopidogrel were not required to be genotyped. Rather, local practice and guidelines were to guide physicians in selecting open-label antiplatelet therapy.

There was one notable global protocol amendment. On 9 March 2011, a little over 4 months after the first patient was enrolled, the protocol exclusion criteria were changed to exclude all subjects with a prior history of any type of stroke at any time, as well as those with history of CNS tumor or vascular abnormality, and also those with intracranial or spinal cord surgery within the last 5 years. Prior to that, patients with intracranial hemorrhages, including those with hemorrhagic strokes, were excluded, along with those who had a ischemic stroke within 14 days of screening. This amendment has labeling implications that will be discussed subsequently.

7.2.2 Patient Disposition and Characteristics

The study ran from 29 October 2010 (1st patient in) to 3 December 2014 (last patient visit). The common study end date (CSED) for censoring purposes was 14 September 2014.

Table 2 is a display of study statistics, analysis populations and disposition for the overall study population. Over 98% of patients overall were followed to the CSED (or their death, if sooner) for the primary endpoint and mortality endpoints.

Table 2 PEGASUS Subject Disposition and Study Statistics

PARAMETER	Value for entire study
Patients randomized (Full analysis set, FAS)	21,162 (100%)
Took One Dose of Study Medication (Safety set)	20,942 (99.0%)
Followed-up for all primary endpoints events from randomization to death or CSED	20,892 (98.7%)
Withdrew consent	154
Lost to follow-up	10
Maximum duration of exposure	48 months
Minimum follow-up (for those who did not withdraw or die)	16 months
Study sites	1164
Countries	31
Targeted number of primary events	1360
Primary events through CSED	1558

Source: Adapted from Clinical Review, Table 8, based on the Applicant's complete study report (CSR)
Perctentages are based on the number randomized.

About 1% of randomized subjects in each arm did not ingest any study drug. Of those who were exposed to study drug, the rate of premature discontinuation of study drug was 32%, 29% and 21% in the ticagrelor 90 mg bid, ticagrelor 60 mg bid and placebo arms, respectively. In each of the 3 arms, the most common cause of discontinuation was the occurrence of an adverse event (20%, 18%, and 11% of those who were exposed, respectively, Table 3). This is discussed further in the section on safety.

Additional follow-up and exposure information by treatment arm is shown in Table 4.

Table 3 Disposition – Study Drug

Number (%) of patients	Ticagrelor 90mg bd N=7050	Ticagrelor 60mg bd N=7045	Placebo N=7067
Patients who received study drug [a]	6988 (99.1%)	6958 (98.8%)	6996 (99.0%)
Completed treatment with study drug [b,c]	4755 (68.0%)	4959 (71.3%)	5500 (78.6%)
Discontinued study drug early [c]	2233 (32.0%)	1999 (28.7%)	1496 (21.4%)
"Inclusion/exclusion criteria violation that places patient at undue risk"[d]	32 (0.5%)	38 (0.5%)	45 (0.6%)
AE/SAE	1434 (20.5%)	1257 (18.1%)	784 (11.2%)
Severe non-compliance with the study protocol	35 (0.5%)	23 (0.3%)	16 (0.2%)
Pregnancy	0	0	0
Patient decision	689 (9.9%)	635 (9.1%)	590 (8.4%)
Other	43 (0.6%)	46 (0.7%)	61 (0.9%)
Unknown	0	0	0

a – Percentage of those randomized (see N in column headers for the treatment arms).
b – Defined as those who did not discontinue early or those who died during treatment
c – Percentage of those who received study drug
d—Applicant's terminology. This category includes patients who took study drug but were discontinued for having a history of ischemic stroke at baseline, which became an exclusion after the study began.

Table 4 PEGASUS Follow-up and Exposure Information
All randomized patients

Parameter	Ticagrelor 90mg bd N=7050	Ticagrelor 60mg bd N=7045	Placebo N=7067	Sum of Patient-Yrs
Follow-up to CSED (median in months)	33.1	33.3	33.1	-
Follow-up to CSED (patient-yrs)	18681	18656	18667	56004
Actual treatment exposure [1] (median in months)	27.7	28.7	30	-
Actual treatment exposure [1] (patient-yrs)	13710	14440	15766	43916

1. From first dose to last dose, minus periods of interruption

Patient Characteristics

Given the size of the study, it is not surprising that the three treatment arms were well balanced for all common demographic characteristics and risk factors. Ranges in the 3 arms for the following parameters of regulatory or medical interest were:

Demographic factors

- Mean age: 76 to 77 years
  - ≥ 65: 53% to 55%
  - ≥75: 14% to 15%
- Women: 24% in each arm
- Race (groups with 2% or more)
  - Caucasian: 86% to 87%
  - Black: 2% in each arm
  - Asian: 9% to 10%
- Hispanic ethnicity: 12% in each arm
- BMI (median): 27.8 to 27.9
- Smoking
  - Current smoker: 16% to 17%
  - Former smoker: 48% in each arm
  - Never smoked: 16% to 17%
- Region
  - US: 12% in each arm
  - Canada: 6% in each arm
  - Europe: 50% to 51%
  - Asia: 14% in each arm
  - Africa: 2% in each arm
  - Other: 2% in each arm

Atherothrombotic qualifying risk factors (having at least one was required for enrollment)

- Age ≥ 65: 53% to 55%
- Diabetes requiring medication: 28% to 29%
- History of >1 MI prior to randomization: 16% to 17%
- Multivessel CAD: 59% to 60%
- Chronic end-stage renal dysfunction: 6% in each arm
- Number of qualifying risk factors at enrollment:
  - 0 (this is a protocol violation): 0.6% to 0.7%
  - 1: 51% to 52%
  - 2: 33% to 34%
  - ≥ 3: 14% to 15%

Other risk factors for CV events

- Time from qualifying MI to randomization:
  - Median (months): 20.5 to 20.7
  - < 1 year (protocol violation): 0.6% to 0.8%
  - ≥ 1 to < 2 years: 61% in each arm
  - ≥2 to ≤ 3 years: 38% in each arm
  - ≥ 3 years (protocol violation): 0.5% to 0.6%
- Time from end of ADP blocker therapy to randomization
  - Ongoing at randomization but stopped prior to first dose of study drug: 0.1% in each arm
  - Continued after first dose of study drug (protocol violation): 0.2% to 0.3%
  - 0-7 days: 26% in each arm

    - 8-90 days: 18% in each arm
    - 3 to 12 months: 21% to 22%
    - > 12 months: 23% to 24%
- Type of qualifying MI
    - STEMI: 53% to 54%
    - NSTEMI: 40% to 41%
    - Unknown: 5% to 6%
- Prior stroke: 0.4% to 0.6%
- Heart failure at baseline: 20% to 21%
- Permanent pacemaker for bradycardia: 1.4% to 1.6%
- Atrial fibrillation or flutter: 4.0% to 4.2%
- Hypertension requiring medical therapy: 77% to 78%
- Hypercholesterolemia requiring medical therapy: 76% to 77%
- Angina pectoris: 31% in each arm
- Family history of premature coronary disease: 30% in each arm
- History of stent placement: 80% in each arm
    - DES: 39% in each arm
    - BMS: 42% to 43%
- History of CABG: 4.4% to 4.8%

Cardiovascular medications taken within 7 days of randomization:

- Antiplatelet medication: 99.8% to 99.9%
    - **Aspirin: 99.7% to 99.8%**
        - Dose < 75 mg: 1 patient in the ticagrelor 90 mg bid arm
        - 75 mg to 100 mg : 94% in each arm
        - 101 mg to 150 mg: 2.3% in each arm
        - > 150 mg: 3.1% to 3.6%
    - Clopidogrel: 26% in each arm
    - Prasugrel: 0.2% to 0.3%
    - Ticagrelor: 0.2% to 0.3%
- Oral anticoagulants: 0.0% to 0.1%
- **Beta blockers: 83% in each arm**
- **ACEs: 58% to 59%**
- **ARBs: 23% to 24%**
- CCBs: 19% to 20%
- "Lipid lowering agents:" 94% to 95%
    - **Statins: 93% to 94%**
        - Atorvastatin: 46% to 47%
        - Rosuvastatin: 19% to 21%
        - Simvastatin: 28% in each arm
        - Pravastatin: 3.3% to 3.8%
        - Lovastatin: 2.4% to 2.5%
        - Others – each was used by less than 2% in any arm
- Nitrates: 23% in each arm
- Digitalis: 0.7% to 0.9%

Over 90% of patients were taking a statin at baseline, and 83% of persons in each arm were taking beta blockers. If there were few patients taking both ACEIs and ARBs, as seems likely,

then about 80% of patients were taking a member of one of these two classes of drugs at baseline.

Of note, the administered dose of a concomitant medication was recorded routinely only for aspirin. In addition, the dose was recorded for antiplatelet drugs started during the study because of an acute event requiring antiplatelet therapy, such as ACS or PCI.

Efficacy Results

Results for the primary endpoint, its components, the two secondary endpoints (CV death and all-cause death; and stroke types are displayed in **Table 5**. The results can be summarized as follows:

- Both ticagrelor arms met the protocol-specified criteria for superiority to placebo (two-sided p<0.2598), with 15-16% reductions in the hazard.
- Both active arms had markedly lower rates of MI than placebo.
- Both active arms had lower rates of stroke than placebo
- There were few hemorrhagic strokes. There did not appear to be an increased risk of hemorrhagic stroke with ticagrelor at either dose.
- Results for CV death as an independent event favored both active arms compared to placebo, but neither active arm met the criteria for superiority over placebo (p<0.02478). Results were more favorable for the 60 bid arm.
- Results for all-cause death compared to placebo were neutral for the 90 mg bid arm and leaned in favor of the 60 mg bid arm.

Overall, the results could support approval of either studied dose of ticagrelor, but appear more favorable for 60 mg bid.

Table 5 PEGASUS – Efficacy Analyses
All randomized subjects, followed from randomization to CSED

Endpoint	Ticagrelor 90 mg bid (N=7050)		Ticagrelor 60 mg bid (N=7045)		Placebo (N=7067)		T 90 vs. P HR (95% CI) p	T 60 vs. P HR (97.5% CI) p
	# of events (%)	KM Event Rate[1]	# of events (%)	KM Event Rate[1]	# of events (%)	KM Event Rate[1]		
Primary Endpoint (CV death, MI, Stroke)	493 (7.0%)	7.8%	487 (6.9%)	7.8%	578 (8.2%)	9.0%	0.85 (0.75, 0.96) 0.008	0.84 (0.74, 0.95) 0.004
CV death	127 (1.8%)		116 (1.6%)		128 (1.8%)			
MI	272 (3.9%)		283 (4.0%)		335 (4.7%)			
Stroke	94 (1.3%)		88 (1.2%)		115 (1.6%)			

(Continued on next page)

(Table 3 continued)

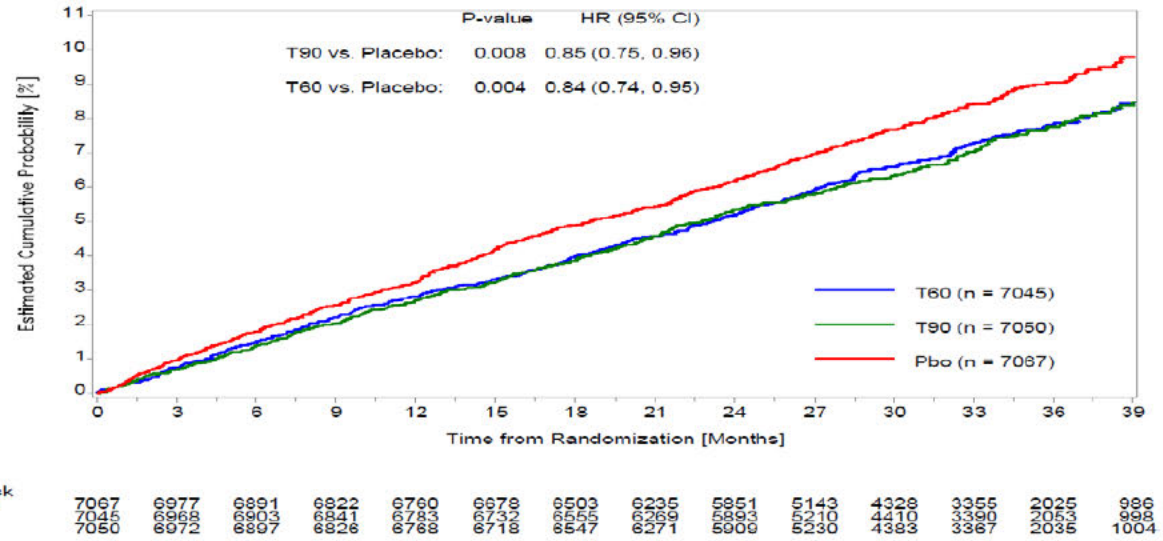
Endpoint	Ticagrelor 90 mg bid (N=7050)		Ticagrelor 60 mg bid (N=7045)		Placebo (N=7067)		T 90 vs. P HR (95% CI) p	T 60 vs. P HR (97.5% CI) p
	# of events (%)	KM Event Rate[1]	# of events (%)	KM Event Rate[1]	# of events (%)	KM Event Rate[1]		
First events of each type considered individually								
CV death	182 (2.6%)	2.9%	174 (2.5%)	2.9%	210 (3.0%)	3.4%	0.87 (0.71, 1.06) 0.15	0.83 (0.68, 1.01) 0.067
All-Cause Death	326 (4.6%)	5.1%	289 (4.1%)	4.7%	326 (4.6%)	5.2%	1.00 (0.86, 1.16) 0.99	0.89 (0.76, 1.04) 0.14
MI	275 (3.9%)	4.4%	285 (4.0%)	4.5%	338 (4.8%)	5.2%	0.81 (0.69, 0.95) 0.01	0.84 (0.72, 0.98) 0.031
Stroke	100 (1.4%)	1.6%	91 (1.3%)	1.5%	122 (1.7%)	1.9%	0.82 (0.63, 1.07) 0.14	0.75 (0.57, 0.98) 0.03
Ischemic	88 (1.2%)		78 (1.1%)		103 (1.5%)			
Hemorr.	6 (0.1%)		10 (0.1%)		13 (0.1%)			
Unknown	6 (0.1%)		4 (0.1%)		6 (0.1%)			

1 -- KM rate to 36 months

Source: PEGASUS CSR Tables 11.2.1; 11.2.2; 11.2.3.1

Figure 3 KM Plot of Primary Endpoint Events

All randomized patients followed to CSED



Source: Statistical Review, reviewer's analysis

Dr. Bai's analysis of the primary endpoint agrees with the Applicant's. He also performed an analysis that indicates that the beneficial effect of ticagrelor was consistent over the course of the study (data not shown). Consistent with that analysis, the KM curves for each ticagrelor dose appear to be diverging from the placebo curve throughout the course of the study (**Figure 3**).

US Sites

Dr. Dunnmon analyzed efficacy for sites in the US with N= 866, 863 and 872 in the ticagrelor 90 mg bid, ticagrelor 60 mg bid and placebo arms, respectively. Components of the primary endpoint were analyzed without regard to endpoints of other types in the same patient. His results were (HR and 95% CI only):

Parameter	Ticagrelor 90 mg bid vs. placebo, HR (95% CI)	Ticagrelor 60 mg bid vs. placebo, HR (95% CI)
Primary endpoint	0.99 (0.73, 1.35)	0.78 (0.56. 1.08)
CV death	1.27 (0.70, 2.35)	0.74 (0.36, 1.47)
MI	0.85 (0.58, 1.24)	0.81 (0.55, 1.17)
Stroke	1.40 (0.69, 2.91)	0.76 (0.33, 1.75)

These results support the efficacy of ticagrelor 60 mg bid.

The statistical review by Drs. Bai and Hung agreed that PEGASUS met its primary objective and demonstrated the efficacy of ticagrelor (at each studied dose) in terms of reducing the rate of MACE compared to placebo. The secondary endpoints of superiority for CV and all-cause death did not meet the protocol's criteria for superiority. However, the study showed consistent benefit for the primary endpoint over time and in most, but not all subgroups. They have no issues with approval of this supplement.

7.2.3 Issues Relating to Efficacy

7.2.3.1 Approval Based on One Study

Pegasus is a large, mostly internally-consistent placebo-controlled trial against a background aspirin therapy. The p for the primary endpoint was 0.004 for ticagrelor 60 mg bid, with reductions in the rate of all 3 components of the primary endpoint compared to placebo, with p <0.05 for stroke and also for MI. The p for 90 mg bid vs. placebo was 0.008, with reductions in the rate of MI and stroke but no benefit for CV death; only the p for MI was less than 0.05. No other secondary prevention study supports approval.

While ordinarily FDA requires two well-controlled studies to support a finding that there is substantial evidence of effectiveness, sometimes one will suffice. The scenarios where one study is enough to provide substantial evidence of effectiveness are discussed in the joint CDER/CBER guidance entitled, "Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products" (1998). These include the following scenarios that apply here:

- **"Studies in other phases of the disease:"** The guidance states that a single study may be adequate to establish effectiveness if the same drug was effective in a well-controlled study in another stage of the disease. The hypothetical given in the guidance involved a drug known to be effective in patients with a refractory phase of a cancer. The guidance indicates that a single study showing effectiveness in patients with an earlier stage of the same cancer "will generally be sufficient" evidence of effectiveness to support the new use." Here, ticagrelor 90 mg bid with a one-time loading dose of 180 mg was shown to be effective in ACS in the PLATO study, where patients were enrolled within 24 hours of the development of chest pain. They were treated with ticagrelor + aspirin or clopidogrel + aspirin for a year. The primary endpoint was MACE, as it in PEGASUS. Ticagrelor was significantly superior to clopidogrel for the primary endpoint, as well as for the MACE components of MI and CV death, and the additional endpoint of all-cause death. Of note, the KM curves for the primary endpoint continued to diverge in favor of ticagrelor out to the end of the one year study period, suggesting that ticagrelor was superior to clopidogrel in reducing new MACE events all the way out to one year.

  Here, we are comparing ticagrelor to placebo (against a background of aspirin therapy) in patients with an MI at least one year prior to randomization. This is a later stage of MI, which was studied in PLATO along with angina pectoris. In fact, we are considering combining the two indications (acute MI and secondary prevention, into one, with continuous dosing of ticagrelor with a dose reduction from 90 mg bid to 60 mg bid after one year of treatment, because the physiology of the two stages is similar. As noted above, the KM curves for MACE in PLATO were growing farther apart in favor of ticagrelor all the way out to one year. One study should be sufficient to show that ticagrelor is superior to placebo in preventing the same kind of events if treatment is continued beyond one year.
- **"A trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible:"** The guideline indicates that repetition of a strongly positive trial in preventing mortality or irreversible morbidity maybe unethical. Here, both tested doses of ticagrelor showed reductions with $p<0.01$ in the composite MACE endpoint compared to placebo. The dose proposed for use, 60 mg bid reduced all 3 MACE components – MI, stroke and CV death. The other dose, 90 mg bid, reduced both stroke and MI, which are both associated with irreversible morbidity. It would be very difficult if not impossible to conduct another study like PEGASUS.

  PEGASUS has most of the characteristics mentioned in the guidance as supporting use of a single study to support approval, even if PLATO did not exist:
  .
  - **Large multicenter study:** There were 1164 study sites on six continents in PEGASUS that randomized 21,162 patients. No one center provided an unusually large fraction of patients or was disproportionately responsible for the favorable effect of ticagrelor.
  - **Consistency across study subsets:** The beneficial effect of ticagrelor was observed in most of the subsets analyzed in PEGASUS, including those based on region, US vs. OUS, persons with or without the a variety of risk factors, and across subsets based on the number of risk factors had by a patient. However, as noted above, the efficacy of ticagrelor was reduced in women randomized to 60 mg bid.

- **Multiple endpoints involving different events:** As noted above, ticagrelor 60 mg bid reduced the rate of the composite of CV death, MI and stroke, as well as each of the components, compared to placebo. Ticagrelor 90 mg bid reduced the rate of the composite endpoint, MI and stroke. While the composite and CV death are not independent of each other or of MI and stroke, MI and stroke are relatively independent of each other.
- **Multiple studies in a study:** The guideline gives the example of factorial studies that are analyzed as a series of pairwise comparisons of the activity of a drug as monotherapy and in combination with another drug, and thus may be more persuasive than the usual single study as support for effectiveness. Obviously, PEGASUS is not a factorial study, but it does include two doses of ticagrelor (reasonably close together on the dose response curve) compared to placebo, with an alpha-conserving statistical plan. Both doses were superior to placebo for the primary endpoint of MACE with $p<0.01$ for each dose. Thus, results for one dose can be considered as support for the other. When the doses were pooled and compared to placebo for the primary endpoint, ticagrelor was superior to placebo with $p=0.0012$. (HR=0.84, 95% CI: 0.76, 0.94).[6] This last analysis was not in the alpha-conserving hierarchy, but is relevant to the question at hand regarding the persuasiveness of the PEGASUS results for efficacy.
- **Statistically very persuasive finding:** The p values for the comparisons of ticagrelor 60 mg bid and 90 mg bid vs. placebo 0.004 and 0.008, respectively, are each less than 0.05 but are not as low as the p in some studies that were supported approval on the basis of a single study, which are often < 0.001. However, the p for the pooled analysis of the two doses discussed above was 0.0012, which is quite persuasive.

In summary, PEGASUS has many of the attributes that are described in the 1998 effectiveness guideline as characteristics of a single study that might provide substantial evidence of effectiveness for a drug. This reviewer concludes that PEGASUS does provide substantial evidence the effectiveness of ticagrelor 60 mg for use in secondary prevention following an MI.

7.2.3.2 **Scope of the Secondary Prevention Indication**

PEGASUS was a prognostically enriched trial. All patients needed to have a history of MI 1 to 3 years prior to enrollment as well as 1 or more of 5 additional risk factors for CV complications:

- Age ≥ 65 years
- Diabetes mellitus requiring pharmacologic treatment
- Cockcroft-Gault creatinine clearance (CrCL) ≤ 60 mL/min
- One or more MIs prior to the MI that established eligibility for the trial
- Angiographic evidence of multi-vessel coronary disease

Prognostic enrichment is undertaken in most cases to increase the event rate in a trial and thus reduce sample size. However, when a trial is limited entirely to high-risk individuals and is successful, it is reasonable to consider whether the resulting indication should be restricted to a population similar to that enrolled in the trial, or whether it should be broadened to include all those with the condition of interest whether or not they have any of the risk factors that were

[6] CSR Table 11.2.4.3

used for enrichment. Because nominally all subjects in PEGASUS had one more of the risk factors in the list above, this question should be addressed.

The review team determined that we would try to resolve this question with data from PEGASUS. After consulting with Drs. Stockbridge and Southworth, we asked Dr. Tzu-Yun McDowell in our Division to perform analyses of the effects of the various risk factors above and also current smoking and the number of risk factors that a patient had on efficacy (the rate of MACE) and safety outcomes (the rate of TIMI major bleeding (TMB)). We also asked her to model the expected MACE and TMB results for a low risk individual who would have been a protocol violator in the study: one who is 55 years old without any of the 5 risk factors above and was not a smoker.

A summary of her findings regarding baseline risk factors follows:

For MACE –

- The presence of each of the 5 risk factors named in the inclusion criteria ("the 5 risk factors") and also smoking and several other factors individually increased the risk of MACE
- The number of protocol-specified risk factors that a patient has (the "risk factor burden") does not consistently affect the hazard ratio for MACE, although increased risk factor burden was associated with increased risk of MACE
- The risk factor with greatest effect on MACE was > 1 MI prior to enrollment (HR=1.97), followed by CrCL < 60 mL/min (HR=1.70 and diabetes requiring medication (HR=1.67)
- For contrast, the HR for placebo vs. ticagrelor was 1.19 (inverse of 0.84)

For TMB –

- The risk of TMB was increased by age, CrCL < 60 mL/min, current smoking, and non-Caucasian race
- The risk factor burden showed a consistent trend for affecting the bleeding hazard ratio. Increased burden was associated with an increased hazard ratio. Increased burden was also associated with increased bleeding rates for ticagrelor 60 mg bid and placebo.
- The risk factor with greatest effect on TMB was CrCL<60 mL/min (HR=1.85), followed by current smoking (HR=1.71) and age HR=1.52 for a 10 year increment)
- For contrast, the HR for ticagrelor vs placebo was 2.35

Modeling of the low risk individual --

- The estimated hazard ratios for MACE and for TMB for a 55 year old with none of 5 risk factors or smoking for 60 mg bid vs. placebo was similar to the observed overall study results for these parameters. For MACE, the respective hazard ratios for the modeled low risk individual the overall study results were both 0.84; for bleeding the respective hazard ratios were 2.44 and 2.35.
- The estimated rates of MACE were 1.27%/yr. for ticagrelor 60 mg bid and 1.52%/yr., yielding a /risk difference (ticagrelor minus placebo) of -0.25%. For TIMI major bleeding, the respective rates were 0.39%/yr. and 0.16%/yr., yielding a risk difference of + 0.23%/yr. If the two RDs, the sum is -0.02%/yr. (minus values are in favor of ticagrelor). Note that the benefits are CV death, MI and stroke, and the risks are TIMI major

bleeding, but there was no excess of ICH or fatal bleeding with ticagrelor. This means that the excess TIMI major bleeding events were probably reversible events, unlike CV death and many strokes and MIs, which cause irreversible loss of function. One should be willing to trade several reversible TIMI major bleeds for one MI or stroke and many such bleeds to avoid death. Here it's slightly better than a 1:1 trade-off, which should make sense for most patients of this type. This is not as favorable as the benefit risk calculation for the entire study (Appendix 3), but it is still favorable.

For more information on Dr. McDowell's modeling, see the clinical review, Appendix 1.

Given these data, this reviewer concludes that the indicated population should include persons a history of MI without any of the protocol-required risk factors.

However, there is another issue related risk factors that might affect labeling. One of the protocol-specified sets of subgroups for analysis was based on time from the last dose of ADP receptor blocker (ADPRB) to randomization. This parameter varied widely in study patients, from essentially 0 days (in fact, a few patients continued taking open-label ADPRB therapy for a short period after randomization, which was a protocol violation) to more than 1 year. Of the 21,162 randomized patients in PEGASUS, 4982 (24%) discontinued their ADPBR more than 12 months prior to randomization.

Because of the way the inclusion criteria were structured, few very patients in the study should have had a MACE event between the index MI and randomization.[7] Thus, nearly ¼ of patients in the study were off of their ADPRB for more than 12 months without a MACE before they were randomized to receive ticagrelor or placebo. These patients demonstrated that they could go for at least a year without taking an ADPRB and not have a MACE event. One would expect reduced benefit of ticagrelor in preventing MACE in this subgroup.

Table 6 shows the primary endpoint results in subgroups of patients based on the length of time between the end of ADPRB therapy and randomization. As the length time from such treatment increased from < 30 days to > 12 months, the HR for the treatment effect was reduced in a stepwise fashion for both ticagrelor treatment arms vs. placebo. There was no benefit of ticagrelor in patients in the > 12 months subgroup. While subgroup analyses that differ from the main effect should be viewed with skepticism, in this case the same pattern was seen with both doses of ticagrelor and the results are consistent with reasonable expectations. If these findings represent reality, then patients who have done well during an extended time off of ADPRB therapy after an MI would be exposed to the bleeding risk of ticagrelor but receive no benefit if they were started on ticagrelor. This finding should be emphasized in labeling beyond simply being included in a forest plot. It is not surprising that this subgroup did not benefit from ticagrelor at either dose compared to placebo.

[7] All patients randomized after a protocol amendment that went into effect 4.5 months after the first patient was enrolled should have had no MACE events between their index MI and randomization. Prior to this amendment, 102 patients with a history of ischemic stroke prior to randomization were enrolled into the study. These patients discontinued treatment at the time of the amendment (which excluded patients with a prior history of ischemic stroke) but they were followed up to CSED. I did not attempt to identify those who had a stroke between the end of ADPRB treatment and randomization. The contribution of such patients, if there were any, to the information relevant to the issue under discussion here would be *de minimus.*

Subgroups of patients based on time from their index MI to randomization likewise show a decreased benefit of ticagrelor in the subgroup with the longest times, but this trend was considerably more evident in the comparison of 60 mg bid to placebo (**Table 7**). Also, the interaction p values for either comparison were less extreme than for the results in subgroups based on time from end of therapy with an ADPRB to randomization (**Table 6**).

Also, there is substantial overlap of subjects between the subgroups with > 12 months from end of ADPRB treatment to randomization and those with 2 or more years from their qualifying MI to randomization. When patients with >12 months from end of ADPBR to randomization are removed from the subgroup with time from qualifying MI > 2 years, the primary endpoint HR decreases (i.e., becomes more favorable for ticagrelor) for both subgroup comparisons vs. placebo. When the patient with qualifying MI ≥ 2 years before randomization are removed from the subgroup with time from end of ADPRB to randomization > 12 months, the hazard ratio for the comparison of 60 mg bid increases but the hazard ratio decreases for 90 mg bid vis. placebo (see Appendix 2). Overall, the data suggest that those who have not taken ADPRB for a year or more after an MI without having a MACE event are less likely to benefit from ticagrelor. Those whose index MI is more than 2 years prior to starting ticagrelor who have not a MACE event in the interim also seem less likely to benefit from ticagrelor, but the data are not as convincing as the data for those have stopped ADPRB therapy for more than a year.

Table 6 Primary Endpoint Results in Subgroups Based on Time from End of Treatment with an ADPRB to Randomization

Time from end of ADPRB treatment		Ticagrelor 90mg bd (N=7050)	Ticagrelor 60mg bd (N=7045)	Placebo (N=7067)
< 30 days	n	2399	2391	2403
	Patients with events	151 (6.3%)	165 (6.9%)	216 (9.0%)
	KM %	7.3%	8.1%	10.0%
	Hazard Ratio (95% CI)	0.69 (0.56, 0.85)	0.76 (0.62, 0.93)	
	p-value	0.0005	0.0075	
30 d to 12 mo	n	2186	2231	2230
	Patients with events	157 (7.2%)	143 (6.4%)	175 (7.8%)
	KM %	8.1%	7.1%	8.7%
	Hazard Ratio (95% CI)	0.91 (0.73, 1.13)	0.81 (0.65, 1.01)	
	p-value	0.3931	0.0584	
> 12 months	n	1676	1661	1645
	Patients with events	97 (5.8%)	108 (6.5%)	100 (6.1%)
	KM %	6.2%	7.0%	6.8%
	Hazard Ratio (95% CI)	0.96 (0.72, 1.26)	1.08 (0.82, 1.42)	
	p-value	0.7508	0.5726	
	p-value for interaction	0.0923	0.1067	

Source: CSR Table 11.2.4.1

Table 7 Primary Endpoint Results in Subgroups Based on Time from Qualifying MI to Randomization

Time from Qualifying MI		Ticagrelor 90mg bd (N=7050)	Ticagrelor 60mg bd (N=7045)	Placebo (N=7067)
< 15 months	**n**	**1842**	**1795**	**1812**
	Patients with events	125 (6.8%)	129 (7.2%)	148 (8.2%)
	KM %	7.9%	8.7%	9.4%
	Hazard Ratio (95% CI)	0.82 (0.65, 1.04)	0.88 (0.69, 1.11)	
	p-value	0.1013	0.2794	
15- < 18 months	**n**	**971**	**991**	**943**
	Patients with events	78 (8.0%)	67 (6.8%)	97 (10.3%)
	KM %	8.6%	7.9%	11.3%
	Hazard Ratio (95% CI)	0.77 (0.57, 1.03)	0.64 (0.47, 0.88)	
	p-value	0.0798	0.0056	
18- < 24 months	**n**	**1503**	**1545**	**1578**
	Patients with events	108 (7.2%)	97 (6.3%)	130 (8.2%)
	KM %	8.1%	6.8%	9.2%
	Hazard Ratio (95% CI)	0.87 (0.68, 1.12)	0.76 (0.58, 0.98)	
	p-value	0.2903	0.0369	
24 - < 30 mo	**n**	**1405**	**1371**	**1395**
	Patients with events	94 (6.7%)	100 (7.3%)	110 (7.9%)
	KM %	7.5%	7.9%	8.1%
	Hazard Ratio (95% CI)	0.83 (0.63, 1.10)	0.91 (0.70, 1.20)	
	p-value	0.1905	0.5199	
>= 30 months	**n**	**1322**	**1333**	**1329**
	Patients with events	86 (6.5%)	94 (7.1%)	92 (6.9%)
	KM %	7.2%	7.6%	7.8%
	Hazard Ratio (95% CI)	0.95 (0.70, 1.27)	1.01 (0.76, 1.35)	
	p-value	0.7110	0.9393	
	p-value for interaction	0.8842	0.2288	
	KM %	6.2%	7.0%	6.8%
	Hazard Ratio (95% CI)	0.96 (0.72, 1.26)	1.08 (0.82, 1.42)	
	p-value	0.7508	0.5726	
	p-value for interaction	0.8842	0.2288	

Source: CSR Table 11.2.4.1

I believe the reduced efficacy in patient with >12 months between end of ADPRB therapy and randomization should be briefly discussed in Section 14, but need not be mentioned elsewhere.

There is another subgroup labeling issue that concerns patients with a prior history of stroke. This will be discussed in the section on safety.

7.2.4 Safety

Safety information in current ticagrelor labeling is largely derived from the PLATO trial, which enrolled ~18,600 patients with ACS within 24 hours of the onset of chest pain and followed these patients for one year. Patients were randomized 1:1 to clopidogrel at doses consistent with US labeling or ticagrelor, with a 180 mg loading dose a maintenance dose of 90 mg bid. When informative, data PEGASUS will be contrasted with data from PLATO.

General safety considerations:
PEGASUS was large and well-run trial. Study drug exposure and follow-up in PEGASUS are quite substantial and are about 3X the corresponding amounts in PLATO, which were sufficient to support approval of an NME and provide safety labeling information. Overall, follow-up for events was as good as or better than in other, recent large CV outcomes trials (**Table 2**, **Table 4**).

Deaths

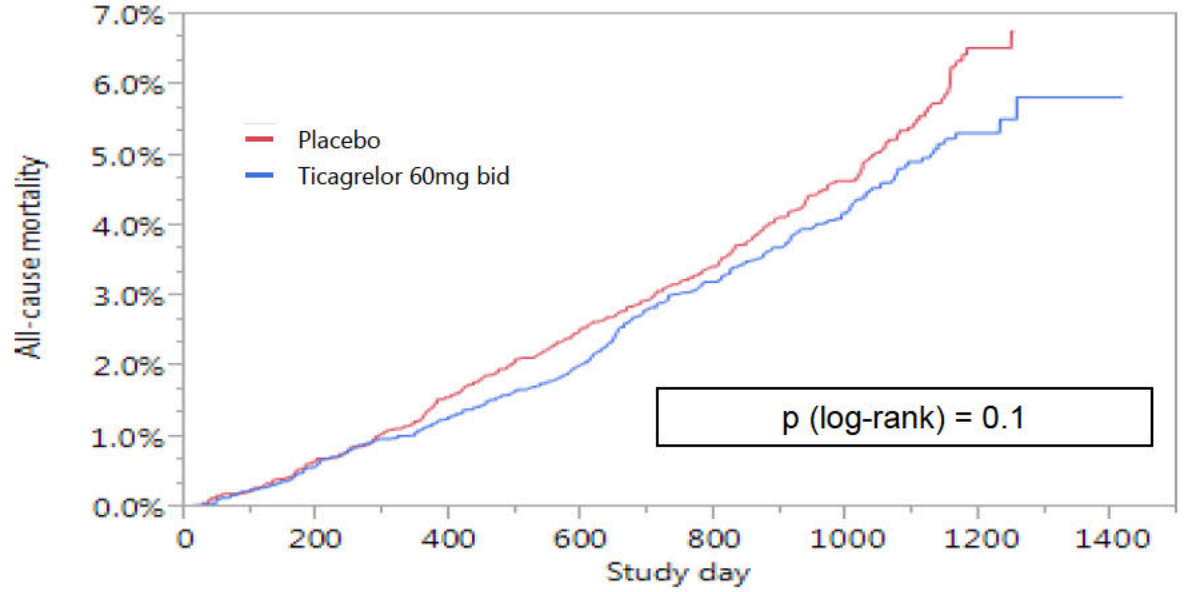
Some Information on death in the ITT population is discussed in the efficacy section. The discussion below will focus largely but not entirely on the safety population, in which there were 961 deaths over the course of the study: 335, 292, and 334 in the ticagrelor 90 mg bid, ticagrelor 60 mg bid and placebo arms, respectively. These figures include 10 deaths in each arm that occurred after the CSED; these deaths were captured per-protocol but are not included in most analyses.

Figure 4 includes KM plots for all-cause death for each of the active treatment arms vs. placebo. There was trend favoring 60 mg bid over placebo (A, p=0.1). The KM curves for 90 mg bid and placebo are superimposed (B, p=0.99).

Figure 5 provides analogous information for CV death. Both active treatments compare favorably to placebo, with p=0.03 for the 60 mg bid arm and p=0.13 for the 90 mg arm.

Figure 4 Time to All-Cause Death
Safety Set, Overall Study Period

A. Ticagrelor 60 mg bid vs. Placebo



B. Ticagrelor 90 mg bid vs. Placebo

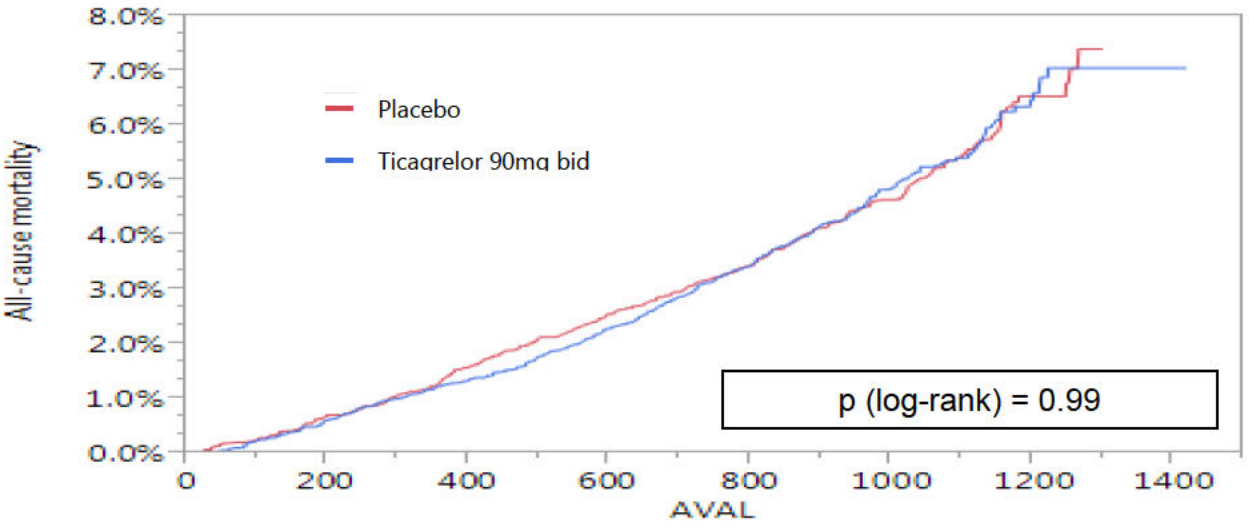
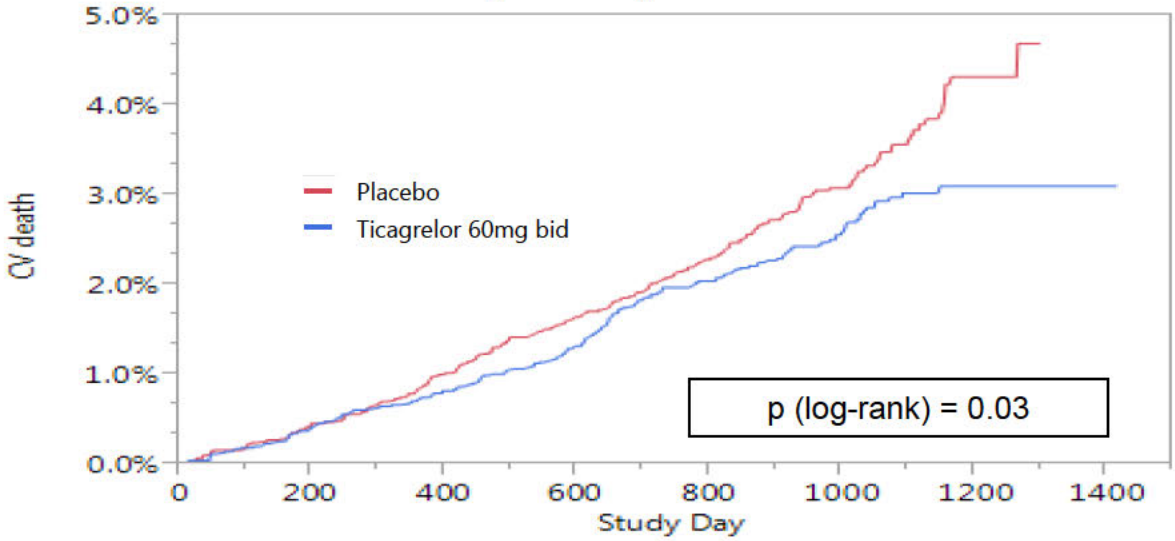


Figure 5 Time to CV Death
Safety Set, Overall Study Period

A. Ticagrelor 60 mg bid vs. Placebo



B. Ticagrelor 90 mg bid vs. Placebo

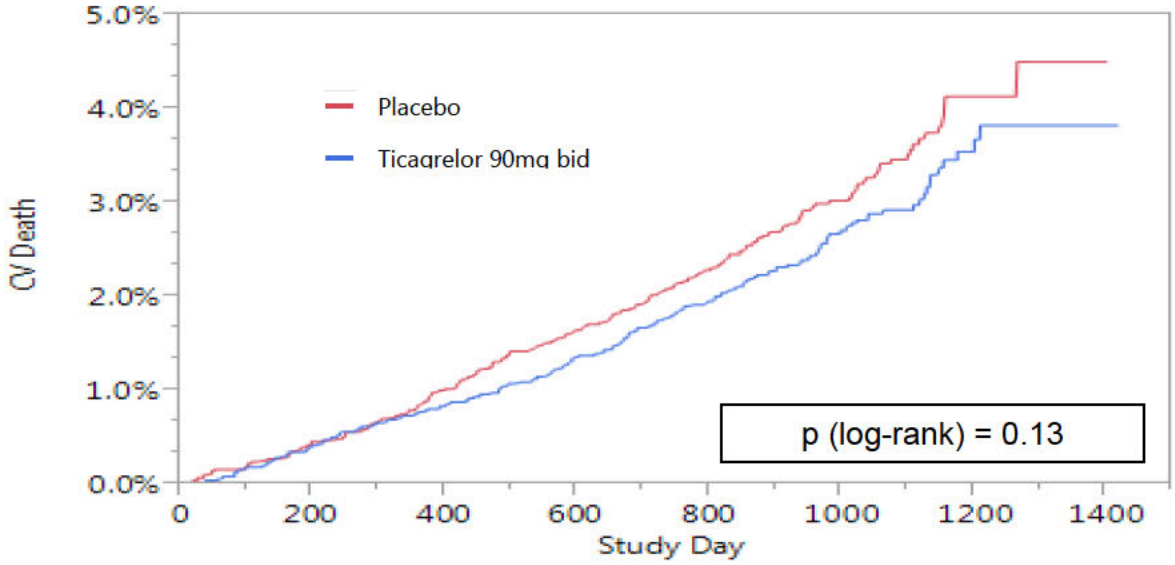


Table 8 is a display of causes of CV and non-CV death in all randomized patients followed to their last study contact. Of note, the advantage for either dose of ticagrelor over placebo in terms of CV death is driven largely by a reduction in sudden cardiac death, which was by far the most common type of CV death. There also an advantage for both arms in deaths caused by acute MI. Consistent with the primary endpoint component data, there was no increase in death due to ICH with ticagrelor.

For non-CV death, both ticagrelor dose groups had more deaths due to neoplasm than placebo, but the excess was greater with 90 mg bid. This will be discussed further below. There was a modest increase in deaths due to infection with 90 mg bid, which may have been related to increased rates of hospitalization for bleeding. The number of bleeding deaths was similar in the three study arms.

Table 8 Causes of CV Death and Non-CV Death
All randomized patients followed to last contact

A. CV Death

Cause of Death	Ticagrelor 90 mg bid N=7050	Ticagrelor 60 mg bid N=7045	Placebo N=7067	SUM
Acute MI	13 (0.2)	22 (0.3)	26 (0.4)	
Heart failure or cardiogenic shock	24 (0.3)	18 (0.3)	22 (0.3)	
Intracranial hemorrhage	6 (0.1)	7 (0.1)	9 (0.1)	
Non- hemorrhagic stroke	15 (0.2)	10 (0.1)	12 (0.2)	
Sudden cardiac death	85 (1.2)	82 (1.2)	106 (1.5)	
Other/ probable or unclassified CV death	47 (0.7)	37 (0.5)	44 (0.6)	
Sum	**190 (2.7)**	**176 (2.5)**	**219 (3.1)**	**585 (2.8)**

B. Non-CV Death

Cause of Death	Ticagrelor 90 mg bid N=7050	Ticagrelor 60 mg bid N=7045	Placebo N=7067	SUM
Malignancy	77 (1.1)	63 (0.9)	53 (0.8)	
Infection (including sepsis)	31 (0.4)	25 (0.4)	24 (0.3)	
Pulmonary Failure	10 (0.1)	9 (0.1)	9 (0.1)	
Renal failure	2 (0.03)	4 (0.06)	4 (0.06)	
Fatal Bleed	6 (0.09)	5 (0.07)	5 (0.07)	
Other	19 (0.3)	10 (0.1)	20 (0.3)	
Sum	**145 (2.1)**	**116 (1.7)**	**115 (1.6)**	**376 (1.8)**
CV + Non-CV Deaths				**961 (4.6)**

Source: Clinical review Table 25 (safety reviewer's analysis)

Serious Adverse Events

SAEs in PEGASUS with a relative risk ≥ 1.5 (ticagrelor 60 mg bd vs. placebo) are displayed in **Table 9.** As one would expect, there was an excess of many varieties of bleeding and bleeding-related terms in the two ticagrelor arms compared to placebo. In addition, there was an excess

of dyspnea-related terms, bradycardia, and renal stones or colic. There was also an excess of upper GI ulcers, erosions or perforations. This last finding could have been result of ascertainment bias related to work-up of bleeding events.

Table 9: Serious Adverse Events
(RR, Ticagrelor 60 mg bid / placebo ≥ 1.5, safety population, on treatment)
Ordered by risk ratio (RR) for ticagrelor 60 mg bid vs. placebo

	T90 mg bid N=6988 n (%)	T60 mg bid N=6958 n (%)	Pbo bid N= 6996 n (%)	RR T90/ Pbo	RR T60/ /Pbo
Epistaxis	19 (0.27)	15 (0.22)	2 (0.03)	9	7.33
Pneumothorax	2 (0.03)	5 (0.07)	1 (0.01)	3	7
Glaucoma, high intraocular pressure	2 (0.03)	4 (0.06)	1 (0.01)	3	6
Ecchymosis, hematoma, bruise	19 (0.27)	27 (0.39)	5 (0.07)	3.86	5.57
Dizziness, light-headedness	9 (0.13)	3 (0.04)	1 (0.01)	13	4
Fe Deficiency	20 (0.29)	11 (0.16)	3 (0.04)	7.25	4
Hemoptysis	4 (0.06)	3 (0.04)	1 (0.01)	6	4
Constipation	2 (0.03)	3 (0.04)	1 (0.01)	3	4
Bacteremia	8 (0.11)	11 (0.16)	3 (0.04)	2.75	4
Dyspnea on exertion	1 (0.01)	3 (0.04)	1 (0.01)	1	4
Nephritis, glomerulonephritis	1 (0.01)	3 (0.04)	1 (0.01)	1	4
Seizure	2 (0.03)	2 (0.03)	1 (0.01)	3	3
High K+	1 (0.01)	2 (0.03)	1 (0.01)	1	3
Ligament rupture	0 (0)	2 (0.03)	1 (0.01)	0	3
Dyspnea, SOB, respiratory distress	23 (0.33)	25 (0.36)	9 (0.13)	2.54	2.77
Hematuria	9 (0.13)	8 (0.11)	3 (0.04)	3.25	2.75
Shock, non-cardiogenic	9 (0.13)	7 (0.1)	3 (0.04)	3.25	2.5
Encephalitis, encephalopathy	4 (0.06)	5 (0.07)	2 (0.03)	2	2.33
GI bleed	89 (1.27)	78 (1.12)	34 (0.49)	2.59	2.29
Anemia	43 (0.62)	31 (0.45)	14 (0.2)	3.1	2.25
Bradycardia	14 (0.2)	14 (0.2)	6 (0.09)	2.22	2.22
Gastric, duodenal, or jejunal ulcer, erosion, perforation	49 (0.7)	33 (0.47)	16 (0.23)	3.04	2.04
Motor vehicle accident	2 (0.03)	4 (0.06)	2 (0.03)	1	2
Hearing loss, deafness	1 (0.01)	4 (0.06)	2 (0.03)	0.33	2
Bleeding	165 (2.36)	168 (2.41)	90 (1.29)	1.83	1.87

	T90 mg bid N=6988 n (%)	T60 mg bid N=6958 n (%)	Pbo bid N= 6996 n (%)	RR T90/ Pbo	RR T60/ /Pbo
Hernia, incarcerated, obstructive, gangrenous, or ruptured	5 (0.07)	5 (0.07)	3 (0.04)	1.75	1.75
Pulmonary edema	3 (0.04)	7 (0.1)	4 (0.06)	0.67	1.67
Asthenia, fatigue, malaise, weakness, narcolepsy	2 (0.03)	7 (0.1)	4 (0.06)	0.5	1.67
UTI	40 (0.57)	26 (0.37)	16 (0.23)	2.48	1.61
Stone, renal colic	32 (0.46)	22 (0.32)	14 (0.2)	2.3	1.6
Hypotension	5 (0.07)	8 (0.11)	5 (0.07)	1	1.57
Hernia	33 (0.47)	37 (0.53)	24 (0.34)	1.38	1.56
Low LVEF, low cardiac output, cardiomyopathy, LV dysfunction	12 (0.17)	4 (0.06)	3 (0.04)	4.25	1.5
Cranial neuropathy, palsy	2 (0.03)	4 (0.06)	3 (0.04)	0.75	1.5
Ocular hemorrhage	2 (0.03)	4 (0.06)	3 (0.04)	0.75	1.5
Cardiac thrombus	1 (0.01)	4 (0.06)	3 (0.04)	0.25	1.5

Source: Clinical review, Table 26 (safety reviewer's analysis)

Discontinuation for Adverse Events

Information regarding discontinuations of study treatment for AEs, including bleeding AEs, is provided in **Table 10** by study arm. There are dose responses for bleeding at any anatomic site, bleeding at a variety of individual sites, and dyspnea. All risks evident here were also evident in PLATO and are already emphasized in labeling. Of note, atrial fibrillation was one of the most common reasons for discontinuation, affecting 0.8%, 1.2%, and 1.1% of patients in the ticagrelor 90 mg bid, ticagrelor 60 mg bid and placebo arms, respectively. Need for oral anticoagulant therapy, which is used to treat most patients with atrial fibrillation, was an exclusion criterion for entry into PEGASUS, and development of the need for such therapy required discontinuation of study drug.

Table 10 Study Drug Discontinuation for Adverse Events
Including bleeding-related PTs ≥ 0.1% and non-bleeding PTs with n ≥ 10 in any arm

Reason for discontinuation, n (%):	Ticagrelor 90 mg bid (N=7050)	Ticagrelor 60 mg bid (N=7045)	Placebo (N = 7067)
Any AE	**1306 (18.7%)**	**1117 (16.1%)**	**596 (8.5%)**
Bleeding at any anatomic site	**454 (6.5%)**	**355 (5.1%)**	**88 (1.3%)**
Preferred Term:			
Dyspnoea	420 (6.0%)	281 (4.0%)	49 (0.7%)
Increased tendency to bruise	90 (1.3%)	61 (0.9%)	5 (0.1%)
Epistaxis	69 (1.0%)	49 (0.7%)	13 (0.2%)
Atrial fibrillation	59 (0.8%)	84 (1.2%)	78 (1.1%)
Spontaneous haematoma	58 (0.8%)	42 (0.6%)	3 (0.0%)
Dizziness	32 (0.5%)	29 (0.4%)	19 (0.3%)
Diarrhoea	24 (0.3%)	27 (0.4%)	14 (0.2%)
Nausea	23 (0.3%)	19 (0.3%)	15 (0.2%)
Headache	20 (0.3%)	19 (0.3%)	12 (0.2%)
Contusion	19 (0.3%)	18 (0.3%)	4 (0.1%)
Ecchymosis	17 (0.2%)	17 (0.2%)	0 (0.0%)
Fatigue	17 (0.2%)	20 (0.3%)	8 (0.1%)
Haematuria	16 (0.2%)	18 (0.3%)	6 (0.1%)
Traumatic haematoma	15 (0.2%)	9 (0.1%)	0
Abdominal pain upper	13 (0.2%)	24 (0.3%)	17 (0.2%)
Asthenia	13 (0.2%)	12 (0.2%)	6 (0.1%)
Traumatic intracranial haemorrhage	12 (0.2%)	13 (0.2%)	7 (0.1%)
Dyspepsia	11 (0.2%)	15 (0.2%)	7 (0.1%)
Iron deficiency anaemia	10 (0.1%)	3 (0.0%)	3 (0.0%)
Gastric ulcer haemorrhage	9 (0.1%)	7 (0.1%)	3 (0.0%)
Atrial flutter	8 (0.1%)	8 (0.1%)	11 (0.2%)
Gingival bleeding	8 (0.1%)	5 (0.1%)	4 (0.1%)
Rectal haemorrhage	8 (0.1%)	8 (0.1%)	3 (0.0%)
Dyspnoea exertional	7 (0.1%)	12 (0.2%)	2 (0.0%)
Gastrointestinal haemorrhage	7 (0.1%)	16 (0.2%)	6 (0.1%)
Haemorrhoidal haemorrhage	7 (0.1%)	4 (0.1%)	1 (0.0%)
Traumatic haemorrhage	7 (0.1%)	5 (0.1%)	1 (0.0%)

Source: CSR Tables 72; 11.3.2.4.1.

Bleeding AEs

Bleeding is the most frequent and worrisome AE associated with ticagrelor therapy. All bleeding events that in the opinion of the investigator merited reporting as an AE were to be adjudicated in a blinded fashion by a centralized CEC.

Bleeding was assessed using the TIMI, PLATO, GUSTO, and ISTH scales, although TIMI and PLATO bleeding were stressed in the study report and were used for the safety analyses described in the study objectives. TIMI major bleeding was the major focus of the safety review of bleeding and was used in the review team's benefit-risk analysis. According, I will focus primarily on TIMI major bleeding.

TIMI major bleeding occurred at a rate roughly 3 and 2 X the placebo arm rate in the ticagrelor 90 mg bid and 60 mg bid arms, respectively. However, fatal bleeding and ICH, the most serious types of bleeding, occurred at similar rates in the three arms (**Table 11**). By far, the most common site of TIMI major bleeding was the GI tract (**Table 12**). Study data indicates that bleeding of any severity occurred most commonly in the Blood and Lymphatic System SOC, suggesting, that documentation of this broad class of bleeding (which includes many non-adjudicated bleeds) was not optimal. The next most common site of such bleeding was the Respiratory, Thoracic and Mediastinal Disorders SOC, consistent with the finding that epistaxis was the most commonly reported bleeding event requiring medical attention and the second most common "minimal" bleeding event (data not shown).

Table 11 TIMI Major and Minor Bleeding
Safety population, on treatment (to last dose + 7 days)

Endpoint	Ticagrelor 90 mg bid (N=6988)		Ticagrelor 60 mg bid (N=6958)		Placebo (N=6996)		T 90 vs. P HR (95% CI)	T 60 vs. P HR (97.5% CI)
	# of pts (%)	KM Event Rate[1]	# of pts (%)	KM Event Rate[1]	# of pts (%)	KM Event Rate[1]		
TIMI Major	127 (1.8%)	2.6%	115 (1.7%)	2.3%	54 (0.8%)	2.3%	2.69 (1.96, 3.70)	2.32 (1.68, 3.21)
Fatal	6 (0.1%)	0.1%	11 (0.2%)	0.3%	12 (0.2%)	0.3%	0.58 (0.22, 1.54)	1.00 (0.44, 2.27)
ICH	29 (0.4%)	0.6%	28 (0.4%)	0.6%	23 (0.3%)	0.5%	1.44 (0.83, 2.49)	1.33 (0.77, 2.31)
Spontaneous	88 (1.3%)	1.8%	83 (1.2%)	1.7%	34 (0.5%)	0.7%	2.96 (1.99, 4.40)	2.66 (1.79, 3.97)
Procedural	16 (0.2%)	0.3%	14 (0.2%)	0.3%	11 (0.2%)	0.2%	1.66 (0.77, 3.58)	1.39 (0.63, 3.05)
Traumatic	23 (0.3%)	0.5%	17 (0.2%)	0.4%	9 (0.1%)	0.2%	2.91 (1.35, 6.29)	2.06 (0.92, 4.62)
TIMI Major or Minor	192 (2.7%)	3.9%	168 (2.4%)	3.4%	72 (1.0%)	1.4%	3.05 (2.32, 4.00)	2.54 (1.93, 3.35)

Source: CSR Table 39

Table 12 Bleeding by System Organ Class

Patients with bleeding event on treatment occurring in at least 0.1% of patients (TIMI major bleed) or 0.5% of patients in any arm (bleeding of any severity)

Bleeding Event Severity/ SOC	Ticagrelor 90 mg bid N=6988 # of pts (%)	Ticagrelor 60 mg bid N=6958 # of pts (%)	Placebo N=6996 # of pts (%)
Patients with at least 1 TIMI major bleed	**127 (1.8%)**	**115 (1.7%)**	**54 (0.8%)**
Gastrointestinal disorders	39 (0.6%)	25 (0.4%)	12 (0.2%)
Injury, poisoning & procedural complications	8 (0.1%)	12 (0.2%)	3 (0.0%)
Infections & infestations	4 (0.1%))	2 (0.0%)	1 (0.0%
Neoplasms	4 (0.1%)	2 (0.0%)	0
Blood & lymphatic system disorders	3 (0.0%)	6 (0.1%)	0
Patients with at least 1 bleeding event of any severity	**2256 (32.3%)**	**2028 (29.1%)**	**807 (11.5%)**
Blood and lymphatic system	772 (11.0%)	667 (9.6%)	108 (1.5%)
Injury, poisoning & procedural complications	740 (10.6%)	670 (9.6%)	253 (3.6%)
Respiratory, thoracic & mediastinal disorders	529 (7.6%)	457 (6.6%)	176 (2.5%)
Gastrointestinal disorders	342 (4.9%)	305 (4.4%)	150 (2.1%)
Skin & subcutaneous tissue disorders	201 (2.9%)	157 (2.3%)	29 (0.4%)
Renal & urinary disorders	119 (1.7%)	130 (1.9%)	64 (0.9%)
Eye disorders	70 (1.0%)	68 (1.0%)	33 (0.5%)
Neoplasms	41 (0.6%)	31 (0.4%)	22 (0.3%)

Source: CSR Tables 11.3.2.6.1 and 11.3.2.6.5

NON-BLEEDING ADVERSE FINDINGS:

The following adverse events may have labeling implications because of differences in the safety profile of ticagrelor between PEGASUS and PLATO or one case, new information about the timing of dyspnea. In evaluating observed differences between the trials, the longer follow-up and substantially greater number of patients on ticagrelor in PEGASUS should be given weight.

Pulmonary fibrosis

Five patients in each arm had AEs of pulmonary fibrosis. SAEs of pulmonary fibrosis were reported in 3, 2, and 0 patients in the ticagrelor 90 mg bid, ticagrelor 60 mg bid and placebo arms, respectively. One of the SAEs in the 90 mg bid group was fatal. One of the patients in the ticagrelor 60 mg bid arm died of an undetermined cause after loss to follow-up. The table below is reproduced from the clinical review.

Tabular Description of Subjects with Pulmonary Fibrosis SAEs

Subject Description	Treatment Arm	Day at which subject developed PF	Action/ outcome
63 y/o white male with no h/o pulmonary fibrosis, heart failure or COPD	Ticagrelor 90 mg	~140	None. Ticagrelor discontinued at ~day 300 because patient had an MI. followed past day 700. Unresolved.
64 y/o white male with "flare-up" of idiopathic pulmonary fibrosis	Ticagrelor 90 mg	~325	None. Outcome recovered/ resolved at ~ day 800.
68 y/o white male with no h/o pulmonary fibrosis but on methotrexate (known to cause pulmonary fibrosis)	Ticagrelor 60 mg	~450	Methotrexate stopped. Ticagrelor temporarily interrupted. Outcome not recovered/ not resolved at day ~950.
73 y/o white male	Ticagrelor 90 mg	~720	Ticagrelor stopped at time of pulmonary investigations. Fatal at around day 950
76 y/o white male	Ticagrelor 60 mg	~800	None. Lost to follow-up but letter was sent to registry office explaining that patient died at ~ day 975, cause of death not provided.

Source: Clinical review, Table 30

The review also notes that there were 6 vs. 4 reports of interstitial lung disease with ticagrelor and placebo, respectively. Apparently these were SAEs because the patients had narratives. The following table describing these cases is reproduced from the clinical review.

Cases of interstitial Pneumonia lung disease (all subjects with background of smoking and/or CHF or other medication known to cause interstitial lung disease)

Subject Description	Treatment Arm	Day at which subject developed ILD	Action/ outcome
79 y/o Asian former smoker male with h/o COPD	Placebo	688	Drug discontinuation 13 days later followed by respiratory arrest 4 days later, followed by Death (attributed to ILD)
76 y/o white former smoker male	Ticagrelor 60 mg	646	None. Did not resolve. Died 25 days later of ventricular tachycardia. That was attributed to pneumonia (bilateral interstitial lung disease pneumonia/pneumonitis) diagnosed as acute interstitial pneumonia on bronchoscopy.
68 y/o white Hispanic female – no smoking by history	Ticagrelor 90 mg	793	None. Recovered 17 days later. Died of CV death ~ 2 months later.
64 y/o Asian male former smoker	Ticagrelor 90 mg	935	Stopped Ticagrelor at day 767 after SAE of hemoptysis. Not recovered or resolved.
63 y/o Asian male, current smoker	Placebo	234	Drug withdrawn. Not recovered
55 y/o white female, current smoker	Ticagrelor 90 mg	1097	Drug interrupted. Recovered. Drug restarted ~1 month later and continued until CSED. Biopsy: "Sections of peripheral pulmonary parenchyma with disseminated fields of non-specific interstitial cellular pneumonia and signs of bronchiolitis with peri-bronchiolar fibrosis"
53 y/o white female, current smoker	Placebo	1087	Drug interrupted and recommenced on the next day after the event was considered as resolved by the investigator.
64 y/o white male, former smoker	Ticagrelor 90 mg	172	Drug temporarily interrupted. SOB started prior to study. Biopsy 6 months after study drug started showed interstitial lung disease. (2 months before starting study drug, CT showed fibrotic changes in upper lobe; 1 month after starting drug, Angio CT showed interstitial lung disease).

Source: Clinical review Table 31

The safety review recommends adding language to labeling about PF/ILD. I agree, and I would recommend putting it in Section 6.

Gout and hyperuricemia

In the Sec. 915 safety review of ticagrelor, it was noted that the large size and duration of PEGASUS might shed additional light on the rate of gout in patients taking ticagrelor. In

PLATO, patients in the ticagrelor arm had an increase from baseline of 0.6 mg/dL in the level of serum uric acid, compared to a 0.2 mg/dL increase with clopidogrel. The difference between the arms disappeared within 30 days of stopping treatment. The rate of gout was 0.6% in each arm. These data are in current labeling for ticagrelor.

In PEGASUS, the increase from baseline in serum uric acid on treatment was xx, 0.2, and 0.0 mg/dL in the ticagrelor 90 mg bid, ticagrelor 60 mg bid and placebo arms, respectively. Again, the differences resolved after discontinuation of study treatment. However, the rate of gout AEs was 2.6%, 2.4% and 1.7% in in the ticagrelor 90 mg bid, ticagrelor 60 mg bid and placebo arms, respectively, showing a dose response and an increase from placebo in both treatment arms. There was also an increased rate of SAEs of gout, although numbers were quite small, and an slightly increased rate of renal stone/colic AEs (1.3%, 1.1% and 0.9% in the ticagrelor 90 mg bid, ticagrelor 60 mg bid and placebo arms, respectively. The increased rate of gout and associated AEs should be reflected in labeling.

Renal failure and increased serum creatinine levels

The Section 915 review also noted that in PLATO, there was an increased rate of >50% increases in serum creatinine with ticagrelor compared to clopidogrel, 7.4% vs. 5.9%. This difference also resolved with discontinuation of therapy and sometimes resolved during extended treatment. Analogous to the situation with uric acid levels and gout, there was no increased rate of renal failure AEs in PLATO. PEGASUS also showed an increased rate of 50% rises in serum creatinine: 4.2%, 3.9% and 3.5% in the ticagrelor 90 mg bid, ticagrelor 60 mg bid and placebo arms, respectively. However, in this case, unlike with gout, there was no increased rate of renal failure AEs with ticagrelor compared to placebo in PEGASUS.

Bradyarrhythmias

The current PI for ticagrelor has the following information about bradycardia:

> "In clinical studies BRILINTA has been shown to increase the occurrence of Holter-detected bradyarrhythmias (including ventricular pauses). PLATO excluded patients at increased risk of bradycardic events (e.g., patients who have sick sinus syndrome, 2nd or 3rd degree AV block, or bradycardic-related syncope and not protected with a pacemaker). In PLATO, syncope, pre-syncope and loss of consciousness were reported by 1.7% and 1.5% of BRILINTA and clopidogrel patients, respectively.
>
> In a Holter substudy of about 3000 patients in PLATO, more patients had ventricular pauses with BRILINTA (6.0%) than with clopidogrel (3.5%) in the acute phase; rates were 2.2% and 1.6% respectively after 1 month."

Dr. Blank notes that bradycardia was reported in PLATO in 4.3% and 4.0% of patients in the ticagrelor and clopidogrel arms, respectively. In PEGASUS, the analogous rates are 0.82%, 1.02% and 0.84% in the ticagrelor 90 mg bid, ticagrelor 60 mg bid and placebo arms, respectively. Serious AEs involving bradycardia occurred in 14, 14, and 6 patients, respectively. There was no difference among the arms in the rate of sick sinus syndrome or sinus block, but there was an excess of syncope or near-syncope with ticagrelor: 1.5%, 1.7%, and 1.2% in the ticagrelor 90 mg bid, ticagrelor 60 mg bid and placebo arms, respectively. PEGASUS had a similar exclusion as the one described in the quote from labeling above.

The Applicant proposes to add syncope (but not the combination of syncope and related events) bradycardia information from PEGASUS to Sec. 6. I would prefer the data to be like the data from PLATO, with the rate of syncope and related events. Dr. Blank would add a warning regarding the fact that we have no data on the risks of ticagrelor in patient with sick sinus syndrome, 2nd or 3rd degree AV

block, or bradycardic-related syncope and not protected with a pacemaker because they were excluded from studies. I agree. The warning should suggest consideration of monitoring of such patients at the initiation of treatment with ticagrelor.

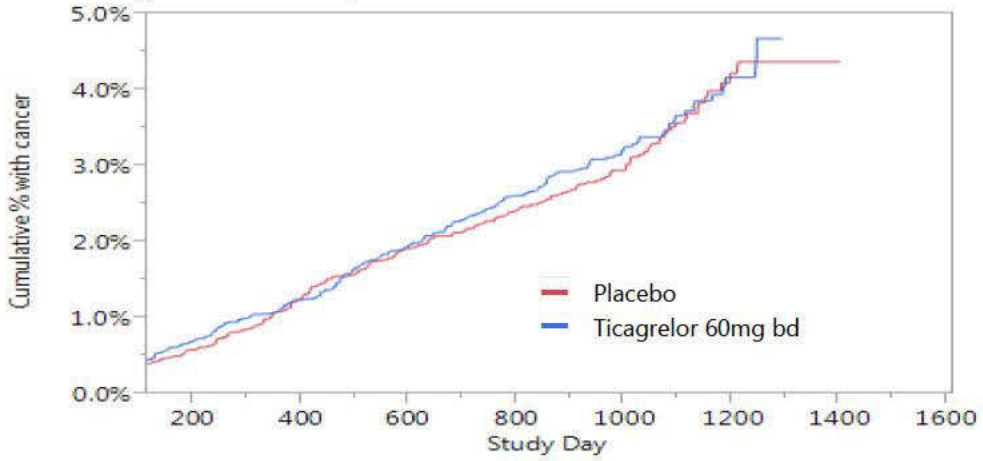
Cancer

Rates of malignancy excluding squamous cell skin carcinoma (Ca) were 3.7%, 3.1% and 3.1% in the ticagrelor 90 mg bid, ticagrelor 60 mg bid and placebo arms, respectively.

KM plots of malignancies, excluding non-melanoma skin cancers, are reproduced from the safety review below.[8]

Figure 6 Time to Cancer AE

A. Ticagrelor 60 bid vs. placebo



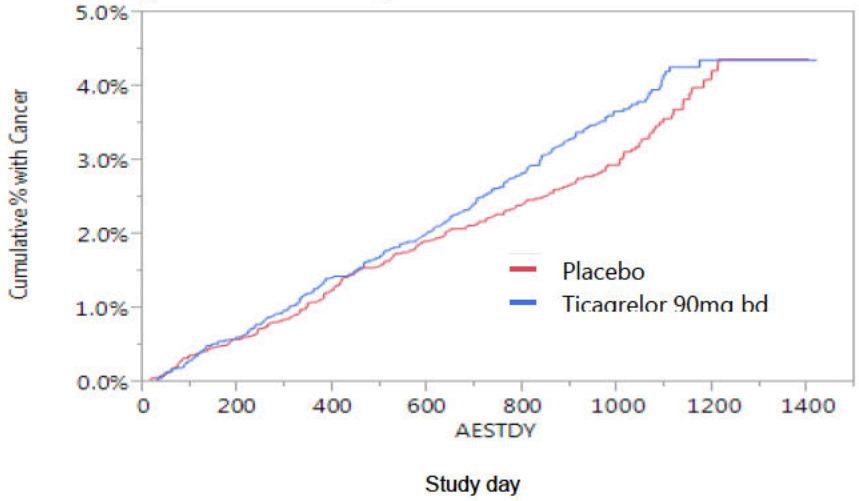
Group	Number failed	Number censored	Mean		Std Error
Placebo	213	6783	1188.03	Biased	1.64245
Ticagrelor 60mg bd	223	6735	1265.21	Biased	1.8988
Combined	436	13518	1265.83	Biased	1.32355

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	0.2586	1	0.6111
Wilcoxon	0.3545	1	0.5516

[8] Dr. Blank discusses in her review the different approaches she took to count malignancies.

Reference ID: 3804867

B. Ticagrelor 90m bid vs. placebo



Group		Number failed	Number censored	Mean		Std Error
Placebo		213	6783	1188.03	Biased	1.64245
Ticagrelor 90mg bd		244	6744	1146.58	Biased	1.63893
Combined		457	13527	1186.43	Biased	1.19265
Test	**ChiSquare**	**DF**	**Prob>ChiSq**			
Log-Rank	2.0665	1	0.1506			
Wilcoxon	2.7217	1	0.0990			

Source: Reviewer's analysis using RSAE dataset

Table 13 Is a display of cancer AEs that occurred in at least 6 treated patients. The largest imbalance disfavoring ticagrelor was for the Preferred Term (PT) Lung neoplasm malignant, which was reported for 20, 10 and 10 subjects ticagrelor 90 mg bid, ticagrelor 60 mg bid and placebo arms, respectively. The largest imbalance favoring ticagrelor was for malignant melanoma, which was reported for 10, 9, and 16 patients, respectively. The Malignancies SMQ, the source of these PTs, also includes Prostatic specific antigen increased, which was reported for 18, 20 and 30 patients, respectively. However, PSA is a marker, not a malignancy, and there was not an imbalance for the term Prostate cancer. The terms named above and related terms are highlighted in the table.

Table 14 is a reproduction of a slide shown at an internal meeting by the safety reviewer. Preferred terms were grouped by Higher Level Terms or Higher Level Group Terms, as well as broad cancer categories. Thee table show a risk difference between the 90 mg bid and placebo arms based the percentage of patients reporting a cancer in each group. Much of the difference in solid cancer rates comes from risk differences in the Malignant GI and Malignant Respiratory/Mediastinal groups.

Reference ID: 3804867

Table 13 Patients with Cancer AEs in PEGASUS
Safety set, Preferred Terms reported for at least 5 patients in the study

Preferred Term	Placebo	Ticagrelor 60 mg bd	Ticagrelor 90 mg bd	Subjects
Basal cell carcinoma	46 (0.7%)	41 (0.6%)	42 (0.6%)	129 (0.6%)
Prostate cancer	42 (0.6%)	37 (0.5%)	43 (0.6%)	122 (0.6%)
Prostatic specific antigen increased	30 (0.4%)	20 (0.3%)	18 (0.3%)	68 (0.3%)
Lung neoplasm malignant	10 (0.1%)	10 (0.1%)	20 (0.3%)	40 (0.2%)
Squamous cell carcinoma	11 (0.2%)	14 (0.2%)	13 (0.2%)	38 (0.2%)
Lung cancer metastatic	10 (0.1%)	11 (0.2%)	14 (0.2%)	35 (0.2%)
Malignant melanoma	16 (0.2%)	9 (0.1%)	10 (0.1%)	35 (0.2%)
Colon cancer	7 (0.1%)	14 (0.2%)	14 (0.2%)	35 (0.2%)
Bladder cancer	11 (0.2%)	15 (0.2%)	5 (0.1%)	31 (0.1%)
Gastric cancer	8 (0.1%)	6 (0.1%)	8 (0.1%)	22 (0.1%)
Bladder neoplasm	4 (0.1%)	8 (0.1%)	9 (0.1%)	21 (0.1%)
Adenocarcinoma of colon	7 (0.1%)	7 (0.1%)	7 (0.1%)	21 (0.1%)
Colon cancer metastatic	8 (0.1%)	5 (0.1%)	7 (0.1%)	20 (0.1%)
Breast cancer female	7 (0.1%)	5 (0.1%)	8 (0.1%)	20 (0.1%)
Prostate cancer metastatic	3 (0.0%)	6 (0.1%)	8 (0.1%)	17 (0.1%)
Skin cancer	2 (0.0%)	5 (0.1%)	9 (0.1%)	16 (0.1%)
Thyroid neoplasm	4 (0.1%)	8 (0.1%)	3 (0.0%)	15 (0.1%)
Pancreatic carcinoma metastatic	6 (0.1%)	4 (0.1%)	5 (0.1%)	15 (0.1%)
Transitional cell carcinoma	3 (0.0%)	6 (0.1%)	6 (0.1%)	15 (0.1%)
Neoplasm skin	4 (0.1%)	4 (0.1%)	4 (0.1%)	12 (0.1%)
Squamous cell carcinoma of skin	3 (0.0%)	2 (0.0%)	7 (0.1%)	12 (0.1%)
Adenocarcinoma gastric	4 (0.1%)	5 (0.1%)	3 (0.0%)	12 (0.1%)
Bladder transitional cell carcinoma	5 (0.1%)	4 (0.1%)	3 (0.0%)	12 (0.1%)
Renal cell carcinoma	4 (0.1%)	2 (0.0%)	5 (0.1%)	11 (0.1%)
Pancreatic carcinoma	3 (0.0%)	2 (0.0%)	6 (0.1%)	11 (0.1%)
Oesophageal carcinoma	2 (0.0%)	4 (0.1%)	5 (0.1%)	11 (0.1%)
Renal cancer	1 (0.0%)	5 (0.1%)	4 (0.1%)	10 (0.0%)
Bowen's disease	3 (0.0%)	5 (0.1%)	2 (0.0%)	10 (0.0%)
Chronic lymphocytic leukaemia	5 (0.1%)	2 (0.0%)	3 (0.0%)	10 (0.0%)
Lung adenocarcinoma	5 (0.1%)	0 (0.0%)	4 (0.1%)	9 (0.0%)
Metastatic gastric cancer	6 (0.1%)	1 (0.0%)	2 (0.0%)	9 (0.0%)
Breast cancer metastatic	4 (0.1%)	1 (0.0%)	4 (0.1%)	9 (0.0%)

Preferred Term	Placebo	Ticagrelor 60 mg bd	Ticagrelor 90 mg bd	Subjects
Rectal cancer	1 (0.0%)	5 (0.1%)	3 (0.0%)	9 (0.0%)
Rectal adenocarcinoma	2 (0.0%)	3 (0.0%)	3 (0.0%)	8 (0.0%)
Small cell lung cancer	2 (0.0%)	2 (0.0%)	4 (0.1%)	8 (0.0%)
Non-Hodgkin's lymphoma	2 (0.0%)	3 (0.0%)	2 (0.0%)	7 (0.0%)
Lung neoplasm	3 (0.0%)	1 (0.0%)	3 (0.0%)	7 (0.0%)
Lymphoma	1 (0.0%)	2 (0.0%)	4 (0.1%)	7 (0.0%)
Renal neoplasm	0 (0.0%)	2 (0.0%)	4 (0.1%)	6 (0.0%)
Diffuse large B-cell lymphoma	2 (0.0%)	1 (0.0%)	3 (0.0%)	6 (0.0%)
B-cell lymphoma	0 (0.0%)	4 (0.1%)	2 (0.0%)	6 (0.0%)
Salivary gland neoplasm	0 (0.0%)	3 (0.0%)	3 (0.0%)	6 (0.0%)
Acute myeloid leukaemia	3 (0.0%)	1 (0.0%)	2 (0.0%)	6 (0.0%)
Squamous cell carcinoma of lung	0 (0.0%)	2 (0.0%)	4 (0.1%)	6 (0.0%)
Colon neoplasm	1 (0.0%)	1 (0.0%)	3 (0.0%)	5 (0.0%)
Metastatic malignant melanoma	0 (0.0%)	1 (0.0%)	4 (0.1%)	5 (0.0%)
Keratoacanthoma	2 (0.0%)	1 (0.0%)	2 (0.0%)	5 (0.0%)
Bladder cancer recurrent	1 (0.0%)	3 (0.0%)	1 (0.0%)	5 (0.0%)
Malignant neoplasm of unknown primary site	3 (0.0%)	0 (0.0%)	2 (0.0%)	5 (0.0%)
Lung adenocarcinoma metastatic	0 (0.0%)	2 (0.0%)	3 (0.0%)	5 (0.0%)
Metastatic bronchial carcinoma	3 (0.0%)	1 (0.0%)	1 (0.0%)	5 (0.0%)

Source: AE dataset, Malignancy SMQ – Analysis by safety reviewer

Table 14 Grouped Cancer AE Terms in PEGASUS

	Placebo		Ticagrelor 60mg bd	Ticagrelor 90mg bd	RR:	RR:	risk difference
	N=6996		N=6958	N=6988	60/P	90/P	(%T90- %P)
	n(%)		n (%)	n (%)			
solid neoplasia all	368(5.26)	372	372(5.35)	424(6.07)	1.0	1.2	0.81
Cancer (non squ)	215(3.07)	218	218(3.13)	256(3.66)	1.0	1.2	0.59
Malignant GI	66(0.94)	73	73(1.05)	80(1.14)	1.1	1.2	0.20
Malignant Respiratory\mediastinal	34(0.49)	30	30(0.43)	57(0.82)	0.9	1.7	0.33
malignant prostate/ male genital	46(0.66)	44	44(0.63)	52(0.74)	1.0	1.1	0.08
GU malignant	28(0.4)	36	36(0.52)	25(0.36)	1.3	0.9	-0.04
melanoma	18(0.26)	9	9(0.13)	11(0.16)	0.5	0.6	-0.10
Breast Malignant	12(0.17)	6	6(0.09)	14(0.2)	0.5	1.2	0.03

Source: AE database, grouping by safety reviewer

Taken together, the two tables indicate that the excess of cancer AEs in the 90 mg bid group over placebo arises from lung and GI tumors, without an excess of any specific tumor type.

As shown previously in **Table 8**, there was an excess of deaths attributed to cancer in both ticagrelor arms compared to placebo: 77 (1.1%), 63 (0.9%) and 53 (0.8%) in the ticagrelor 90 mg bid, ticagrelor 60 mg bid and placebo arms, respectively.

The death information above and the plots and incidence data in the above tables show section show an increased rate of cancer in the 90 mg bid arm compared to placebo, but no such increase in the 60 mg bid arm, except perhaps for cancer death. Rates of non-malignant neoplasia were similar in the three treatment arms (data not shown).

The Applicant was asked to address this signal and provided information suggesting that the excess of cancer was observed in the 90 mg bid arm only in those exposed for 0-12 months (**Table 15**, **Table 16**). In those exposed for longer durations, rates of cancer were similar in the three arms. The Applicant argues that this is not what one would expect from a carcinogenic drug. However, the data are difficult to interpret without additional information. We know there were more discontinuations from treatment in the 90 mg bid arm, so a greater percentage of patients in the 90 mg arm might fall into the subset of those exposed from 0-12 months. One might expect a disproportionate share of cancer AEs in the 0-12 subgroup if the N there was larger. The Applicant shows us only numerators, not denominators. The Applicant suggests that the excess of Ca AE's with the 90 mg bid dose could have resulted from ascertainment bias related to increased bleeding that prompted a diagnostic workup. This is not unreasonable, but it cannot explain the observed excess of cancer death in the ticagrelor 90 mg bid arm, and to a lesser extent, in the ticagrelor 60 mg bid arm. On the hand, it is puzzling that

The Applicant also argues that concentrations in the 90 and 60 mg arms were not that different, and the 60 mg arm was not notably different from placebo in terms cancer AEs. They provided tables suggesting that there is no concentration-response for cancer incidence. They argue that this suggests that the findings in 90 mg arm are an aberration and likely to be due to chance. Of course this argument could be turned on its head to support a conclusion that the findings in the 60 mg arm were an aberration and due to chance, and we should be concerned about cancer incidence if we approve the 60 mg bid regimen.

As Dr. Blank points out, there was no signal of cancer in PLATO with ticagrelor 90 mg bid, although the control there was clopidogrel, not placebo. However, the most convincing argument in favor ticagrelor is that there was a strong lean towards benefit for all-cause death in the ITT analysis of PEGASUS with ticagrelor 60 mg bid and a finding of superiority over clopidogrel for all-cause death in PLATO with ticagrelor 90 mg bid. Given these favorable findings for death, the fact that there is no specific tumor type or types with notably increased rates in either ticagrelor arm compared to placebo and the clear evidence of reduction of all components of MACE with ticagrelor 60 mg bid in PEGASUS, it seems reasonable not to take action on cancer findings in the study because they seem likely to be due to chance.

Table 15 Applicant's Table of Time to Cancer Event by Time of Exposure to Study Drug

Exposure	Time to event	Number of patients Ticagrelor 90mg bd (N=376)	Ticagrelor 60mg bd (N=335)	Placebo (N=328)
0-12 months	0-12 months	89	62	53
	12-24 months	32	25	9
	>24 months	20	12	6
12-24 months	0-12 months	16	18	17
	12-24 months	40	50	44
	>24 months	6	3	8
>24 months	0-12 months	49	61	51
	12-24 months	53	41	60
	>24 months	71	63	80

Events are those in the SMQ of "Malignant or unspecified tumours"

Table 16 Malignancy AEs by time of Exposure

Duration of Exposure	Ticagrelor 90 mg bid	Ticagrelor 60 mg bid	Placebo
0-12 mo	141	99	68
12-24 mo	62	71	69
`> 24 mo	173	165	191
Sum	376	335	328

Data were derived from Table 15 by combining the 3 time to event categories for each duration of exposure.

Use in Patients with a History of Stroke

(b) (4)

Patients with a history of ICH were excluded from both PLATO and PEGASUS. In PEGASUS, the protocol initially stated that patients with an ischemic stroke in the 14 days prior to enrollment were excluded, but otherwise they could be entered. About 41/2 months after the first patient was enrolled, in global amendment 1 in 2011, this was changed to an exclusion for

all patients with a history of ischemic stroke. The 102 subjects with a history of ischemic stroke already enrolled in the study were discontinued from treatment but continued to be followed.

The Applicant's stated rationale for this amendment is that they became aware of a 2011 Merck press release regarding vorapaxar. Merck announced that they stopped enrolling patients with a prior ischemic stroke into the TRA2P study and also discontinued treatment in already-enrolled subjects with a prior stroke following a communication from the study DSMB recommending such action. We know that Merck did this because of an increased rate of ICH in the vorapaxar arm in those with a prior history of stroke.

(b) (4)

The Applicant provided us with information about efficacy and bleeding events in these patients, who were on study drug for no more than about 4 months (**Table 17**).

The table shows no increased rate of primary endpoint events, strokes of any type, or bleeding in these patients for ticagrelor compared to placebo.

Table 17 PEGASUS - Primary Endpoint and Major Bleeding Results in Treated Patients with a History of Ischemic Stroke

	Ticagrelor 90 mg bd (N=36)		Ticagrelor 60 mg bd (N=25)		Placebo (N=29)	
Characteristic	Number (%) of patients	Event rate (per 100 pt years)[a]	Number (%) of patients	Event rate (per 100 pt years)[a]	Number (%) of patients	Event rate (per 100 pt years)[a]
Composite of CV death/MI/stroke	5 (13.89)	4.81	2 (8.00)	2.80	4 (13.79)	4.73
Composite of CV Death/MI /Stroke (excluding hemorrhagic stroke)	5 (13.89)	4.81	2 (8.00)	2.80	4 (13.79)	4.73
MI	0 (0.00)	0	0 (0.00)	0	2 (6.90)	2.37
Stroke	2 (5.56)	1.92	1 (4.00)	1.40	1 (3.45)	1.18
Hemorrhagic stroke	0 (0.00)	0	0 (0.00)	0	0 (0.00)	0
TIMI Major bleeding	0 (0.00)	0	0 (0.00)	0	0 (0.00)	0

Source: Table AA6.4.
Includes events with onset date on or after the date of first dose and up to and including last visit or study withdrawal.
a Number of patients with event divided by the total duration of follow-up across all patients in given group, multiplied by 100.
The total duration of follow-up across all patients in ticagrelor 90mg = 104 years; ticagrelor 60mg = 71.5 years; Placebo = 84.5 years.

Note that exposure to study drug was quite limited: there were 6, 8 and 5 patient-years of exposure to study drug in the ticagrelor 90 mg bid, ticagrelor 60 mg bid and placebo arms, respectively.

PLATO did not exclude patients with a history of ischemic stroke; in fact, it was on a list of risk factors, one of which was required for enrollment. The Applicant provided results from PLATO for MACE, its components (except for CV death), and TIMI major bleeding in patients with and without a history of ischemic stroke. There were many more such patients than in PEGASUS, and they were not discontinued because of their prior stroke status. The data suggest that compared to patients without a stroke history, those with a history of stroke have higher rates of thrombotic events, but do no worse on ticagrelor than they do with clopidogrel, which has secondary prevention indication in a broad group of patients that includes those with ischemic stroke (**Table 18**).

Thus, neither study provides a signal of harm for ticagrelor in patients with a prior history of stroke. (b) (4)

Table 18 PLATO - Primary Endpoint and Major Bleeding Results in Treated Patients with a History of Ischemic Stroke

	Ticagrelor 90 mg bid (N=9235)		Clopidogrel 75 mg od (N=9186)	
Characteristic	N (%)	KM rate /100 pt-yr	N (%)	KM rate /100 pt- yr
Total N				
History of Stroke	348		362	
No History of Stroke	8887		8824	
Total follow-up time (Years)				
History of stroke	275.31		277.02	
No history of stroke	7384.27		7336.51	
Composite of CV death/MI/stroke				
History of stroke	68 (0.74)	24.70	80 (0.87)	28.88
No history of stroke	784 (8.49)	10.62	919 (10.00)	12.53
Composite of CV Death/MI /Stroke (excluding hemorrhagic stroke)				
History of stroke	67 (0.73)	24.34	78 (0.85)	28.16
No history of stroke	774 (8.38)	10.48	911 (9.92)	12.42
MI				
History of stroke	41 (0.44)	14.89	41 (0.45)	14.80
No history of stroke	460 (4.98)	6.23	551 (6.00)	7.51
Stroke				
History of stroke	7 (0.08)	2.54	14 (0.15)	5.05
No history of stroke	116 (1.26)	1.57	90 (0.98)	1.23
Hemorrhagic stroke				
History of stroke	1 (0.01)	0.36	3 (0.03)	1.08
No history of stroke	21 (0.23)	0.28	10 (0.11)	0.14
TIMI Major bleeding				
History of stroke	28 (0.30)	10.17	33 (0.36)	11.91
No history of stroke	679 (7.35)	9.20	669 (7.28)	9.12

7.2.5 Benefit-Risk Analysis

Appendix 3 includes benefit-risk information for the overall study population and a variety of subsets. The BR data were calculated for each ticagrelor arm vs. placebo in the following manner:

- The safety population was the population of interest. Events were accrued during the on-treatment period (first dose to last dose + 7 days).
- Benefit was the rate of MACE- (MACE minus, the composite of CV death, MI and stroke excluding hemorrhagic strokes, which are also counted as TIMI major bleeding events and should not be double-counted). In the group of interest, calculated as the % of patients with an event. The risk difference (RD) for MACE was calculated as the rate for rate for placebo (P) minus the rate for ticagrelor (T) or P - T. In the overall study population and in most subgroups, this difference was positive, i.e. favorable for ticagrelor.
- Risk was the rate of TIMI major bleeding, calculated in the same way as for MACE. However, the RD for TIMI major bleeding was calculated as T-P. In the overall study population and in most subgroups, this difference was positive, i.e. unfavorable for ticagrelor.
- The final step was to subtract the RD for bleeding from the RD for MACE. This yields a B-R difference. Thus, if the RD for MACE was 2% and RD for bleeding was 1%, the B-R difference would be +1%, favoring ticagrelor. Positive numbers favor ticagrelor, and negative numbers favor placebo.
- Using the same example as in the previous bullet, one could say that that for every 2 MACE events prevented with use of ticagrelor instead of placebo, there would be 1 additional TIMI major bleed. That is a ratio approach.
- Results were calculating using an EXCEL program developed by Dr. Ellis Unger.

Results that follow are from the comparison of ticagrelor 60 mg bid vs. placebo, from **Table 25** in Appendix 3. In the overall study population, the MACE- RD for ticagrelor vs. placebo was 2.3%, while the TIMI major bleeding RD was 0.9%, yielding a B-R difference of 0.9%, which is quite favorable for ticagrelor. As noted earlier, there was no excess of ICH or fatal bleeding with ticagrelor compared to placebo, meaning that most TIMI major bleeding events were reversible. On the other hand the MACE- components of CV death, ischemic and unknown strokes and MIs may bring irreversible harm. Thus even a negative B-R might be acceptable for many patients and physicians, provided there was some benefit of ticagrelor to offset the larger number bleeds.

In most subgroups, B-R was positive, signaling benefit for ticagrelor without need for taking into account the relatively more serious nature of MACE compared to TIMI major bleeding in this study. Notable subgroups with negative B-R included several non-Caucasian races (in which bleeding rates were high in the ticagrelor arm); women, in whom ticagrelor was less effective than in men, although less than a quarter of the patients were women; those with time from index MI to randomization > 2.5 years (about 20% of patients); and those with time from last ADP receptor blocker to randomization > 353 days (2 groups combined with about 24% of study subjects).

The overall study B-R favorable results and the favorable results in most subgroups support approval.

8 Advisory Committee Meeting

There was no meeting of the CRDAC to discuss this supplement because the evidence of efficacy was strong and the results consistent with the benefit observed in PLATO in an earlier stage of CAD.

9 Financial Disclosure

No issues.

10 Labeling:

Many labeling issues raised by the clinical review team and Division management have been discussed in the text of this review. Major issues include:

- Combining the current indication for ACS with the proposed indication for secondary prevention to create an indication to reduce MACE events in patients with ACS and those with a prior history of MI, as well as to reduce the rate of stent thrombosis in patients with ACS: The clinical review is in favor of this approach.
- To add language to the indication for use of ticagrelor in patients with a history of MI limiting such use should be limited to patients at high risk of thrombotic events because of the enriched nature of the study population. Only Dr. Dunnmon supports this approach. Dr. Blank feels that labeling should suggest that the risk of bleeding should be the risk of bleeding should be considered in evaluating whether a patient should receive ticagrelor for secondary prevention. This reviewer believes that the study data suggest that patients who stopped ADP receptor blocker treatment more than one year before enrolling received little or no benefit from ticagrelor and that this should be emphasized in Sec. 14.
- The clinical reviewers and I agree that (b) (4) .
- A warning should be added indicating that patients with 2nd and 3rd degree heart block and sick sinus syndrome were excluded from PLATO and PEGASUS because the risk of bradycardic events, so we have little information about the risks of use in these patients. If ticagrelor is used in these patients, outpatient monitoring should be considered when the drug is initiated.
- New information about the risk of gout and pulmonary fibrosis should be added to Sec. 6.

11 DSI Audits

There were no DSI audits.

12 Recommended Regulatory Action

I recommend approval of the 60 mg bid regimen with no postmarketing commitments or requirements and no REMS.

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5. Lepist EI, Zhang X, Hao J, Huang J, Kosaka A, Birkus G, Murray BP, Bannister R, Cihlar T, Huang Y, et al. Contribution of the organic anion transporter OAT2 to the renal active tubular secretion of creatinine and mechanism for serum creatinine elevations caused by cobicistat. Kidney Int. 2014 Aug;86(2):350-7. PMCID:PMC4120670

Appendix 1: Analyses by Dr. McDowell
Reproduced from Appendix 2 of the Clinical Review

Assessment of Risk of Primary Efficacy Endpoint and TIMI Major Bleeding by Quantity and Type of PEGASUS-Qualifying Risk Factors for Heart Disease

Because very few low-risk patients, i.e., those with none of 5 named qualifying risk factors for CV disease listed in Table 20(~120) were enrolled in PEGASUS, empiric data are lacking and it is hard to make any conclusions about potential risk-benefit in that population. Yet, these patients could possibly benefit from long-term use of ticagrelor post-MI. Several analyses were done to address the question of benefit-risk difference in a lower-risk population.

The first analysis looked at the primary efficacy endpoint results by number of PEGASUS-qualifying risk factors at baseline to see if the treatment benefit (i.e., the hazard ratio vs. placebo for MACE) was associated with the number of risk factors. Table 19 shows there is no obvious trend in benefit for ticagrelor 60 mg related to the number of qualifying risk factors at baseline. This analysis suggests that the beneficial effect of ticagrelor is not lower among patients with a lower number of risk factors. In fact, the majority of subjects had just one risk factor (age ≥ 65 and multivessel CAD were the most common risk factors overall) and a favorable treatment effect in this subgroup of subjects with just one risk factor was observed.

Table 19: Primary efficacy endpoint (CV death, MI or Stroke) by number of qualifying risk factors at baseline

		Ticagrelor 60 mg N=7045		*Placebo N=7067*				
event	*Number of risk factor*	*n/N*	*ER*[a]	*n/N*	*ER*[a]	*HR*	*95CI*	*p_value*
CV Death, MI & stroke	0	3 / 47	2.31	2 / 41	1.83	1.18	(0.20, 7.09)	0.8529
	1	180 / 3676	1.90	224 / 3586	2.45	0.78	(0.64, 0.95)	0.0120
	2	174 / 2315	2.96	178 / 2406	2.93	1.01	(0.82, 1.25)	0.9138
	3	94 / 816	4.69	126 / 826	6.28	0.74	(0.57, 0.97)	0.0304
	4	30 / 171	7.49	41 / 186	9.85	0.76	(0.48, 1.22)	0.2616
	5	6 / 20	13.1	7 / 22	14.0	0.93	(0.31, 2.78)	0.9012

[a] Event Rate (per 100 patient-years)
Reviewer's Table, Data Source: ADTTE, ADSL and RSMH

We were also interested in knowing if the treatment effect was consistent among subjects who had different single PEGASUS-qualifying risk factors. In table 37, treatment effect appeared to be fairly consistent regardless of the specific type of risk factor among subjects who only had one qualifying risk factor at baseline.

Table 20: Primary efficacy endpoint by type of risk factors among patients who had one qualifying risk factor at baseline

		Ticagrelor 60 mg N=3676		*Placebo N=3586*				
event	*Type of risk factors*	*n/N*	*ER*[a]	*n/N*	*ER*[a]	*HR*	*95CI*	*p_value*
CV Death, MI & stroke	Age≥65	69 / 1341	1.99	82 / 1353	2.33	0.85	(0.62, 1.17)	0.3215
	CRCL<60	1 / 26	1.49	1 / 29	1.29	1.09	(0.07, 17.49)	0.9493
	Diabetes requiring Tx	35 / 581	2.32	36 / 523	2.70	0.86	(0.54, 1.36)	0.5150
	>1 MI	12 / 157	3.06	19 / 170	4.40	0.69	(0.33, 1.42)	0.3088
	Multivessel CAD	63 / 1571	1.57	86 / 1511	2.26	0.70	(0.50, 0.96)	0.0286

[a] Event Rate (per 100 patient-years)
Reviewer's Table, Data Source: ADTTE, ADSL and RSMH

To further address the question of benefit-risk in a lower-risk population, a Cox Proportional Hazard (Cox PH) model was used to examine the treatment effect of ticagrelor 60 mg vs. placebo on time to first primary efficacy endpoint (CV death, MI or stroke) in a multivariable model controlling for any potential risk factor at baseline and any identified interaction between treatment and risk factors. Age, diabetes requiring treatment, history of more than one MI, multivessel CAD, chronic non-end stage renal dysfunction (CrCl <60), history of stent implant, history of angina pectoris, <30 days since ADP blocker (compared to >12 months since ADP blocker) and current smoker were identified as significant risk factors for the primary efficacy endpoint and included in the final Cox-PH model. There were no significant qualitative interaction effects found between the treatment arm and risk factors, particularly the qualifying risk factors for PEGASUS. After adjusting for the identified risk factors, the beneficial effect of ticagrelor 60 mg vs placebo on reducing the risk of primary efficacy endpoint remained significant.

Table 21 shows the parameter estimates and hazard ratios from the Cox PH model. The adjusted HR for the treatment effect is very close to the crude estimate (HR: 0.84, 95% CI: 0.74-0.95) reported in PEGASUS. This analysis suggests that the treatment effect remains consistent regardless of the type of risk factor and patients with lower risk than the study population would likely have the same treatment effect. Of note, all the PEGASUS-qualifying risk factors were identified as significant risk factors for the primary efficacy endpoint in the model. The magnitude of these risk factors was different (HR ranged from 1.25-1.97). These findings highlight the potential problem of looking at any particular subgroup analysis in PEGASUS. Because PEGASUS was a large randomized trial, the distribution of the risk factors between treatment arms would be expected to be similar overall. However, the differences in the distribution of risk factors among the treatment arms within subgroups might not have been balanced and could have conceivably confounded the HR estimates in any particular subgroup.

Table 21: Parameter Estimates and Hazard Ratios from Cox-Proportional Hazard model for the association between the treatment effect and primary efficacy endpoint

Parameter	Estimate (SE)	P-value	HR (95% CI)	
Age[a]	0.02 (0.004)	<.0001	1.25	(1.16, 1.35)
Diabetes requiring treatment (Y vs. N)[b]	0.51 (0.06)	<.0001	1.67	(1.47, 1.90)
>1 MI (Y vs. N)[b]	0.68 (0.07)	<.0001	1.97	(1.72, 2.25)
Chronic non-end stage renal dysfunction (Y vs. N)[b]	0.53 (0.10)	0.04	1.70	(1.40, 2.08)
Multivessel CAD (Y vs. N)[b]	0.27 (0.07)	0..0001	1.30	(1.14, 1.49)
Current Smoker (Y vs. N)	0.31 (0.08)	0.0001	1.36	(1.16, 1.60)
History of Stent Implant (Y vs. N)	-0.44 (0.08)	<.0001	0.65	(0.55, 0.76)
History of Angina Pectoris (Y vs. N)	0.25 (0.06)	0.0001	1.28	(1.13, 1.45)
Time since ADP blocker (30d-12M vs. <30 days)	-0.13 (0.08)	0.08	0.88	(0.75, 1.02)
Time since ADP blocker (>12M vs. <30 days)	-0.32 (0.09)	0.0003	0.73	(0.61, 0.86)
Treatment (Ticagrelor 60 mg vs. placebo)	-0.18 (0.06)	0.0036	0.84	(0.74, 0.94)

[a] HR for age was estimated with a unit of 10. HR of 1.25 means every 10-year increase in age increases risk of CV death, MI and Stroke by 25%.
[b] These risk factors were qualifying risk factors used in PEGASUS.
Reviewer's Table, Data Source: ADTTE, ADSL and RSMH

We also looked at the primary safety endpoint results by number of PEGASUS-qualifying risk factors at baseline to see if the treatment effect (i.e., the hazard ratio vs. placebo for TIMI major

bleed) was associated with the number of qualifying risk factors (Table 22). It is noted that the bleeding event rate increased as number of risk factors increased in the ticagrelor arm. This trend was less obvious in the placebo arm. Accordingly, the hazard ratio increased as the number of risk factor increased (Of note, HR in overall population is 2.32 in PEGASUS). These findings suggest that patients at higher risk for CV events may also be likely to have concurrent bleeding risk factors; thus they are more susceptible for bleeding when treated with ticagrelor. However, as mentioned earlier, the HR in this subgroup analysis could be conceivably confounded if bleeding risk factors were not distributed evenly between the two arms in each level of the subgroup.

Table 22 Primary safety endpoint (TIMI Major Bleed) by number of qualifying risk factors at baseline

[a] Event Rate (per 100 patient-years)
Reviewer's Table, Data Source: ADTTE, ADSL and RSMH

estimates and hazard ratios from the Cox PH model. There were no significant interaction effects found between the treatment arms and risk factors.

		Ticagrelor 60 mg N=7045		*Placebo N=7067*				
Event	*Number of risk factors*	*n/N*	*ER[a]*	*n/N*	*ER[a]*	*HR*	*95CI*	*p_value*
TIMI Major Bleeding	0	0 / 47	0.00	0 / 41	0.00	---	---	---
	1	49 /3676	0.51	32 /3586	0.34	1.50	(0.96, 2.34)	0.0760
	2	52/ 2315	0.87	33/ 2406	0.53	1.64	(1.06, 2.54)	0.0262
	3	27 / 816	1.30	10 / 826	0.47	2.74	(1.33, 5.67)	0.0064
	4	8 / 171	1.92	3 / 186	0.66	2.87	(0.76, 10.83)	0.1189
	5	2 / 20	4.78	0 / 22	0.00	---	---	---

To further explore the treatment effect of ticagrelor 60 mg vs. placebo on time to first Major bleeding event (on treatment), a Cox PH model was performed. Age, chronic non-end stage renal dysfunction, smoking, non-Caucasian were identified as significant risk factors for TIMI major bleeding and included in the final Cox-PH model. Table 23 shows the parameter

Table 23: Parameter Estimates and Hazard Ratios from Cox-Proportional Hazard model for the association between treatment effect and TIMI Major bleeding

Parameter	Estimate (SE)	P-value	HR (95% CI)	
Age[a]	0.04 (0.01)	<.0001	1.52	(1.25, 1.83)
Chronic non-end stage renal dysfunction (Y vs. N)[b]	0.61 (0.25)	0.01	1.85	(1.14, 3.00)
Current Smoker (Y vs. N)	0.54 (0.19)	0.005	1.71	(1.18, 2.50)
Caucasian (Y vs. N)	-0.50 (0.19)	0.009	0.61	(0.42, 0.88)
Treatment (Ticagrelor 60 mg vs. placebo)	0.85 (0.17)	<.0001	2.35	(1.70,3.25)

[a] HR for age was estimated with a unit of 10. HR of 1.52 means every 10-year increase in age increases risk of TIMI Major bleeding by 52%
[b] The qualifying risk factor used in PEGASUS.
Reviewer's Table, Data Source: ADTTE, ADSL and RSMH

Patients who are older or who have CrCl <60 are at an increased risk of having both an efficacy endpoint and a bleeding event. Because there was no significant qualitative interaction effect between these two risk factors and the treatment arms for both efficacy and safety models, there is no obvious evidence to suggest that the benefit and risk of treating with ticagrelor compared to placebo would be different between patients with lower risk for MACE and patients studied in PEGASUS.

While the Cox model demonstrates that the treatment effect (HR, both efficacy and bleeding) is likely to be consistent among MI patients with lower risk than what was enrolled in PEGASUS, the question remains as to whether the absolute benefit-risk difference is still favorable in this population.

To address the question, the Cox model was used to estimate the probability of MACE (CVD, MI, or stroke) within a year in a patient who would not have qualified for the study, i.e., a 55 y/o with no multivessel CAD, no diabetes, only 1 MI at least a year prior, and CrCl ≥ 60 mL/min or other identified risk factors*. The Cox model was also used to estimate TIMI Major bleeding probability within a year in a 55 y/o patient without any identified bleeding risk factors.* (See Table 24).

The model estimates that the absolute risk reduction in MACE (RD: -0.25%) is similar to the absolute risk increase in bleeding (RD: 0.23%) among patients with lower risk for MACE (55 y/o without any identified risk factors). This result suggests that benefit- risk difference of treating ticagrelor 60 mg will be ~0, meaning that one will likely trade 1 CVD, MI or stroke event for 1 TIMI major bleeding event in this population if treating with ticagrelor 60 mg. Considering that the majority of excess TIMI major bleeding in the ticagrelor arms is reversible in PEGASUS (i.e., it is not ICH and is not fatal), I would consider that the benefit-risk is likely to remain favorable in patients with lower risk for a MACE event, in general. However, one should note that the data regarding some bleeding risk factors such as history of prior bleeding are not available in PEGASUS. It is possible that a minority of patients at lower risk for MACE who fall within the category of higher risk for bleeding would have an unfavorable risk-benefit difference. While I think ticagrelor 60mg should be available for patients with lower risk for MACE,

treatment decisions should be individualized. Prescribers should decide whether or not to treat a patient based on an individual's risk factor for CV outcomes and bleeding.

Table 24: Cox model prediction of absolute risk of MACE and TIMI major bleeding in a 55 y/o patient with no identified risk factors*

Age 55 y/o without identified risk factors*	Ticagrelor 60 mg	Placebo
	% (95% CI)	% (95% CI)
Probability of CVD, MI or stroke within a year	1.27% (0.94, 1.59)	1.52%(1.13,1.90)
Hazard Ratio* Risk Difference (RD)	0.84 -0.25%	
Probability of TIMI Major bleed within a year	0.39% (0.24,0.53)	0.16% (0.09,0.24)
Hazard Ratio Risk Difference (RD)	2.44 0.23%	

* MACE risk factors: PEGASUS-qualifying risk factors + current smoker, without history of stent, history of angina, <30 days since ADP blocker
TIMI Major risk factor: CrCl <60 mL/min, current smoker, non-Caucasian
Reviewer's Table, Data Source: ADTTE, ADSL and RSMH
* Hazard ratio data added by MR

Appendix 2: Primary Endpoint Results for Selected Subgroups in PEGASUS

All randomized patients followed to the CSED

	ARM	Censor[a]	N	RR vs. P
All pts	Placebo	0	578	
	Placebo	1	6489	
	Placebo	ALL	7067	
	Ticagrelor 60mg bd	0	487	**0.85**
	Ticagrelor 60mg bd	1	6558	
	Ticagrelor 60mg bd	ALL	7045	
	Ticagrelor 90mg bd	0	493	**0.85**
	Ticagrelor 90mg bd	1	6557	
	Ticagrelor 90mg bd	ALL	7050	
	ALL		21162	
ADPRB1	Placebo	0	100	
	Placebo	1	1545	
	Placebo	ALL	1645	
	Ticagrelor 60mg bd	0	108	**1.07**
	Ticagrelor 60mg bd	1	1553	
	Ticagrelor 60mg bd	ALL	1661	
	Ticagrelor 90mg bd	0	97	**0.95**
	Ticagrelor 90mg bd	1	1579	
	Ticagrelor 90mg bd	ALL	1676	
	ALL		4982	
MI2	Placebo	0	202	
	Placebo	1	2522	
	Placebo	ALL	2724	
	Ticagrelor 60mg bd	0	194	**0.97**
	Ticagrelor 60mg bd	1	2510	
	Ticagrelor 60mg bd	ALL	2704	
	Ticagrelor 90mg bd	0	180	**0.89**
	Ticagrelor 90mg bd	1	2547	
	Ticagrelor 90mg bd	ALL	2727	
	ALL		8155	
ADPRB1 AND MI2	Placebo	0	78	
	Placebo	1	1223	
	Placebo	ALL	1301	
	Ticagrelor 60mg bd	0	82	**1.06**
	Ticagrelor 60mg bd	1	1210	
	Ticagrelor 60mg bd	ALL	1292	

	Ticagrelor 90mg bd	0	78	**1.00**
	ARM	**Censor[a]**	**N**	**RR vs. P**
	Ticagrelor 90mg bd	1	1224	
	Ticagrelor 90mg bd	ALL	1302	
	ALL		3813	
ADPRB1 not MI2	Placebo	0	22	
	Placebo	1	321	
	Placebo	ALL	343	
	Ticagrelor 60mg bd	0	26	**1.11**
	Ticagrelor 60mg bd	1	340	
	Ticagrelor 60mg bd	ALL	366	
	Ticagrelor 90mg bd	0	19	**0.79**
	Ticagrelor 90mg bd	1	354	
	Ticagrelor 90mg bd	ALL	373	
	ALL		1082	
MI2 not ADPRB1	Placebo	0	87	
	Placebo	1	964	
	Placebo	ALL	1051	
	Ticagrelor 60mg bd	0	80	**0.92**
	Ticagrelor 60mg bd	1	972	
	Ticagrelor 60mg bd	ALL	1052	
	Ticagrelor 90mg bd	0	62	**0.71**
	Ticagrelor 90mg bd	1	992	
	Ticagrelor 90mg bd	ALL	1054	
	ALL		3157	

a - censor code: 0=event, 1=no event
ADPRB1 - Patients with > 12 months between the end of ADPRB1 treatment and randomization
MI2 - Patients with at least 2 years between their index MI and randomization
ADPBR1 AND MI2 – Only patients who each satisfy both criteria

Appendix 3 -- Benefit Risk Tables from the Clinical Review

Table 25: Benefit/Risk: MACE (-hemorrhagic infarct) vs. TIMI Major Bleeding for Ticagrelor 60 mg vs. Placebo

Safety set, on treatment (until last dose or + 7 days if study drug discontinued before end of study). The percentages were calculated by dividing the number of events by the number in the subgroup. RR = %ticagrelor/% placebo. B-R = risk difference between ticagrelor and placebo for MACE(-) minus the risk difference between ticagrelor and placebo for TIMI Major Bleeding

		% of population	Tic 60	Pbo	↓ in MACE- %	RR	Tic 60	Pbo	↑ in bleed- ing %	RR	B-R
All		100%	4.7%	6.5%	**1.8%**	0.72	1.7%	0.8%	**0.9%**	2.14	**0.9%**
Age quintile	1 (<57 y/o)	17.4%	4.2%	6.5%	**2.3%**	0.64	1.2%	0.4%	**0.8%**	2.81	**1.6%**
	2 (≥57 and < 63)	20.7%	4.5%	6.0%	**1.5%**	0.75	1.1%	0.8%	**0.4%**	1.53	**1.1%**
	3 (≥63and < 67)	17.5%	5.3%	6.0%	**0.7%**	0.88	1.4%	0.6%	**0.8%**	2.24	**-0.1%**
	4(≥67 and < 73)	23.8%	4.5%	5.5%	**1.0%**	0.82	2.0%	0.8%	**1.2%**	2.59	**-0.2%**
	5(≥73)	20.5%	5.1%	8.6%	**3.5%**	0.60	2.3%	1.2%	**1.2%**	1.99	**2.3%**
Age	≥ 65	54.5%	4.9%	6.6%	**1.8%**	0.73	2.1%	0.9%	**1.2%**	2.40	**0.5%**
	≥ 75	14.5%	5.4%	9.0%	**3.6%**	0.60	2.5%	1.2%	**1.3%**	2.11	**2.2%**
Sex	Male	76.1%	4.4%	6.6%	**2.2%**	0.67	1.7%	0.8%	**0.9%**	2.11	**1.3%**
	Female	23.9%	5.7%	6.2%	**0.5%**	0.92	1.6%	0.7%	**0.9%**	2.25	**-0.4%**
Race	American Indian	0.2%	5.6%	0.0%	**-5.6%**	-	0.0%	0.0%	**0.0%**	-	**-5.6%**
	Asian	9.5%	3.9%	4.8%	**0.9%**	0.81	2.5%	0.4%	**2.1%**	5.63	**-1.2%**
	Black	1.7%	7.9%	9.6%	**1.7%**	0.82	4.8%	0.9%	**3.9%**	5.43	**-2.2%**
	Pacific Islander	1.2%	7.1%	9.1%	**2.0%**	0.78	3.5%	3.4%	**0.1%**	1.04	**1.9%**
	Other	0.7%	7.7%	2.0%	**-5.7%**	3.85	1.9%	0.0%	**1.9%**	-	**-7.6%**
	White	86.7%	4.6%	6.6%	**2.0%**	0.70	1.5%	0.8%	**0.7%**	1.89	**1.3%**
US vs. OUS	US	12.3%	4.8%	6.9%	**2.1%**	0.69	2.4%	1.0%	**1.3%**	2.26	**0.8%**
	OUS	87.7%	4.7%	6.4%	**1.7%**	0.73	1.6%	0.7%	**0.8%**	2.12	**0.9%**
Region	Asia/Pacific	11.1%	3.9%	4.9%	**1.0%**	0.79	3.1%	1.0%	**2.1%**	3.01	**-1.1%**
	Eastern EU	29.8%	5.3%	7.7%	**2.4%**	0.69	1.3%	0.7%	**0.6%**	1.93	**1.8%**
	North America	18.5%	4.2%	6.7%	**2.5%**	0.63	2.3%	0.9%	**1.3%**	2.44	**1.2%**
	South America	11.6%	5.9%	8.3%	**2.3%**	0.72	1.2%	0.9%	**0.4%**	1.44	**1.9%**
	Western EU	28.9%	4.2%	5.0%	**0.8%**	0.84	1.2%	0.6%	**0.6%**	1.93	**0.2%**
Weight quintile (All patients)	<=68 kg	20.6%	3.9%	6.8%	**2.8%**	0.58	1.9%	1.3%	**0.6%**	1.42	**2.2%**
	>68 and <= 76 kg	18.4%	5.0%	7.4%	**2.5%**	0.67	1.2%	0.6%	**0.6%**	2.02	**1.8%**
	>76 kg and <=83 kg	17.9%	5.2%	6.3%	**1.1%**	0.83	2.1%	0.7%	**1.4%**	3.00	**-0.4%**
	>83 kg and <=93 kg	20.8%	4.3%	5.8%	**1.5%**	0.74	1.8%	0.7%	**1.1%**	2.64	**0.4%**
	>93 kg	22.2%	5.1%	6.3%	**1.2%**	0.82	1.3%	0.5%	**0.7%**	2.37	**0.4%**

		% of population	Tic 60	Pbo	↓ in MACE-%	RR	Tic 60	Pbo	↑ in bleeding %	RR	B-R
Weight: Males by quintile	<=67 kg	15.3%	4.0%	7.3%	**3.4%**	0.54	1.8%	1.7%	**0.1%**	1.07	**3.2%**
	> 67 and <=76 kg	17.4%	4.4%	6.6%	**2.2%**	0.67	1.7%	0.6%	**1.1%**	2.65	**1.1%**
	> 76 and <=83 kg	13.8%	4.1%	5.8%	**1.7%**	0.70	1.9%	0.5%	**1.4%**	3.73	**0.3%**
	> 83 and <=93 kg	14.8%	4.6%	6.3%	**1.7%**	0.73	1.5%	0.6%	**0.9%**	2.54	**0.8%**
	> 93 kg	14.8%	4.8%	6.7%	**1.9%**	0.71	1.4%	0.5%	**0.9%**	2.87	**1.0%**
Weight: Females by quintile	<=60 kg	5.1%	4.0%	9.1%	**5.1%**	0.44	1.9%	0.9%	**1.0%**	2.20	**4.1%**
	>60 and <=68 kg	4.7%	4.0%	4.5%	**0.5%**	0.89	1.5%	0.6%	**0.9%**	2.56	**-0.4%**
	> 68 and <=76 kg	4.9%	7.7%	6.8%	**-0.9%**	1.13	1.2%	0.0%	**1.2%**	-	**-2.1%**
	> 76 and <=85 kg	4.4%	5.9%	6.3%	**0.4%**	0.94	1.3%	0.6%	**0.7%**	2.08	**-0.3%**
	> 85 kg	4.8%	7.1%	4.0%	**-3.1%**	1.76	1.9%	1.4%	**0.5%**	1.34	**-3.5%**
BMI	<=24.5	20.0%	3.7%	7.2%	**3.5%**	0.52	1.9%	1.6%	**0.3%**	1.21	**3.2%**
	>24.5 and <=27	19.9%	4.0%	5.6%	**1.6%**	0.71	1.9%	0.6%	**1.3%**	3.37	**0.3%**
	>27 and <=29	20.0%	3.9%	6.1%	**2.2%**	0.64	1.2%	0.6%	**0.6%**	1.93	**1.6%**
	> 29 and <= 32	20.0%	5.7%	6.3%	**0.7%**	0.89	1.5%	0.2%	**1.2%**	6.80	**-0.6%**
	> 32	20.0%	6.0%	7.1%	**1.1%**	0.84	1.8%	0.9%	**0.9%**	2.01	**0.2%**
Ethnicity	Hispanic or Latino	12.1%	6.0%	8.3%	**2.3%**	0.73	1.4%	1.2%	**0.3%**	1.22	**2.0%**
	Not Hispanic or Latino	84.8%	4.5%	6.3%	**1.8%**	0.71	1.7%	0.7%	**0.9%**	2.24	**0.9%**
Time from last ADP blocker	<57 days	12.2%	4.7%	7.2%	**2.5%**	0.66	2.2%	0.7%	**1.5%**	3.22	**0.9%**
	58-179 days	12.2%	4.9%	6.9%	**2.0%**	0.71	1.3%	0.7%	**0.6%**	1.84	**1.4%**
	180-352 days	12.2%	3.9%	6.2%	**2.4%**	0.62	2.2%	0.8%	**1.4%**	2.68	**1.0%**
	353 days -547 days	12.2%	4.9%	5.4%	**0.5%**	0.90	1.4%	0.7%	**0.7%**	2.02	**-0.2%**
	>547 days	12.2%	3.3%	3.9%	**0.6%**	0.85	1.4%	0.7%	**0.7%**	1.94	**-0.1%**
Time from index MI	< 1.1 yrs	20.1%	5.1%	7.3%	**2.2%**	0.70	2.3%	0.6%	**1.7%**	3.68	**0.5%**
	1.1 yrs to 1.5 yrs	19.9%	4.3%	7.1%	**2.8%**	0.60	0.8%	0.9%	**0.0%**	0.95	**2.9%**
	>1.5 yrs to 2 yrs	20.0%	4.3%	6.6%	**2.3%**	0.65	1.9%	1.1%	**0.8%**	1.72	**1.5%**
	2.0 yrs to 2.5 yrs	20.0%	4.6%	6.2%	**1.7%**	0.73	1.6%	0.8%	**0.8%**	2.05	**0.8%**
	> 2.5 yrs	19.9%	5.2%	5.2%	**-0.1%**	1.01	1.6%	0.4%	**1.2%**	4.39	**-1.3%**
MI type	STEMI	53.6%	4.0%	5.8%	**1.8%**	0.69	1.6%	0.7%	**0.9%**	2.26	**0.9%**
	NSTEMI	40.6%	5.4%	7.1%	**1.7%**	0.77	1.8%	0.8%	**1.0%**	2.33	**0.6%**
	unknown	5.8%	6.1%	9.2%	**3.1%**	0.66	1.4%	1.2%	**0.2%**	1.13	**2.9%**
	no MI	0.1%	0.0%	0.0%	**0.0%**	-	0.0%	11.1%	**-11.1%**	0.00	**11.1%**

		% of population	Tic 60	Pbo	↓ in MACE-%	RR	Tic 60	Pbo	↑ in bleeding %	RR	B-R
STENT											
Type of stent	DES, any	39.2%	4.6%	6.4%	**1.8%**	0.72	1.7%	1.0%	**0.7%**	1.75	**1.1%**
	BMS, only	36.5%	3.5%	4.9%	**1.4%**	0.71	1.7%	0.6%	**1.1%**	2.62	**0.3%**
	Stent, unknown type	4.1%	3,5%	7.0%	**3.4%**	0.5	2.5%	0.0%	**2.5%**	-	**0.9%**
	no stent	19.9%	7.4%	9.3%	**1.9%**	0.65	1.3%	0.8%	**0.6%**	1.72	**1.3%**
	unknown	0.3%	0%	0%	0%	-	0%	0%	**0%**	-	**0%**
Multivessel Disease	yes	59.3%	4.8%	6.9%	**2.1%**	0.70	1.8%	0.7%	**1.1%**	2.46	**1.0%**
	no	40.7%	4.4%	5.8%	**1.3%**	0.77	1.4%	0.8%	**0.6%**	1.71	**0.8%**
Smoking history	former smoker	48.3%	4.9%	6.2%	**1.4%**	0.78	1.4%	0.6%	**0.8%**	2.46	**0.5%**
	never smoked	35.0%	4.1%	6.1%	**2.1%**	0.66	1.7%	1.0%	**0.6%**	1.61	**1.4%**
	current smoker	16.7%	5.5%	8.1%	**2.6%**	0.68	2.4%	0.8%	**1.6%**	2.95	**1.0%**
Creatinine Clearance at baseline (C-G)	<=58 mL/min	19.1%	4.3%	6.2%	**2.0%**	0.69	1.3%	0.8%	**0.5%**	1.56	**1.5%**
	> 58 and <=74 mL/min	19.9%	5.3%	5.1%	**-0.2%**	1.04	2.0%	1.2%	**0.8%**	1.69	**-1.1%**
	>74 and < =89 mL/min	19.9%	4.2%	6.5%	**2.3%**	0.65	1.3%	0.5%	**0.8%**	2.54	**1.5%**
	>89 and <=108 mL/min	19.9%	4.4%	7.0%	**2.6%**	0.63	1.7%	0.4%	**1.3%**	3.95	**1.3%**
	>108 mL/min	19.9%	5.4%	7.7%	**2.3%**	0.71	1.9%	0.9%	**0.9%**	1.95	**1.4%**
SSRI at baseline	yes	4.6%	6.5%	7.2%	**0.7%**	0.90	1.5%	0.9%	**0.6%**	1.65	**0.1%**
	no	95.4%	4.6%	6.4%	**1.8%**	0.71	1.7%	0.8%	**0.9%**	2.17	**1.0%**
H/o COPD or asthma or dyspnea	yes	10.9%	7.3%	8.0%	**0.7%**	0.91	2.2%	0.6%	**1.6%**	3.48	**-0.9%**
	no	89.1%	4.4%	6.3%	**1.9%**	0.70	1.6%	0.8%	**0.8%**	2.01	**1.1%**

*Any intracranial bleeding (excluding microhemorrhages <10 mm evident only on gradient-echo MRI)
Clinically overt signs of hemorrhage associated with a drop in hemoglobin of ≥5 g/dL or a ≥15% absolute decrease in hematocrit. Fatal bleeding (bleeding that directly results in death within 7 d

Table 26: Benefit/Risk: MACE (-hemorrhagic infarct) vs. TIMI Major Bleeding for Ticagrelor 90 mg vs. Placebo

		% of population	MACE (-) Tic 90	MACE (-) Pbo	↓ in MACE-%	RR	Bleeding Tic 90	Bleeding Pbo	↑ in bleeding %	RR	B-R
ALL		100%	4.5%	6.5%	**2.0%**	0.70	1.8%	0.8%	**1.0%**	2.35	**0.9%**
Age quintile	1 (<57 y/o)	17%	3.2%	6.5%	**3.3%**	0.49	1.6%	0.4%	**1.2%**	3.79	**2.1%**
	2 (≥57 and < 63)	20.7%	4.6%	6.0%	**1.3%**	0.78	1.5%	0.8%	**0.8%**	2.01	**0.6%**
	3 (≥63and < 67)	17.5%	3.4%	6.0%	**2.5%**	0.57	1.5%	0.6%	**0.9%**	2.34	**1.7%**
	4(≥67 and < 73)	23.8%	4.6%	5.5%	**0.9%**	0.84	1.7%	0.8%	**0.9%**	2.17	**0.0%**
	5(≥73)	20.5%	6.4%	8.6%	**2.1%**	0.75	2.7%	1.2%	**1.5%**	2.30	**0.6%**
Age	≥ 65	54.5%	4.9%	6.6%	**1.7%**	0.74	2.0%	0.9%	**1.1%**	2.23	**0.6%**
	≥ 75	14.50%	6.90%	9.00%	**2.0%**	0.77	2.80%	1.2%	**1.6%**	2.39	**0.4%**
Sex	Male	76.1%	4.7%	6.6%	**1.8%**	0.72	2.0%	0.8%	**1.2%**	2.46	**0.7%**
	Female	23.9%	3.8%	6.2%	**2.3%**	0.62	1.4%	0.7%	**0.7%**	1.96	**1.6%**
	American Indian	0.2%	0.0%	0.0%	**0.0%**	-	0.0%	0.0%	0.0%	-	**0.0%**
	Asian	9.5%	2.9%	4.8%	**1.9%**	0.61	2.5%	0.4%	**2.0%**	5.46	**-0.1%**
	Black	1.7%	4.7%	9.6%	**4.9%**	0.49	0.9%	0.9%	**0.1%**	1.08	**4.9%**
	Other	0.7%	2.0%	2.0%	**0.0%**	1.02	6.1%	0.0%	**6.1%**	-	**-6.2%**
	White	86.7%	4.6%	6.6%	**2.0%**	0.70	1.8%	0.8%	**1.0%**	2.27	**1.0%**
	US	12.3%	5.0%	6.9%	**1.9%**	0.72	2.1%	1.0%	**1.1%**	2.02	**0.9%**
	OUS	87.7%	4.5%	6.4%	**2.0%**	0.69	1.8%	0.7%	**1.0%**	2.42	**0.9%**
Region	Asia/Pacific	11.1%	3.6%	4.9%	**1.3%**	0.73	2.2%	1.0%	**1.2%**	2.12	**0.1%**
	Eastern EU	29.8%	5.1%	7.7%	**2.5%**	0.67	1.5%	0.7%	**0.9%**	2.30	**1.7%**
	South America	11.6%	5.5%	8.3%	**2.8%**	0.67	2.6%	0.9%	**1.7%**	2.97	**1.1%**
	Western EU	28.9%	4.2%	5.0%	**0.8%**	0.84	1.6%	0.6%	**1.0%**	2.54	**-0.2%**
Weight: by quintile	<=68 kg	20.6%	4.8%	6.8%	**1.9%**	0.72	2.3%	1.3%	**1.0%**	1.73	**1.0%**
	>68 and <= 76 kg	18.4%	3.6%	7.4%	**3.8%**	0.48	1.9%	0.6%	**1.3%**	3.15	**2.5%**
	>76 kg and <=83 kg	17.9%	5.4%	6.3%	**0.9%**	0.86	1.4%	0.7%	**0.7%**	1.96	**0.2%**
	>83 kg and <=93 kg	20.8%	4.7%	5.8%	**1.0%**	0.82	1.5%	0.7%	**0.9%**	2.26	**0.2%**
	>93 kg	22.2%	3.9%	6.3%	**2.4%**	0.62	1.9%	0.5%	**1.4%**	3.55	**1.0%**
Weight: Males by quintile	<=67 kg	15.3%	5.2%	7.3%	**2.2%**	0.70	2.6%	1.7%	**1.0%**	1.57	**1.2%**
	>67 and <= 76 kg	17.4%	4.3%	6.6%	**2.3%**	0.65	1.9%	0.6%	**1.3%**	3.01	**1.0%**
	> 76 and <=83 kg	13.8%	5.7%	5.8%	**0.1%**	0.97	1.3%	0.5%	**0.8%**	2.47	**-0.6%**
	> 83 and <=93 kg	14.8%	4.8%	6.3%	**1.5%**	0.76	1.7%	0.6%	**1.1%**	2.92	**0.4%**
	> 93 kg	14.8%	3.9%	6.7%	**2.8%**	0.58	2.1%	0.5%	**1.6%**	4.19	**1.2%**

			MACE (-)		↓ in		Bleeding		↑ in		
		% of population	Tic 90	Pbo	MACE-%	RR	Tic 90	Pbo	bleeding %	RR	B-R
Weight: Females by quintile	<=60 kg	5.1%	3.1%	9.1%	**6.0%**	0.34	2.0%	0.9%	**1.1%**	2.31	**4.9%**
	>60 and <= 68 kg	4.7%	5.5%	4.5%	**-0.9%**	1.20	1.5%	0.6%	**0.9%**	2.51	**-1.8%**
	> 68 and <=76 kg	4.9%	3.7%	6.8%	**3.1%**	0.55	1.1%	0.0%	**1.1%**	-	**1.9%**
	> 76 and <=85 kg	4.4%	4.5%	6.3%	**1.8%**	0.71	1.4%	0.6%	**0.7%**	2.19	**1.1%**
	> 85 kg	4.8%	2.7%	4.0%	**1.4%**	0.66	0.9%	1.4%	**-0.5%**	0.62	**1.9%**
BMI quintile	<=24.5	20.0%	4.7%	7.2%	**2.5%**	0.66	2.0%	1.6%	**0.4%**	1.26	**2.1%**
	>24.5 and <=27	19.9%	4.7%	5.6%	**1.0%**	0.83	1.5%	0.6%	**0.9%**	2.67	**0.0%**
	>27 and <=29	20.0%	4.4%	6.1%	**1.8%**	0.71	2.2%	0.6%	**1.5%**	3.44	**0.2%**
	> 29 and <= 32	20.0%	4.2%	6.3%	**2.1%**	0.66	1.4%	0.2%	**1.2%**	6.69	**0.9%**
	> 32	20.0%	4.4%	7.1%	**2.8%**	0.61	2.0%	0.9%	**1.1%**	2.25	**1.7%**
Ethnicity	Hispanic or Latino	12.1%	5.5%	8.3%	**2.9%**	0.66	2.3%	1.2%	**1.1%**	1.96	**1.7%**
	Not Hispanic or Latino	84.8%	4.4%	6.3%	**1.9%**	0.70	1.6%	0.7%	**0.8%**	2.12	**1.1%**
Time from last ADP blocker	<57 days	12.2%	5.0%	7.2%	**2.1%**	0.70	1.9%	0.7%	**1.2%**	2.76	**0.9%**
	58-179 days	12.2%	4.4%	6.9%	**2.5%**	0.64	2.3%	0.7%	**1.6%**	3.19	**0.9%**
	180-352 days	12.2%	3.5%	6.2%	**2.8%**	0.56	1.0%	0.8%	**0.2%**	1.23	**2.6%**
	353 days -547 days	12.2%	2.6%	5.4%	**2.8%**	0.49	1.3%	0.7%	**0.6%**	1.79	**2.2%**
	>547 days	12.2%	3.8%	3.9%	**0.1%**	0.96	2.8%	0.7%	**2.1%**	3.97	**-2.0%**
Time from index MI	< 1.1 yrs	20.1%	4.8%	7.3%	**2.5%**	0.65	2.0%	0.6%	**1.4%**	3.22	**1.1%**
	1.1 yrs to 1.5 yrs	19.9%	4.7%	7.1%	**2.4%**	0.66	1.6%	0.9%	**0.7%**	1.76	**1.7%**
	>1.5 yrs to 2 yrs	20.0%	4.6%	6.6%	**2.0%**	0.70	1.5%	1.1%	**0.4%**	1.32	**1.6%**
	2.0 yrs to 2.5 yrs	20.0%	4.5%	6.2%	**1.7%**	0.73	1.7%	0.8%	**1.0%**	2.22	**0.7%**
	> 2.5 yrs	19.9%	3.9%	5.2%	**1.2%**	0.76	2.2%	0.4%	**1.9%**	6.27	**-0.6%**
MI type	STEMI	53.6%	3.8%	5.8%	**2.0%**	0.65	1.9%	0.7%	**1.2%**	2.76	**0.8%**
	NSTEMI	40.6%	5.5%	7.1%	**1.6%**	0.77	1.7%	0.8%	**1.0%**	2.23	**0.6%**
	unknown	5.8%	4.7%	9.2%	**4.5%**	0.52	1.6%	1.2%	**0.3%**	1.27	**4.1%**
	no MI	0.1%	16.7%	0.0%	**16.7%**	-	0.0%	11.1%	**11.1%**	0.00	**-5.6%**

		% of population	MACE (-) Tic 90	MACE (-) Pbo	↓ in MACE (-) %	RR	Bleeding Tic 90	Bleeding Pbo	↑ In bleeding %	RR	B-R
Type of stent	DES, any	39.2%	4.2%	6.4%	**2.2%**	0.66	2.0%	1.0%	**1.0%**	1.99	**1.2%**
	BMS, only	36.5%	4.4%	4.9%	**0.5%**	0.9	2.0%	0.6%	**1.4%**	3.17	**-0.9%**
	Stent, unknown type	4.1%	2.9%	7.0%	**1.2%**	0.41	0.4%	0.0%	**0.4%**	-	**0.8%**
	no stent	19.9%	5.7%	9.3%	**3.7%**	0.61	1.5%	0.8%	**0.7%**	1.92	**3.0%**
	unknown	0.3%	0%	0%	**0%**	-	0%	0%	**0%**	-	**0%**
Multivessel Disease	yes	59.3%	4.6%	6.9%	**2.4%**	0.66	1.8%	0.7%	**1.0%**	2.35	**1.4%**
	no	40.7%	4.5%	5.8%	**1.3%**	0.77	1.9%	0.8%	**1.1%**	2.36	**0.2%**
Smoking history	former smoker	48.3%	4.1%	6.2%	**2.1%**	0.66	1.9%	0.6%	**1.3%**	3.30	**0.8%**
	never smoked	35.0%	4.5%	6.1%	**1.6%**	0.74	1.4%	1.0%	**0.3%**	1.31	**1.3%**
	current smoker	16.7%	5.7%	8.1%	**2.3%**	0.71	2.6%	0.8%	**1.8%**	3.29	**0.5%**
Creatinine Clearance at baseline (C-G)	<=58 mL/min	19.1%	3.8%	6.2%	**2.4%**	0.61	1.8%	0.8%	**0.9%**	2.16	**1.5%**
	> 58 and <=74 mL/min	19.9%	3.8%	5.1%	**1.2%**	0.76	1.8%	1.2%	**0.6%**	1.48	**0.7%**
	>74 and < =89 mL/min	19.9%	4.7%	6.5%	**1.8%**	0.72	1.9%	0.5%	**1.3%**	3.68	**0.5%**
	>89 and <=108 mL/min	19.9%	5.4%	7.0%	**1.5%**	0.78	2.4%	0.4%	**1.9%**	5.55	**-0.4%**
	>108 mL/min	19.9%	4.3%	7.7%	**3.4%**	0.56	1.2%	0.9%	**0.2%**	1.22	**3.2%**
SSRI at baseline	yes	4.6%	6.9%	7.2%	**0.3%**	0.96	**3.8%**	0.9%	**2.8%**	4.01	**-2.5%**
	no	95.4%	4.4%	6.4%	**2.0%**	0.68	1.7%	0.8%	**1.0%**	2.26	**1.1%**
H/o COPD or asthma or dyspnea	yes	10.9%	6.4%	8.0%	**1.6%**	0.80	3.2%	0.6%	**2.5%**	4.94	**-0.9%**
	no	89.1%	4.3%	6.3%	**2.0%**	0.68	1.7%	0.8%	**0.9%**	2.10	**1.1%**

[i] 2.7.3 Summary Of Clinical Efficacy - Ticagrelor for the Prevention of Thrombotic Events in Patients with History of Myocardial Infarction on a Background of Acetyl Salicylic Acid Therapy, Table 6

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/s/

MARTIN ROSE
08/11/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-433/S015

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	sNDA
Application Number(s)	022433 Suppl-15
Priority or Standard	Priority
Submit Date(s)	March 6, 2015
Received Date(s)	March 6, 2015
PDUFA Goal Date	September 6, 2015
Division / Office	DCRP/ODE-1
Reviewer Name(s)	Preston Dunnmon, MD, MBA - efficacy Melanie Blank, MD - safety
Review Completion Date	August 7, 2015
Established Name	Ticagrelor
(Proposed) Trade Name	Brilinta
Therapeutic Class	P2Y12 platelet inhibitor
Applicant	AstraZeneca (AZ)
Formulation(s)	60 mg Tablets
Dosing Regimen	60 mg twice daily (bd)
Indication(s)	(b) (4)
Intended Population(s)	(b) (4)

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

After a thorough review of the applicant's submission, independent analyses of the data from the new pivotal trial, PEGASUS, reanalysis of safety data from the pivotal trial that supported ticagrelor's initial approval, PLATO, and review of the literature, both the efficacy and the safety reviewers (Dr. Dunnmon and Dr. Blank, respectively) recommend an approval decision for ticagrelor efficacy supplement 15.

The proposed label adds the following indication:

(b) (4)

The reviewers, however, differ upon their recommendation of the populations for whom this new indication should be indicated. The nature of this disagreement will be elucidated in the last few paragraphs of this section. The first part of this section will provide insight into our recommendation for approval.

According to the 2012 ACCF/AHA Focused Update to the Guideline for the Management of Patients with Unstable Angina/Non-ST-Elevation Myocardial Infarction (UA/NSTEMI) (Updating the 2007 guideline and Replacing the 2011 Focused Update), for UA/NSTEMI patients in whom an initial conservative (i.e., noninvasive) strategy is selected, clopidogrel or ticagrelor (loading dose followed by a daily maintenance dose) should be added to aspirin (ASA) and anticoagulant therapy as soon as possible after admission and administered for up to 12 months. (Level of Evidence: B). The recommendations (according to the 2013 ACCF/AHA Guideline for the Management of ST-Elevation myocardial Infarction: Executive Summary) are to do the same for patients with STEMI as early as possible or at the time of PCI and to maintain the therapy for 1 year in the setting of drug eluting stent (DES) placement or bare metal stent (BMS) placement (Level of Evidence: B) and to continue beyond a year in the setting of DES placement (Level of evidence: C).

Dual anti-platelet therapy (DAPT) with ticagrelor plus low dose ASA was approved following ticagrelor's first pivotal trial, PLATO. PLATO compared ticagrelor 90 mg twice daily (bd) to clopidogrel 75 mg daily (od) (after loading doses and in addition to aspirin) in > 18,500 post-MI subjects and found that ticagrelor was superior for reducing major adverse cardiac events (MACE), a composite of cardiovascular (CV) death, myocardial

infarction (MI), and stroke (p = 0.0003). The difference between treatments was driven by CV death and MI with no difference in stroke. There were independent successes on CV death (p =0.0013) and MI (p = 0.0045). In patients treated with PCI, it also reduced the rate of stent thrombosis. It should be noted that the ticagrelor label is silent on how long to continue ticagrelor post-MI despite the fact that the average length of follow-up in PLATO was < 1 year. The ACCF/AHA guidelines provide a conservative approach by recommending the treatment for only 1 year and calling the level of evidence a B (limited population evaluated and data derived from a single randomized trial). Strictly speaking, the level of evidence is a B, but ticagrelor was superior to another antiplatelet agent on a background of aspirin. This provides great confidence that ticagrelor + aspirin is superior to aspirin alone for the prevention of MACE (at least CV death and MI) in the immediate post-MI period, at least up through a year.

The pivotal trial that is the subject of this clinical review, PEGASUS, was designed to answer the questions of whether to treat post-MI patients beyond the first year with DAPT, specifically ticagrelor + aspirin, and also how long post-MI to continue DAPT. It was conducted in a population of higher-risk post-MI patients with at least one of the following risk factors: age > 65 y/o, diabetes mellitus requiring medication, documented history of a second prior MI (> 1 year ago), CrCl < 60 mL/min, and/or angiographic evidence of multivessel disease. For this reason, the interpretation of the study results might be considered limited to only being able to provide a definitive answer to the question of whether to continue DAPT beyond one year in patients with these risk factors. However, as will be discussed later, there was information that supported extrapolation to a lower-risk post-MI population. Also, without extrapolation, the study results might only be considered reliably supportive of DAPT (ticagrelor + aspirin) use up to the length of time that a substantial portion of the subjects were studied in PEGASUS which was ~ 3 years because there was a high drop-off in subject numbers between 36 months and the maximum treatment duration of 48 months. However, as will be discussed later, the Kaplan-Meier time to event plot provides insights that are useful for addressing the question of how long to treat.

PEGASUS was an event-driven, randomized, double blind, placebo-controlled, parallel group, international multicenter study to assess the prevention of cardiovascular events with ticagrelor given at 2 doses (90 mg bd and 60 mg bd) compared to placebo on a background of ASA in patients with history of MI (1-3 years ago) and additional risk factors for atherothrombosis.

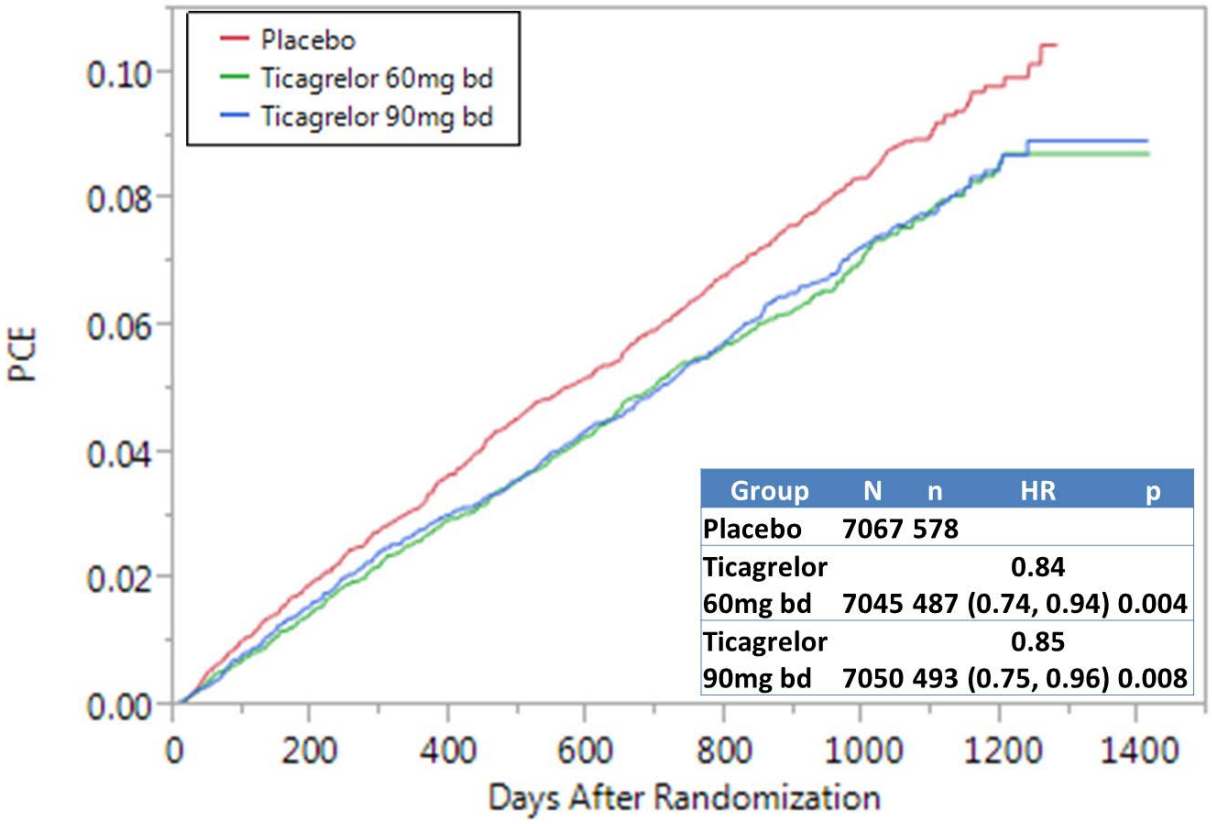
Over 21,000 patients were randomized in a 1:1:1 ratio to each of the three study arms (approximately 7,000 subjects in each study arm).

The minimum and maximum dosing periods were planned to be 12 months and 38 months, respectively.

The primary efficacy endpoint of PEGASUS was the time to first occurrence of CV death, non-fatal MI, or non-fatal stroke. PEGASUS convincingly achieved significance as defined in the analytical plan (see section 5.3.1.14) for both doses of ticagrelor versus placebo in reducing the composite of first occurrence of CV death, MI, or stroke.

The Kaplan Meier plot of the efficacy results shown in Figure 1 suggests that the effect of ticagrelor on MACE (CV death, MI, or stroke) increases over time. There is no concern of diminished effectiveness over time and therefore, it may be wise to continue treatment with DAPT long after the 3 year period studied in this trial. It is not possible to know from these data if or when the effectiveness would diminish at some time later beyond 3 years.

Figure 1: PEGASUS primary composite efficacy endpoint (time to first occurrence of CV Death, MI, or stroke). FAS to CSED (FDA Clinical Efficacy Reviewer, ADTTE and RSYB)



Subgroup analyses of effectiveness are presented in section 6.1.7. Notable is the finding in the 60 mg bd ticagrelor arm of essentially no benefit in those patients who were at least two years out from their most recent MI and those greater than 12 months out from their prior ADP receptor blocker therapy at the time of randomization. One

might believe that these two subgroup findings are reflective of truth and not just a chance occurrence because such patients may have either re-endothelialized and/or stabilized their coronary arteries by the time that they have been out two or more years from their most recent myocardial infarction (or greater than 1 year from prior ADP receptor blocker therapy), or alternatively, that those with the most unstable coronary artery disease did not survive long enough to be enrolled into PEGASUS. Therefore, one could argue that if PEGASUS subjects had been atherothrombotic event-free for two years without the benefit of DAPT, their chances of benefiting from DAPT were lower and therefore not worth the risk, mostly the risk of bleeding. There was also decreased efficacy noted in females on the 60 mg dose (still better than aspirin alone but not as good as in males), but this finding is most likely a spurious finding for the following reasons: 1) the subset of females was small (24%) and MACE in females only accounted for 26% of MACE in the study; 2) there was no decrease in exposure in females compared to males noted in the clinical pharmacology substudy of PEGASUS; 3) efficacy in females was preserved in the 90 mg dose treatment group, and 4) there was significant overlap in exposures among the subjects who were enrolled in both the 60 mg and 90 mg dose ticagrelor arms.

Patients with a history of ischemic stroke at baseline were originally enrolled but then disenrolled because of findings from another study wherein patients with a prior ischemic stroke who received vorapaxar (which antagonizes thrombin-mediated activation of the protease-activated receptor-1 on platelets) in addition to standard antiplatelet therapy were shown to have increased risk of intracranial hemorrhage without an improvement in major vascular events, including ischemic stroke compared to standard antiplatelet therapy alone.[1] The protocol amendment was instituted approximately 4 months after the first subject was enrolled into PEGASUS. Thus, only 102 subjects fell within this category at the time of first amendment which is when the change occurred to the protocol regarding exclusion of patients with h/o ischemic stroke (patients with history of hemorrhagic stroke had been excluded from the beginning), and their exposure to study drug during the trial was brief. Of these 102 subjects, only 90 received study drug, but all were followed for efficacy and safety outcomes for the remainder of the study in the same manner as other subjects who discontinued study drug prematurely. MACE and bleeding events through the CSED for these subjects were included in the efficacy ITT analyses, safety analyses, and on-treatment analyses. Six of these subjects withdrew from the trial, though vital status was known for all at the end of the study. For these 102 subjects with prior ischemic stroke, no on-treatment MACE or TIMI major bleeding events were reported. As might be expected for a small subgroup, the total number of primary composite events was small (5 versus 2 versus 4 for the ticagrelor 90 bd, ticagrelor 60 bd, and placebo arms respectively). The absence of an ominous signal in this small subgroup is still reassuring.

[1] Morrow, DA et al, Efficacy and Safety of Vorapaxar in Patients with Prior ischemic Stroke, *Stroke,* 2013;44:691-8.

The most significant safety finding in PEGASUS was bleeding. The incidence of TIMI major bleeding (defined as any intracranial bleeding or clinically overt signs of hemorrhage associated with a fall in Hb ≥ 5 g/dL or fatal bleeding which is defined by death within 7 days of major bleeding) was 1.8% (KM 2.6%) in the ticagrelor 90 mg group, 1.7% (KM 2.3%) in the ticagrelor 60 mg group and 0.8% (KM 1.1%) in the placebo group. Of note, there was no increase in fatal bleeding in either of the ticagrelor groups compared to placebo, and ICH rates were similar (0.4% event rates in ticagrelor groups and 0.3% event rates in placebo). The somewhat improved TIMI major bleeding rate in ticagrelor 60 mg group (compared to ticagrelor 90 mg) with preserved efficacy and overall preserved benefit-risk difference of 0.9% when comparing MACE minus hemorrhagic infarct to TIMI major bleeding (to avoid double counting) makes the applicant's choice to only market the 60 mg dose reasonable.

The main questions regarding the approval of this application that require consideration are for whom it should be indicated (i.e., should it be restricted to patients less than 2.5 years out from MI and/or who have the same high-risk factors that qualified patients for enrollment in PEGASUS and/or who have no prior history of stroke?) and for how long after index MI should it be given.

The clinical reviewers explain their views on this topic in the sections below.

<u>Safety reviewer</u>

1. Should the amount of time since last MI or last DAPT determine whether patients should be treated with ticagrelor + aspirin? Ticagrelor plus aspirin should be indicated for all post-MI patients without regard to how much time has passed since previous MI or previous last dose of DAPT because this reflects the population studied in PEGASUS. Patients who are between 2.5 years and 3.0 years out from their MI should have the benefit of ticagrelor, as should patients whose MI occurred more than 3 years prior even though this population was not studied in PEGASUS. The observation of decreased efficacy in the subgroup of subjects in the 60 mg ticagrelor arm who were between 2.5 and 3 years out from their previous MI may have been a spurious finding. This is supported by the observation that the pattern of diminished efficacy in patients 2.5 years or more out from their most recent MI is not seen as clearly in the 90 mg ticagrelor arm. See Table 35 and

Table 36 in APPENDIX 1. While I acknowledge that it is biologically plausible that there is diminishment of effectiveness as time passes after index MI, the benefit-risk is still positive when compared to aspirin alone in all of the post-MI quintiles. I also acknowledge that the B-R becomes negative for subjects who were out > 353 days from their last ADP blocker (-0.1 to -0.2) but this negative benefit-risk difference is very small. One cannot be sure that the balance of underlying risk factors for MACE was the same among the subjects who were out > 353 days from their last ADP blocker. In other words, it is possible that, by chance, the patients who were out >353 days from their last ADP blocker and were randomized to ticagrelor had a higher underlying risk of MACE than the patients who were out >353 days from their last ADP blocker and were randomized to placebo. Furthermore, I believe that it is important to refrain from counting TIMI major bleeding episodes as equivalent events to MACE. While MACE fatalities were increased in the aspirin only arm, bleeding fatalities were NOT increased in the ticagrelor arms. Because PEGASUS was a large randomized trial, the distribution of risk factors between treatment groups would be expected to be similar overall (and it was, as shown in Table 38). However, the differences in the distribution of risk factors among the treatment arms within subgroups might not have been balanced and could have conceivably confounded the HR estimates in any particular subgroup.

2. Should continuation of ticagrelor + aspirin be indicated for high-risk patients only or for all patients who are 1 year out from their MI? Only patients who met at least one PEGASUS-qualifying criterion were enrolled in PEGASUS in an attempt to enrich the population with subjects who would be more likely to have endpoint events. The PEGASUS-qualifying criteria were: age ≥ 65 years, multivessel disease, diabetes mellitus, previous additional MI or CrCl < 60 mL/min. Therefore, there are no empiric data to help answer the question of whether the risk-benefit difference is favorable for these subjects who fell outside of criteria for enrollment in PEGASUS. To answer the question of whether patients who would not have qualified for PEGASUS a thorough analysis of risk for MACE and TIMI Major bleeding by number and type of cardiovascular risk factors was performed by Dr. Tzu-Yun McDowell and is presented in APPENDIX 2. To summarize her analysis, there is no obvious trend in benefit of ticagrelor 60 mg compared to placebo for decreasing MACE by number and type of qualifying or other risk factors for MACE that were identified during her analysis of the PEGASUS results. There also was no significant qualitative interaction effect found between the treatment arm and risk factors, particularly the qualifying risk factors for PEGASUS, suggesting that the treatment effect is likely to be consistent among MI patients at lower risk for recurrent MI, CV death or stroke. Additionally, another analysis was performed to examine the treatment

effect of ticagrelor vs. placebo on TIMI major bleeding by risk factors for increased bleeding. The analysis showed no significant interaction between treatment arm and risk factors. One can anticipate that there will be some decrease in effect size as the absolute risk for recurrent MI decreases. However, the risk for bleeding should also decrease in those subjects at lower risk for recurrent MI because younger age is associated with a reduced risk of bleeding.

Dr. McDowell used a Cox model to estimate the probability of MACE (CVD, MI, or stroke) within a year in a patient who would not have qualified for the study, i.e., a 55 y/o with no multivessel CAD, no diabetes, only 1 MI at least a year prior, and CrCl ≥ 60 mL/min or other identified risk factors; See Table 42. The model estimates that the absolute risk reduction in MACE (RD: -0.25%) will be similar to the absolute risk increase in bleeding (RD: 0.23%) among 55 y/o post-MI patients without any additional identified risk factors for MACE. This result suggests that the benefit- risk difference of treating such patients with ticagrelor 60 mg will be ~0, meaning that one will likely trade 1 CVD, MI or stroke event for 1 TIMI major bleeding event in this population. Considering that the majority of excess TIMI major bleeding in the ticagrelor arms was reversible in PEGASUS (i.e., not intracranial hemorrhage (ICH) and not fatal), I would consider that the benefit-risk is likely to remain favorable in patients with lower risk for a MACE event, in general. However, one should note that the data regarding some major bleeding risk factors such as history of prior bleeding were not available in PEGASUS. It is possible that patients with higher risk for bleeding would have an unfavorable risk-benefit difference. I agree with Dr. McDowell when she states that ticagrelor 60mg should be available for patients with lower risk for MACE than those who were enrolled in PEGASUS but that treatment decisions should be individualized, taking into consideration the patient's risks for CAD and bleeding. I believe it is important to remind ourselves that even though major bleeding may result in dire health consequences, MACE usually carries an even larger impact (death and disability) than major bleeding. While it would be nice to know for sure the degree to which patients at lower risk for MACE benefit from DAPT, the modeling from the available data does not suggest that treatment effect would be significantly altered. It is logical to believe that post-MI patients at lower-risk for MACE will derive some benefit from ticagrelor and if they are at low-risk for bleeding, I believe that there will be net benefit. This is enough for me to feel comfortable recommending that lower-risk post-MI patients (unless they are at high-risk for major bleeding) should receive DAPT for at least 4 years and possibly longer. Specifically, I am recommending that the indication statement should not include any limitation of use but might include some language regarding the importance

of weighing risk and benefit, taking into consideration the patients' underlying risks for recurrent MACE and major bleeding.

3. How long to continue ticagrelor? I believe that there should be no restriction on length of time to continue ticagrelor after index MI because the benefit appears to continue to increase with time (Figure 1).

4. (b) (4)

(b) (4)

Efficacy Reviewer

Based on supplement 15 to the ticagrelor NDA 22433, the efficacy reviewer recommends approval for the extension of ticagrelor's labeled indication to read as modified (underlined) below:

> To reduce the rate of thrombotic cardiovascular events in patients with a history of myocardial infarction (MI that occurred at least one year ago) who are at high-risk for recurrent atherothrombotic events.

This indication statement is in agreement with the following statement by the sponsor (clinical overview, page 8):

(b) (4)

(b) (4)

[redacted] (b) (4)

Contrary to these statements in the clinical overview, the sponsor now seeks labeling that extrapolates PEGASUS results to all post-MI patients by omitting the "high-risk" qualifier from the indication statement, arguing that the high-risk criteria used in PEGASUS were but a subset of numerous known risk factors for recurrent MI, and that these five (age > 65 y/o, diabetes mellitus requiring medication, documented history of a second prior presumed spontaneous MI, CrCl < 60 mL/min, angiographic evidence of multivessel disease) were chosen for inclusion criteria in PEGASUS because they were objectively identifiable within the bounds of a clinical trial. Furthermore, the sponsor correctly points out that all patients having suffered a prior myocardial infarction are at higher risk for suffering a second event than those who have not. However, in the rationale for the PEGASUS trial, the sponsor also points out that some post-MI subjects are at higher risk than others, as excerpted below (clinical overview, page 9):

> Individuals who have previously experienced MI remain at increased risk for atherothrombotic events (Bhatt et al 2010, Fox et al 2010); concomitant diabetes and polyvascular disease substantially elevate this risk (Bhatt et al 2010). Prior MI has been documented in over 20% of patients with acute MI treated in contemporary practice (Shen et al 2014). Statistics reported by the American Heart Association (AHA) illustrate the level of continued risk, showing that within 5 years of having a first MI, 36% of men and 47% of women aged over 45 years will die; 15% of men and 22% of women aged 45 to 64 years and 22% of men and women aged ≥65 years will experience recurrent MI or fatal coronary heart disease; and 2% of men and 6% of women aged 45 to 64 years will have a stroke (Go et al 2013).

Subjects not considered being at high-risk for recurrent atherothrombotic events by the protocol-driven presence of one of the five above-noted risk factors were not studied in PEGASUS. Extrapolating PEGASUS results to all post-MI patients will effectively commit all post-MI patients to DAPT indefinitely by applying two assumptions:

- The efficacy assumption that there is no continuum of risk for recurrent MI, and that the degree of MACE reduction seen in the high-risk patients as defined by PEGASUS risk factors will be seen in all patients considered to be at lower risk for recurrent MI (those without PEGASUS defined risk factors)

- The safety assumption that excess major bleeding is a reasonable price to pay for the unproven possibility that ticagrelor-based DAPT may confer the same clinical benefit with respect to MACE reduction in lower-risk patients as was seen in the high-risk PEGASUS subjects, because increased major bleeding in PEGASUS did not result in increased fatal bleeding.

With regards to casting doubt on the efficacy assumption, the following points are relevant:

- There is a biologically plausible indicator within PEGASUS that this unproven assumption may not be true. Specifically, in the 5437 PEGASUS subjects whose qualifying MI was at least two years prior to randomization who received the 60 mg bd dose of ticagrelor, the point estimate for the hazard ratio of ticagrelor's treatment effect on the primary composite endpoint of CV death, MI, and stroke was essentially unity (HR 0.97, CI 0.79 – 1.18). A similar lack of effect was seen in the 3308 PEGASUS subjects whose last ADP receptor blocker was taken more than 12 months prior to randomization to 60 mg bd of ticagrelor, who demonstrated a hazard ratio for treatment effect on the PEGASUS primary composite endpoint of 1.08 (CI 0.82 – 1.42).

- Dr. McDowell's B-R assessment demonstrating no evidence that the presence of multiple risk factors confers additional atherothrombotic risk cannot be used to back-extrapolate that patients with none of these PEGASUS risk factors have an equivalent risk to the group having the lowest number of these risk factors in PEGASUS because:
    - Low-risk patients were actively excluded from PEGASUS
    - Most all of the subjects in PEGASUS had undergone intervention therapy for their coronary artery disease (approximately 83% of subjects in all three treatment arms had undergone PCI and approximately 4.6% of subjects in all three treatment arms had undergone CABG), and so their coronary anatomies had been defined and evidence-based device and medical interventions initiated and/or intensified prior to randomization into PEGASUS. Once this kind of intense invasive therapy is applied, a subject's baseline risk profile may not carry the same prognosis it did before these aggressive therapies and interventions were brought to bear. Therefore, back-extrapolating efficacy responses to low-risk subjects based on the fact that the presence of multiple risk-factors does not appear to confer incremental risk in the PEGASUS population, and thereby concluding that even the lowest risk post-MI subjects need DAPT therapy essentially is a conclusion that imposes an increased risk of major bleeding on low-risk patients indefinitely, without data to justify this risk.

- There are certainly other risk factors for progression of coronary disease and recurrent MI such as hypertension, smoking, hyperlipidemia, and obesity that were not incorporated into PEGASUS' inclusion criteria. This supports the sponsor's current argument that by the time you include these risk factors with the five that were inclusion criteria for the trial, essentially everybody would have been considered high-risk, so therefore the PEGASUS results can and should be extrapolated to everyone post-MI. However, this argument does not account for

> the fact that many patients quit smoking following a myocardial infarction, some lose weight and exercise, and other have their blood pressure and cholesterol well controlled. PEGASUS does not demonstrate that the 49 year old hypercholesterolemic smoker with single vessel LAD disease who post-MI stops smoking and has an excellent response to statin therapy will glean the same benefit from indefinite 60mg bd ticagrelor therapy plus ASA after one year of DAPT therapy as will subjects with the one or more of the five risk factors used in PEGAUS to define a relatively high-risk group for MI recurrence.

Similar to this continuum of efficacy responses to ticagrelor-based DAPT that may be a function of the underlying severity/stability of a patient's underlying atherosclerotic cardiovascular disease, there will certainly be a continuum of incremental major bleeding risk in patients taking DAPT as opposed to ASA monotherapy based on their underlying bleeding risk. In order to minimize this risk of major bleeding, patients with a known bleeding diathesis or coagulation disorder, and patients with any condition which in the opinion of the investigator would have made long-term DAPT unsafe, were all excluded from PEGASUS. These exclusions very effectively kept patients out of PEGASUS who had previously stopped an ADP receptor blocker due to bleeding, per the table below (adapted from sponsor table 17, PEGASUS FSR p 98/9148):

Table 1: Reason prior ADP receptor blocker stopped, FAS

Reason Stopped	Ticagrelor 90 bd N=7050	Ticagrelor 60 bd N=7045	Placebo N=7067
Bleeding	9 (0.1%)	9 (0.1%)	9 (0.1%)

Source: sponsor FSR Table 17, p. 98/9148

Accordingly, with regards to the safety assumption (that excess major bleeding is a reasonable price to pay for the unproven possibility that ticagrelor-based DAPT may confer the same clinical benefit with respect to MACE reduction in relatively low-risk post-MI patients as was seen in high-risk PEGASUS subjects because increased major bleeding in PEGASUS did not result in increased fatal bleeding), the efficacy reviewer is skeptical that the occurrence of major bleeding and fatal bleeding in the "real world" will be as infrequent as it was in PEGASUS where subjects with known bleeding risks were excluded. Furthermore, the efficacy reviewer is not of the opinion that the only major bleeding that is important is the bleeding that results in death – transfusions, critical organ bleeding, and hospitalizations for bleeding are not without costs to the patients experiencing them or to the medical system. In summary, it is the opinion of the efficacy reviewer that an indication supporting the indefinite treatment of subjects with ticagrelor-based DAPT that do not demonstrate the high-risk profile as defined in the PEGASUS trial would be based on data that are less secure than subgroup analysis – it would be based on back-extrapolation of PEGASUS efficacy and safety results to a

population at relatively low-risk for repeat atherothrombotic events that was not studied at all.

1.2 Risk Benefit Assessment

See APPENDIX 1 for the risk benefit assessment table. The table compares the benefit of reducing the absolute risk (incidence during PEGASUS) of a modification of the primary efficacy endpoint [MACE minus hemorrhagic stroke, referred to as MACE minus (-)] to the increase in the absolute risk (incidence during PEGASUS) of TIMI major bleeding which includes hemorrhagic stroke. The Benefit-Risk (B-R) is the absolute difference between the benefit and risk as just defined. A positive B-R (Benefit – Risk) means a positive risk-benefit outcome (i.e., % reduction in MACE- events is higher than % increase in TIMI major bleeding events for that subgroup). This analysis was done only in subjects who had received at least one dose of study drug (the safety set). The counted events for the purpose of this analysis occurred during the on-treatment period (time on drug + 7 days and included periods of drug interruption). The reason for excluding hemorrhagic stroke from MACE was to avoid double counting these events. We believe, because of the antiplatelet activity of ticagrelor that hemorrhagic stroke is not probably prevented by ticagrelor and thus, is more likely a side effect, i.e., caused or worsened by ticagrelor.

Comparing MACE- to TIMI major bleeds is comparing a generally graver outcome (MACE-) to an outcome that is usually clinically manageable. It should be noted that deaths from bleeding were no higher in the ticagrelor arms than in the placebo arm. . Therefore, while the risk of bleeding was higher in the ticagrelor arm, the risk of fatal bleeding was not higher. Also, there no substantial difference in the rates of ICH between the ticagrelor 60 mg bd and placebo arms. The lower risk of MACE- in the ticagrelor arms, however, was associated with a lower risk of CV death. Notable findings when analyzing the data for difference in R-B difference among subgroups are the following:

1. For both the 60 mg bd dose and 90 mg bd dose, ticagrelor had a positive benefit –risk difference of 0.9%. There were ~ 2% fewer MACE – and ~1% more TIMI major bleed in the ticagrelor arm which can be interpreted as a net benefit of ~1%. However, this is truly an underestimate of net benefit because there were overall ~70 fewer CV deaths in the combined ticagrelor arms than in the placebo arm and no more bleeding deaths.

2. Time from index MI and time from last ADP blocker (probably reflective of time from index MI) have an effect on benefit-risk difference with improved risk-benefit difference (higher value) in subjects who had their MIs within 2.5 years of enrollment (best was within 2.0 years). One can invoke a biological

plausibility argument to explain this finding. Patients who have survived MI-free off ADP blockers at 2 years after their MIs probably have more stable coronary disease than patients who have had more recent MIs and/or are still on ADP blockers or recently discontinued. One can surmise that patients with stable coronary disease are at lower risk for a myocardial infarction or other CV event. Their risk of bleeding from ticagrelor, however, would remain the same. Thus, this observed improved benefit-risk difference with more recent index MI may be reflective of a true difference. Counter to this argument, one could argue that this subgroup finding occurred by chance. It is possible that the subjects who were enrolled in the study who had their last MI >2.5 years prior to enrollment were unevenly distributed among the treatment groups with respect to their underlying risk factors for MACE.

3. Subjects >=75 years of age had a larger decrease in MACE- because of a high rate (9.0%) in the placebo group. This resulted in a more favorable benefit-risk (2.2%) in this subgroup. This may have been a chance finding. Subjects in the highest quintiles of age had slightly higher absolute rates of TIMI major bleeding than younger subjects as one would expect. The incidence of MACE (-) in the ticagrelor groups was fairly constant regardless of age.

4. The benefit-risk difference for females was negative for the 60 mg dose and positive for the 90 mg dose of ticagrelor (-0.4% vs. 1.6%, respectively). This resulted from a trend for higher MACE- and increased bleeding in the 60 mg bd treatment group compared to the 90 mg treatment group. This is likely a chance finding because the women were a small subgroup (~24%), exposures in women were somewhat higher than those observed in men (see Dr. Sabarinath's Clinical Pharmacology review). Furthermore, there's no reason to suspect that the impact of ticagrelor on platelet function in women would be different than in men. Therefore there is no pharmacokinetic or pharmacodynamic explanation for this finding.

5. The benefit-risk difference was most favorable for the subjects who were lower weight because of a trend toward decreased MACE- (TIMI major bleeding rates did not appear to be affected by weight). This trend was apparent in both males and females for the 60 mg dose but only in females in the 90 mg dose. One would expect to see improved overall benefit-risk in the 90 mg dose group compared to the 60 mg dose group if these small differenced in exposure between weight groups reflected a true difference in efficacy. For this reason, we suspect that the observed risk-benefit difference by weight is a chance finding.

6. Latinos appeared to have a more favorable benefit-risk difference than non-Latinos because of better efficacy and less TIMI-major bleeding in the ticagrelor treatment arms. Because Latinos were only ~12% of the population, it is likely that this was a chance finding.

7. The benefit-risk difference between MACE- and TIMI major bleeding was not favorable for American Indians, Asians, Blacks and "other race". The number of subjects in each of these racial groups was too low to be concerned that this signal is reflective of true differences in efficacy and bleeding risk.

8. There was no trend for decreased or increased benefit-risk difference when patients were divided by age quintile, race, or region. There was also no difference in net benefit-risk when dividing subjects by US sites vs. sites outside of US. Creatinine clearance at baseline is an absolute risk factor for MACE and TIMI major bleeding but did not appear to affect benefit-risk difference.

9. There was no consistency in the results of the benefit-risk profile between the ticagrelor 60 mg and 90 mg treatments among the different stent subgroups (yes for stent but unknown type, BMS only, DES any, no or unknown).

10. Subjects with multivessel disease had a better benefit-risk difference than those without multivessel disease in the ticagrelor 90 mg group but there was not much of a difference in the 60 mg treatment group. This may be a chance finding.

11. Current smokers had a less favorable benefit-risk difference than non-smokers or former smokers, because of increased bleeding in the 90 mg ticagrelor arm. The effect was not as pronounced in the 60 mg ticagrelor arm. A minority of subjects were smokers (~17%). Therefore, this could be a chance finding.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

None.

2 Introduction and Regulatory Background

2.1 Product Information

Established name (proposed trade name): Ticagrelor (Brilinta)

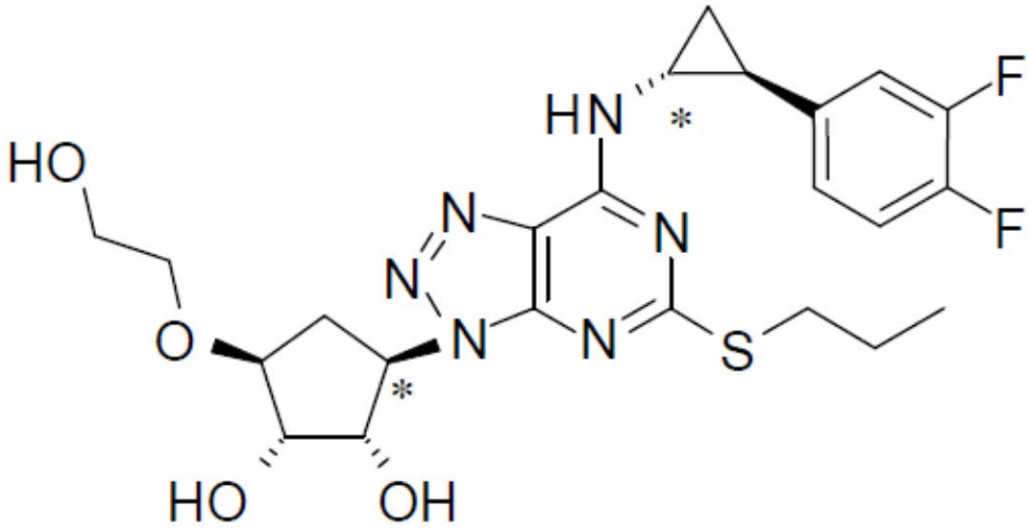
Chemical name:

Difluorophenyl)cyclopropyl]amino}-5-(propylthio)-3H- [1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-5-(2- hydroxyethoxy)cyclopentane-1,2-diol

Molecular formula: C23H28F2N6O4S

Chemical class: Cyclopentyltriazolopyrimidine

Chemical Structure:



Pharmacologic class: Ticagrelor is an oral adenosine diphosphate (ADP) receptor antagonist, reversibly binding to the P2Y12 receptor on platelet surfaces and blocking ADP-mediated platelet activation and aggregation. Ticagrelor does not require hepatic or other metabolic activation.

Proposed indications, dosing regimens, age groups: (b) (4)

Brief Product Description of the 60 mg tablets:

The 60 mg ticagrelor product are round, biconvex, pink, film-coated tablets in an immediate release formulation intended for twice-daily oral administration (see section 4.1, Chemistry Manufacturing and Controls).

2.2 Currently Available Treatments for Proposed Indications

Ticagrelor was approved in the United States in 2011 based on the PLATO trial in which a 180 mg loading dose followed by 90 mg bd of ticagrelor was compared to with 75 mg od for clopidogrel for up to 12 months, with all patients on a background of low-dose ASA therapy. The approved indication was for the reduction of the rate of thrombotic cardiovascular events in patients with ACS (unstable angina, non-ST elevation myocardial infarction, or ST elevation myocardial infarction).

Current ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guidelines assign a class I recommendation to indefinite treatment with low dose aspirin (75 to 162 mg) in patients with stable ischemic heart disease (SIHD). A class IIb recommendation is assigned to the addition of long-term 75 mg clopidogrel treatment for SIHD patient with clinical features that put them at high-risk of recurrent cardiovascular event.[2]

In patients with Non–ST-Elevation Acute Coronary Syndromes (NSTE ACS) treated medically, P2Y12 inhibitor therapy with clopidogrel or ticagrelor, in addition to ASA, is recommended for up to 12 months (Class I). In subjects with NSTE ACS treated with coronary stenting, P2Y12 inhibitor therapy with clopidogrel, Prasugrel, or ticagrelor, in addition to ASA, is recommended for at least 12 months (Class I).[3]

In patients with ST-Elevation Myocardial Infarction (STEMI), current guidelines assign a Class I recommendation to P2Y12 inhibitor therapy with clopidogrel, Prasugrel, or Ticagrelor for 1 year in subjects receiving either a DES or a BMS, but acknowledge that continuation of a P2Y12 inhibitor beyond 1 year may be considered in patients undergoing DES placement. (Level of Evidence: C).[4]

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2 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease. JACC. 2012; 60(24): e44–e164.
3 2014 AHA/ACC Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes. JACC. 2014; 64(24): e139-e228.
4 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction. JACC. 2013; 61(4):e78–E140.

The above recommendations reflect current labeling for those antiplatelet agents that are in clinical use in the United States for secondary prevention of ACS, as shown in the following table:

Table 2.Currently available oral antiplatelet treatments for secondary prevention of acute MI

Drug	Indication	Mechanism of Action
Aspirin	Reduce the risk of vascular mortality in patients with a suspected acute MI. Reduce the combined risk of death and nonfatal MI in patients with a previous MI or unstable angina pectoris.	Inhibitor of platelet activation and aggregation through the irreversible inactivation of the cyclooxygenase (COX) enzyme, thus blocking the formation of thromboxane-A2 in platelets
Clopidogrel (Plavix)	**Acute Coronary Syndrome** For patients with non-ST-segment elevation ACS [unstable angina (UA)/non-ST-elevation myocardial infarction (NSTEMI)], Plavix has been shown to decrease the rate of a combined endpoint of cardiovascular death, myocardial infarction (MI), or stroke as well as the rate of a combined endpoint of cardiovascular death, MI, stroke, or refractory ischemia. For patients with ST-elevation myocardial infarction (STEMI), Plavix has been shown to reduce the rate of death from any cause and the rate of a combined endpoint of death, re-infarction, or stroke. The benefit for patients who undergo primary PCI is unknown. **Recent MI, Recent Stroke or Established Peripheral Arterial Disease** To reduce the rate of a combined endpoint of new ischemic stroke (fatal or not), new MI (fatal or not), and other vascular death.	Inhibitor of platelet activation and aggregation through the irreversible binding of its active metabolite to the P2Y12 class of ADP receptors on platelets.
Prasugrel (Effient)	Prasugrel is indicated to reduce the rate of thrombotic cardiovascular (CV) events (including stent thrombosis) in patients with acute coronary syndrome (ACS) who are to be managed with	Inhibitor of platelet activation and aggregation through the irreversible

	percutaneous coronary intervention (PCI) as follows: Patients with unstable angina (UA) or non-ST-elevation myocardial infarction (NSTEMI). Patients with ST-elevation myocardial infarction (STEMI) when managed with primary or delayed PCI.	binding of its active metabolite to the P2Y12 class of ADP receptors on platelets.
Ticagrelor (Brilinta)	To reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) (unstable angina, non-ST elevation myocardial infarction, or ST elevation myocardial infarction). In patients treated with PCI, it also reduces the rate of stent thrombosis. Studied in combination with low dose aspirin.	Direct inhibitor of platelet activation and aggregation through reversible binding to the P2Y12 class of ADP receptors on platelet surfaces(ticagrelor does not require hepatic or other metabolic activation)

Source: Adapted from the currently approved labels for the listed drugs and the aspirin monograph

PEGASUS was designed to evaluate whether long-term DAPT with either 60 mg or 90 mg bd of ticagrelor in combination with ASA compared to ASA alone (ASA dose 75 to 150 mg for all subjects) would result in a reduction in the rate of MACE (CV death, MI, and stroke) in subjects with a prior MI (at least 1 year ago) who were at high-risk for experiencing yet another MI, as defined by the presence of one or more of the following risk-factors: age ≥65 years, diabetes mellitus requiring medication, documented history of a second prior presumed spontaneous MI (>1 year ago), angiographic evidence of multivessel coronary artery disease (CAD), or chronic, or non-end stage renal dysfunction (creatinine clearance [CrCl] calculated by Cockcroft Gault equation <60 mL/min). The requirement for at least one year between the prior MI and enrollment in PEGASUS allowed for the assessment of CV outcomes in subjects who had completed one full year of DAPT following their prior MI.

2.3 Availability of Proposed Active Ingredient in the United States

Ticagrelor (Brilinta) is approved and marketed in the United States to reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) (unstable angina, non-ST elevation myocardial infarction, or ST elevation myocardial infarction).

2.4 Important Safety Issues with Consideration to Related Drugs

As with all anti-thrombotic therapies, the primary concern is the increased risk of major bleeding events with these agents. The risk of major bleeding events increases with DAPT as opposed to low dose ASA monotherapy. Accordingly, careful consideration must be given to the potential benefit gleaned in MACE reduction with long-term DAPT with 60mg bd ticagrelor and low dose ASA as opposed to the increased risk of clinically important and major bleeding events with this DAPT combination in comparison to ASA alone.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The first request for a Special Protocol Assessment (SPA) for clinical trial protocol D5132C0001 (PEGASUS) dated October 1, 2009 was followed by a "No Agreement" letter from the Division dated November 13, 2009, in which the Division provided input regarding:

- Enrollment of patients with peripheral artery disease (PAD) and consideration of prior stroke as a risk factor for subsequent MACE events
- Definitions of CV outcome events
- Disagreement with the proposed approach to control the overall type I error rate for the primary endpoint
- Concern regarding the proposed sample size based on CHARISMA
- The difficulty of determining the suitability of PEGASUS as a single trial supporting the sought indication in that PLATO had not been reviewed by the Division.

The second request for an SPA for PEGASUS dated December 29, 2009 was followed by a second "No Agreement" letter from the Division dated February 18, 2010, in which various elements of the trial were discussed, including CYP2C19 poor metabolizers who might develop an indication for use of an ADP receptor blocker, the definition of completed subjects, CV outcome definitions, timing of ECGs, and statistical details of the planned primary and secondary analyses, as well as the planned interim analysis. In addition, the Division communicated concern regarding the plan to test only the 90 mg bd dose of Ticagrelor in PEGASUS, and strongly advised that more than one dose of ticagrelor be tested to determine the relationships of clinical outcomes with dose.

AstraZeneca subsequently proposed adding a third arm to PEGASUS in which subjects would receive ticagrelor 60 mg bd. In a meeting with the sponsor on July 1, 2010, the Division reiterated support for testing more than one dose of ticagrelor in PEGASUS, but remained skeptical regarding the choice of 60 mg bd as the additional dose because:

- It was the Division's belief that there is only 40% between-patient variability in exposure between the 60 mg bd and the 90 mg bd doses, and

- The Division did not understand the rationale of choosing a ticagrelor dose on the basis of the level of inhibition of platelet aggregation (IPA) in the subgroup of subjects with prior MI administered Plavix in CHARISMA, given that clopidogrel had not been demonstrated to be effective in this clinical situation.

The Division did agree, however, that if successful, PEGASUS could support the indication being sought, and that the proposed statistical plan was acceptable. The Division reiterated, however, that it would not require that each dose be independently assessed in the analysis of the primary endpoint. However, the recommendation was made to collect samples for PK analysis in all subjects instead of a 7500 patient subgroup to better characterize the exposure-response (efficacy and safety) relationship.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was an electronic submission that followed the eCTD guidance. There was an adequate index, text was searchable, the data sets and fields were well defined, and the appropriate sections for completing the review were present. Content of Labeling was submitted in SPL format. The sponsor was agreeable and responded promptly when asked to supply datasets or other analyses, and worked collaboratively with the FDA reviewers to resolve minor differences in tabular analyses of efficacy and safety outcomes.

3.2 Compliance with Good Clinical Practices

The sponsor attests that PEGASUS was performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

3.3 Financial Disclosures

Disclosure packages were submitted from eight investigators per the table below:

Table 3. Disclosure packages from PEGASUS investigators

Investigator (site #)	E	R	Disclosure(s)
(b) (6)			$100,145.90 USD (speeches bureau)
			Jan – Oct 2011: 497.000 SEK for phase I ECG external review at (b) (6) Nov 2011 – Oct 2012: Fulltime employee at (b) (6) @ 92.000 SEK/month Nov 2012 – May 2013: 50% employee at (b) (6) @ 46.900 SEK/month June 2013 – onward: fulltime employee at (b) (6) @ 93.800 SEK/month
			Stock in AZ, valuation $121,000 as of Nov 2010
			$26,456.06 (Advisory boards, honoraria for CME talks)
			$30,000 (local wellness program)
			Approximately $100,000 USD (speaker fees)
			Consulting fees of $53,132 (£34,059) Speaker fees of $129,099 (£82,756)
			$35,250 (honorarium for personal consultation, unrestricted grant budget to support speakers (b) (6))

AZ – AstraZeneca, E – Number of subjects enrolled, R – Number of subjects randomized, PI – Principle Investigator,
SI – Sub-investigator

It is noted that only two of these investigators ((b) (6)) received payments for non-study related costs substantially in excess of the $25,000 reporting threshold and enrolled a large number of subjects. The SI (b) (6) undoubtedly received a substantially higher amount than the $25,000 reporting limit, but this was for work performed as an employee at (b) (6), the number of subjects enrolled from this site was not large, and the PI from this site (Paren) responded to the financial interests request with no disclosures.

The potential influence that data from sites (b) (6) may have had on the outcome of PEGASUS was examined using the FDA Site Selection Tool, version 2.4.13. The raw outputs for analyses of the data from these two sites regarding safety

and efficacy results relative to the study as a whole are shown for sites (b) (6) in the following two figures, respectively:

Figure 2. Site (b) (6) data analysis, FDA Clinical Efficacy Reviewer, Site Selection Tool version 2.4.13

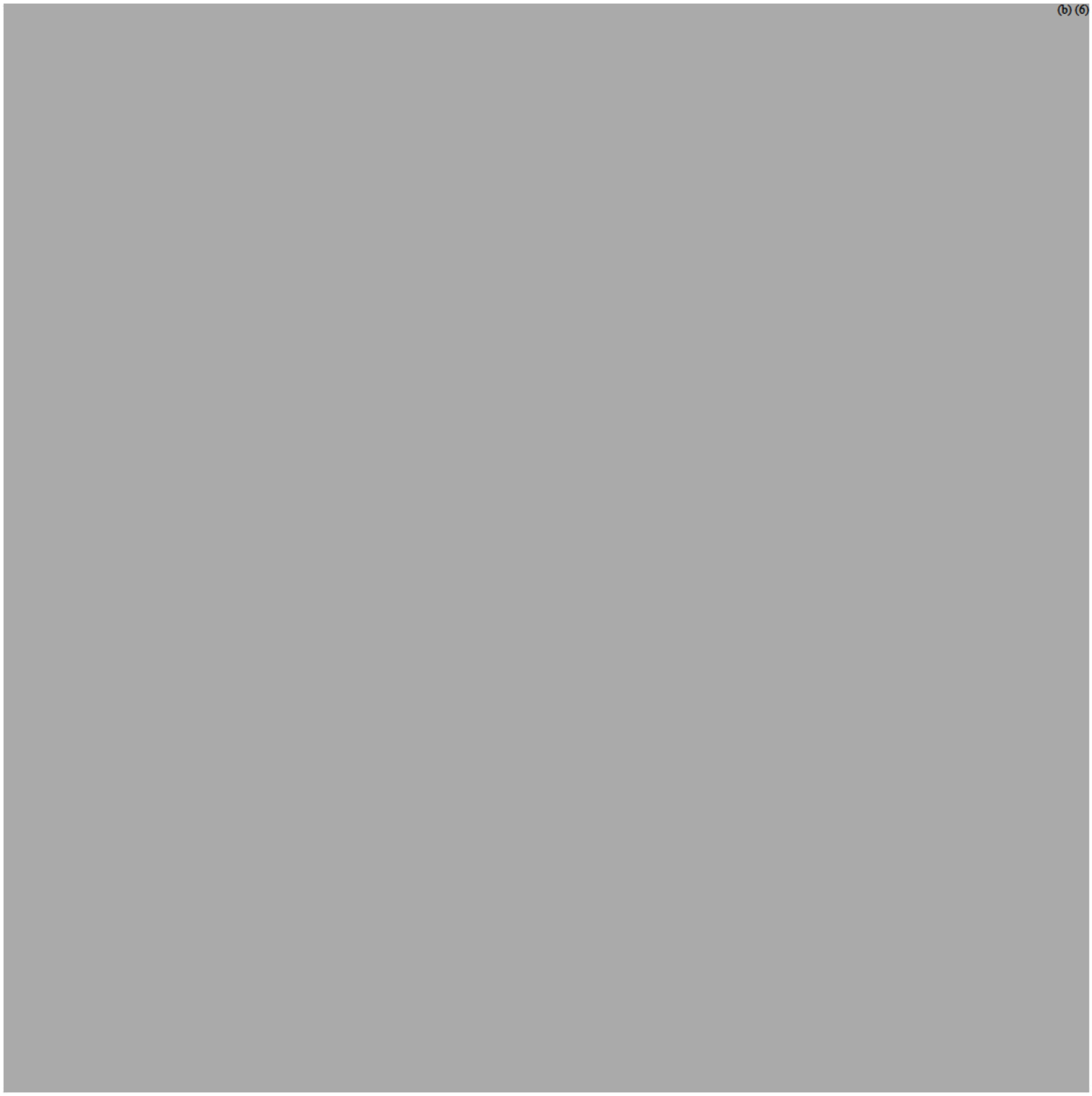
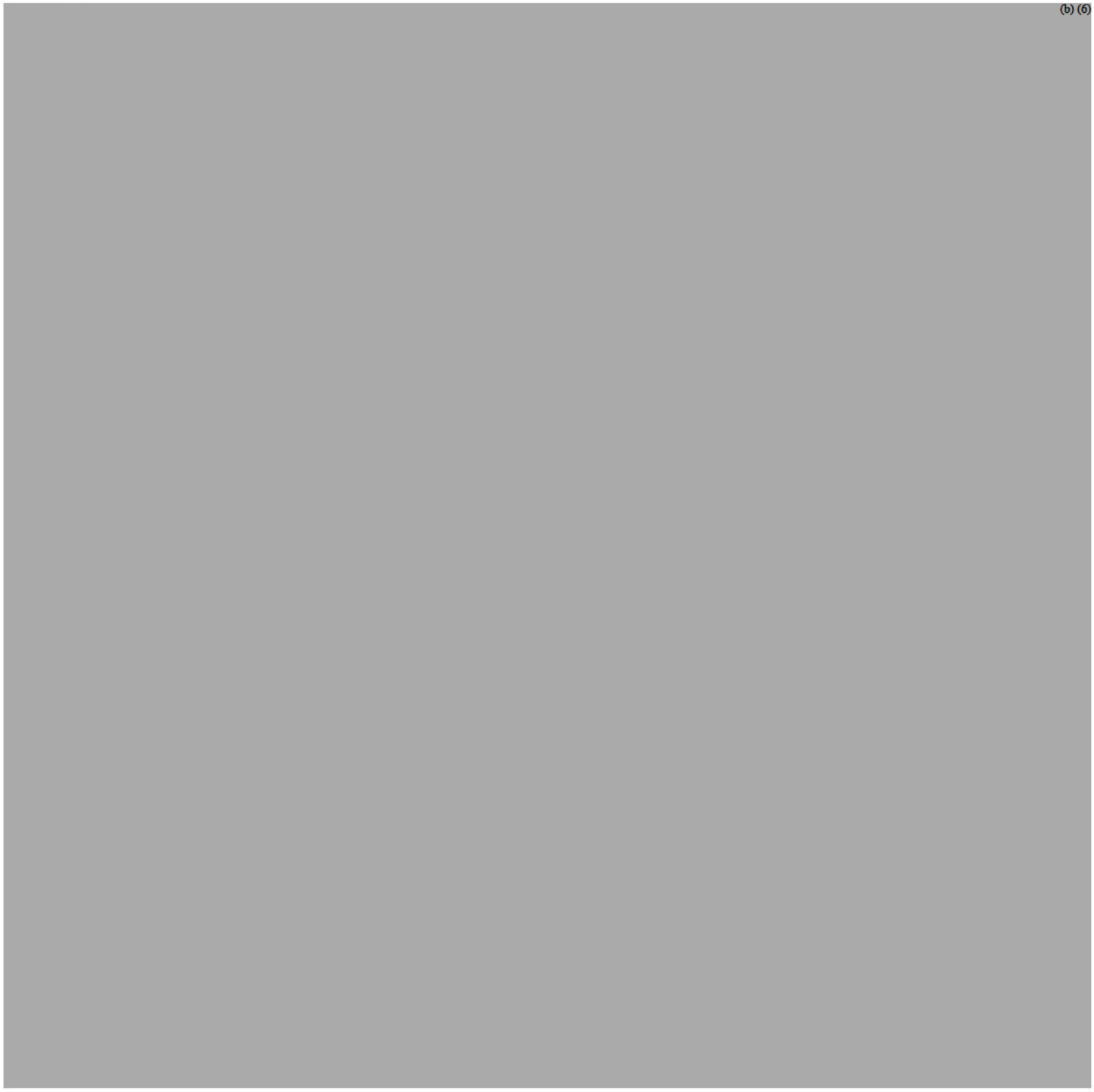


Figure 3. Site (b) (6) data analysis, FDA Clinical Efficacy Reviewer, Site Selection Tool version 2.4.13



For both of these sites, the percentage of patients experiencing the treatment primary efficacy endpoint/result (TRTEFFR) was low in both treatment arms and the site-specific efficacy effect size (SITEEFFE) for 60 mg ticagrelor was right at the median for the trial. Site-specific enrollment weighted efficacy EW WITEEFF favoring 60 mg ticagrelor was driven by the high enrollment rate as opposed to a large difference between the treatment effect between the trial arms.

Forty-six investigators provided no responses to sponsor requests for financial disclosure. All 46 of these non-responders were sub-investigators (SI) who's enrolled subjects were accounted for on the disclosures of the site's principle investigator (PI), as shown in the table below listing each non-responder, confirmation that this individual was a site SI, the site ID, number randomized of patients enrolled and randomized, and in the last column, confirmation that the principle investigator (PI) of that site had listed that same number of patients and either responded with no disclosures regarding all subjects (y-all), or the PI listed the same number of patients as the non-responsive SI and disclosed financial interests (disclosed-all):

Table 4. PI responders vs SI non-responders to financial disclosure requests

Investigator	*SI/PI*	*Site ID*	*Enrolled*	*Randomized*	*PI Resp*
(b) (6)					*y-all*
					y-all
					y-all
					y-all
					y-all
					y-all
					y-all
					y-all
					y-all
					y-all
					y-all
					y-all
					y-all
					y-all
					y-all
					y-all
					y-all
					Disclosed-all

[redacted] (b) (6)					*y-all*
[redacted]					*y-all*
[redacted]					*y-all*
[redacted]					*y-all*
[redacted]					*y-all*
[redacted]					*y-all*
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[redacted]					*y-all*
[redacted]					*y-all*
[redacted]					*y-all*
[redacted]					*y-all*
[redacted]					*y-all*
[redacted]					*y-all*
Total				*1322*	
% FAS				*6.25*	

.
The remaining investigators confirmed no disclosures.

Reviewer Conclusion: There is no evidence that a systemic or site-specific conflict of interest influenced the outcome of PEGASUS.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

(b) (4)

The composition of both the 60mg and 90mg tablets are shown in the table below (Quality Overall Summary – Drug Product, 6/30):

Table 5. Composition of both the 60mg and 90mg tablets

Ticagrelor tablets core formulation (%w/w)	(b) (4)
Ticagrelor	
Mannitol	
Dibasic calcium phosphate	
Sodium starch glycolate	
Hydroxypropyl cellulose	
Magnesium stearate	

For further details, see the quality review for this efficacy supplement.

4.2 Clinical Microbiology

The sponsor states that, "As part of the development strategy a microbial limit test method was developed for ticagrelor tablets; however, it is not considered necessary to perform the test on the product at the time of manufacture." For further details, see the FDA quality review for this efficacy supplement.

4.3 Preclinical Pharmacology/Toxicology

No new non-clinical data are provided in this supplement. For more information, wee the toxicology review by FDA for the original NDA 022433.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Ticagrelor is rapidly absorbed following oral administration, and is a direct-acting, selective, and reversibly binding P2Y12 receptor antagonist that prevents ADP-mediated platelet activation and aggregation. When bound to the P2Y12 receptor, ticagrelor does not inhibit ADP binding, but prevents ADP-induced signal transduction. Ticagrelor and its active metabolite are approximately equipotent.

4.4.2 Pharmacodynamics

This efficacy supplement included supporting study D5130L00012, entitled "A Randomized, Open Label, Multiple Dose, Crossover, Multiple Center Study of the Antiplatelet Effects of Ticagrelor versus Clopidogrel in Hispanic Patients with Stable Coronary Artery Disease." This study enrolled 40 subjects with stable coronary artery disease (CAD) who self-identified as being of Hispanic ethnic group. It was of short duration (treatment for a maximum of 18 days), with no deaths, serious adverse events (SAEs), or discontinuations due to adverse events (DAEs) reported. The sponsor reports that results from Study D5130L00012 and the PEGASUS population PK analysis demonstrated that the exposure to ticagrelor and AR-C124910XX in patients self-identified as Hispanic or Latino is similar to that in Caucasians.

For details, see the FDA clinical pharmacology review for this efficacy supplement.

4.4.3 Pharmacokinetics

Table 6. ADME (Source: FDA Clinical Pharmacology)

Absorption:	t_{max} ~ 1.5 h (~ 2.5 h for active metabolite)
Distribution:	>99 % protein binding, V_{ss} ~ 88 L
Metabolism:	CYP3A4 Weak P-gp substrate and inhibitor
Excretion:	By hepatic metabolism < 1% in urine $t_{1/2}$ ~ 7 h for ticagrelor (9 h for active metabolite*)
Bioavailability:	36 %, no significant food effects

*30-40 % of ticagrelor exposure, equipotent to ticagrelor

The sponsor's population PK data from PEGASUS demonstrated that the PK of ticagrelor and its active metabolite AR-C124910XX in the PEGASUS population were:

- Generally similar to that in the ticagrelor ACS application
- Approximately dose-proportional
- Stable over the 1-year studied treatment period.

From PEGASUS, five covariates were reported as statistically significant ((p<0.001) on oral clearances of ticagrelor and its active metabolite AR-C124910XX: Japanese ethnicity, sex, age, body weight, and smoking. The estimated differences, however, were small to moderate and consistent with those seen in the ACS application. Current labeling recommends no adjustment based on body weight, race, or sex.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 7. Clinical trials supporting ticagrelor efficacy supplement 15

Study Number	Study Title
D5132C00001 (PEGASUS)	A randomized, double-blind, placebo controlled, parallel group, multinational trial, to assess the prevention of thrombotic events with ticagrelor compared to placebo on a background of acetyl salicylic acid (ASA) therapy in patients with history of myocardial infarction
D5130L00012	A randomized, open label, multiple dose, crossover, multiple center study of the antiplatelet effects of ticagrelor versus clopidogrel in Hispanic patients with stable coronary artery disease

5.2 Review Strategy

This is a joint clinical review of efficacy supplement 15 to NDA 22433 based on the results of a single clinical trial (PEGASUS, trial D5132C00001). Preston Dunnmon, MD, was author of sections two through six and the efficacy portion of the recommendation for regulatory action. Melanie Blank, MD, was the author of sections seven, eight, the safety section of the recommendation for regulatory action, and the safety/benefit-risk assessment.

Because this is an efficacy supplement to a prior NDA which seeks marketing authorization for a lower dose of ticagrelor for the long-term reduction in the rate of MACE (composite of cardiovascular death, MI and stroke) than is labeled for the Acute Coronary Syndrome (ACS) indication (60 mg bd as opposed to dosing with a 180 mg one-time loading dose followed by 90 mg bd, respectively), appropriate subsections of sections 2, 3, 4, and 5 will refer back to the original NDA 22433.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 PEGASUS (Trial D5132C00001)

5.3.1.1 Title

PEGASUS-TIMI 54

A Randomized, Double-Blind, Placebo Controlled, Parallel Group, Multinational Trial, to Assess the Prevention of Thrombotic Events with Ticagrelor Compared to Placebo on a Background of Acetyl Salicylic Acid (ASA) Therapy in Patients with History of Myocardial Infarction

5.3.1.2 Study Objectives

Primary Objective

To compare the effect of long-term treatment with ticagrelor vs. placebo on a background of acetyl salicylic acid (ASA) on the event rate of the composite of cardiovascular death, non-fatal myocardial infarction (MI), or non-fatal stroke in patients with history of MI and high-risk of developing atherothrombotic events

Secondary Objectives

1. To compare the effect of long-term treatment with ticagrelor vs. placebo on a background of ASA on the event rate of cardiovascular death in patients with history of MI and high-risk of developing atherothrombotic events

2. To compare the effect of long-term treatment with ticagrelor vs. placebo on a background of ASA on the event rate of all-cause mortality (ACM) in patients with history of MI and high-risk of developing atherothrombotic events

Other Objectives

- To compare the effect of long-term treatment with ticagrelor vs. placebo on a background of ASA on the event rate of the composite of cardiovascular death, non-fatal MI, non-fatal stroke, or urgent coronary revascularization
- To compare the effect of long-term treatment with ticagrelor vs. placebo on a background of ASA on the event rate of the composite of cardiovascular death or coronary or cerebrovascular arterial thrombosis hospitalization (including non-

fatal MI, non-fatal stroke, urgent coronary revascularization, unstable angina, or transient ischemia attack)
- To compare the effect of long-term treatment with ticagrelor vs. placebo on a background of ASA on the event rate of the composite of coronary heart disease death, non-fatal MI, or nonfatal stroke
- To evaluate the net clinical benefit of long-term treatment with ticagrelor vs. placebo on a background of ASA
- To compare the effect of the long-term treatment with ticagrelor vs. placebo on a background of ASA on the incidence of coronary stent thrombosis
- To collect health care utilization associated with hospitalizations and utilities assessed by Euro Quality of Life-5 Dimensions (EQ-5D) to support health technology assessment and health economic modeling

Safety Objectives

- To assess the safety and tolerability of long-term therapy with ticagrelor compared to placebo on a background of ASA in patients with history of MI and high-risk of developing atherothrombotic events
- To analyze bleeding events using the TIMI, PLATO, GUSTO, and ISTH definitions

5.3.1.3 Endpoints

Primary Efficacy Endpoint

- Time to first occurrence of any event after randomization from the composite of cardiovascular death, non-fatal MI, or non-fatal stroke (Cox proportional hazards model with a factor for treatment group – each ticagrelor dose was tested separately vs. placebo)

Secondary Endpoints

1. Time to occurrence of cardiovascular death after randomization
2. Time to occurrence of all-cause mortality after randomization

Other Endpoints

- time to first occurrence of any event after randomization from the composite of cardiovascular death, non-fatal MI, non-fatal stroke, or urgent coronary revascularization
- Time to first occurrence of any event after randomization from the composite of cardiovascular death or coronary or cerebrovascular arterial thrombosis hospitalization
- Time to first occurrence of any event after randomization from the composite of coronary heart disease death, non-fatal MI, or non-fatal stroke
- Time to first occurrence of any event after randomization from the composite of cardiovascular death, non-fatal MI, non-fatal stroke or TIMI major bleeding
- Time to first occurrence of coronary stent thrombosis after randomization

Safety Endpoints

- Time to first TIMI major bleeding event, as well as time to first TIMI major or minor bleeding event and time to first PLATO major bleeding event
- Time to discontinuation of study medication due to any bleeding event
- Evaluation of AEs

5.3.1.4 Trial Design

PEGASUS was an event-driven, randomized, double blind, placebo controlled, parallel group, international multicenter study to assess the prevention of cardiovascular events with ticagrelor given at 2 doses (90 mg bd and 60 mg bd) compared to placebo on a background of ASA in patients with history of MI (1-3 years ago) and additional risk factors for atherothrombosis.

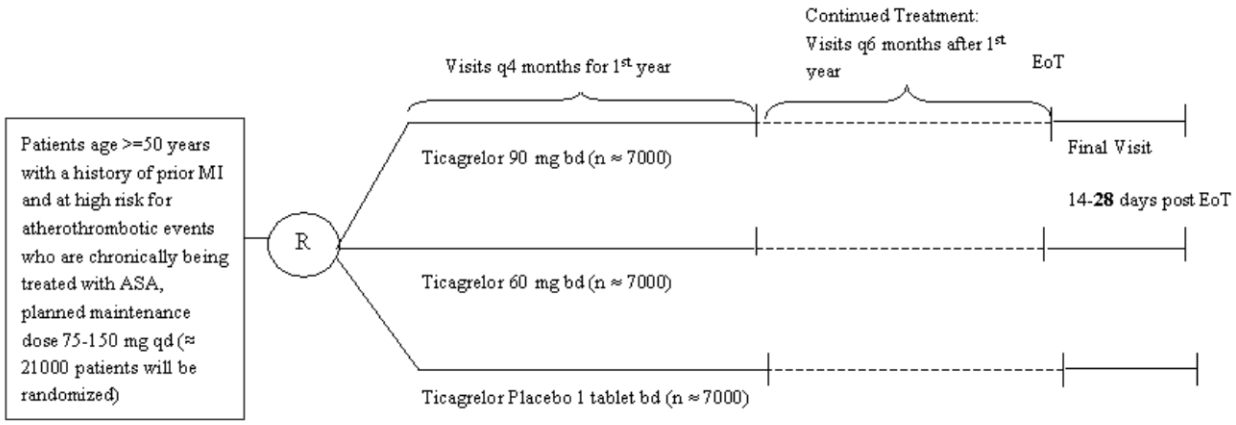
Approximately 21,000 were to be randomized in a 1:1:1 ratio to each of the three study arms (approximately 7,000 subjects in each study arm).

The minimum dosing period was 12 months with a planned maximum follow-up duration of 38 months unless enrollment had to be extended to achieve the targeted number of primary efficacy events (1360).

Per amendment 1, it was intended that all randomized patients perform the End-of-Treatment (EoT) Visit as the last visit on treatment with study medication. A Follow-up Visit off treatment should then be done 14-28 days after the EoT Visit. This Follow-up Visit was to be the last visit in the study for most of the patients participating in the study.

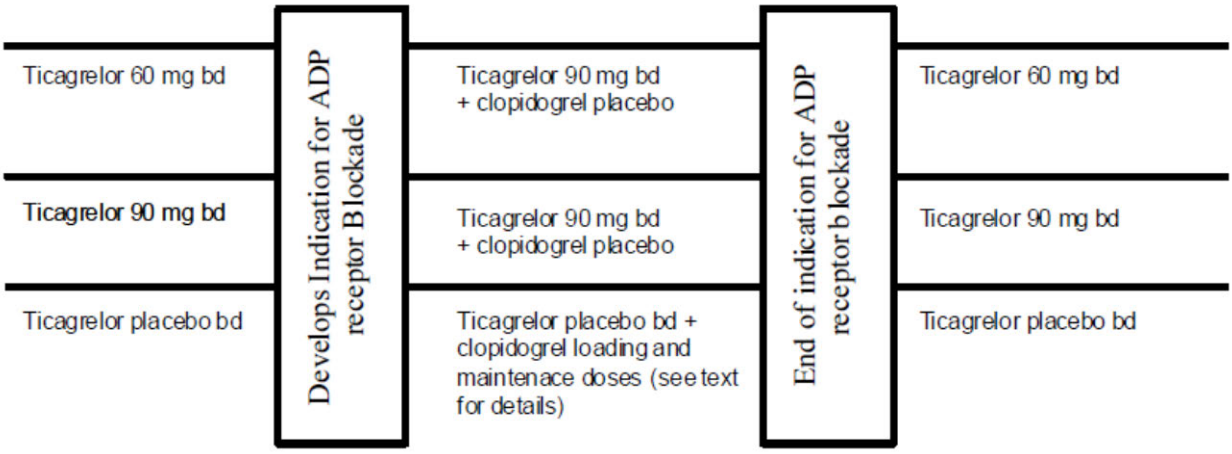
The PEGASUS trial schematic is shown in the following figure (Sponsor):

Figure 4. PEGASUS trial schematic



For subjects who developed an indication for ADP receptor blockade during the trial (e.g. ACS and/or PCI), selection of the ADP receptor blocker was per the investigator according to local medical guidelines and standard of care. If clopidogrel was determined to be suitable, it was recommended that the patient be reassigned to either ticagrelor 90 mg bd or clopidogrel 75 mg od in a blinded fashion by the IVRS/IWRS to replace their previously assigned study medication. Accordingly, this blinded, modified dosing algorithm resulted in patients taking either ticagrelor 90 mg bd + ASA or clopidogrel 75 mg od + ASA per the following schematic (Sponsor):

Figure 5. PEGASUS modified dosing schematic



For patients in whom a loading dose of ADP receptor blocker was desired, one additional tablet of ticagrelor study medication (90 mg ticagrelor) and either 4 capsules (i.e. 300 mg) or 8 capsules of clopidogrel study medication could be taken. Prasugrel could be taken instead on an open-label basis as an alternative, following which study medication could be resumed per the modified dosing algorithm at the discretion of the investigator.

After the medical indication for ADP receptor blockade had passed (per medical guidelines), patients were to resume their originally assigned PEGASUS study drug treatment plus low-dose ASA.

5.3.1.5 Study Population

5.3.1.5.1 Inclusion Criteria (Original Protocol)

For inclusion in PEGASUS, subjects had to fulfill all of the following criteria:

1. Men and women >50 years of age
2. Documented history of presumed spontaneous MI (excluding known peri-procedural or definite secondary MI [e.g., due to profound hypotension, hypertensive emergency, tachycardia, or profound anemia]) with their most recent MI occurring 1 to 3 years prior to randomization and have <u>at least 1 of the following risk factors</u>:
    a. Age ≥65 years
    b. Diabetes mellitus requiring medication
    c. Documented history of a second prior presumed spontaneous MI (>1 year ago)
    d. Angiographic evidence of multivessel coronary artery disease (CAD) (stenosis ≥50% in two major coronary artery territories [i.e., left anterior descending, ramus intermedius, left circumflex, right coronary artery] involving the main vessel, a major branch, or a bypass graft)
    e. Chronic, non-end stage renal dysfunction (creatinine clearance calculated by Cockcroft Gault equation <60 mL/min)
3. Patient currently prescribed and tolerating ASA, and able to be prescribed the protocol mandated dose of 75 - 150 mg once daily for the duration of the study
4. Females of child-bearing potential (i.e., who are not chemically or surgically sterilized or who are not post-menopause) must have had a negative urine pregnancy test at enrollment (to be confirmed by blood pregnancy test at the central lab). Females of child-bearing potential must have been willing to use a medically accepted method of contraception that was considered reliable in the judgment of the investigator.
5. Written informed consent prior to any study specific procedures.

5.3.1.5.2 Exclusion Criteria

Patients with any of the following conditions were excluded from PEGASUS:

1. Planned use of ADP receptor blockers (e.g., clopidogrel, ticlopidine, prasugrel), dipyridamole, or cilostazol
2. Planned coronary, cerebrovascular, or peripheral arterial revascularization
3. Concomitant oral or intravenous therapy with strong cytochrome P450 3A (CYP3A) inhibitors, CYP3A substrates with narrow therapeutic indices, or strong CYP3A inducers which could not be stopped for the course of the study
4. Need for chronic oral anticoagulant therapy or chronic low-molecular-weight heparin (at venous thrombosis treatment not prophylaxis doses)
5. Patients with a known bleeding diathesis or coagulation disorder
6. History of previous intracranial bleed at any time, gastrointestinal (GI) bleed within the past 6 months, or major surgery within 30 days
7. Ischemic stroke within the previous 14 days*
8. Patients considered to be at risk of bradycardic events (e.g. known sick sinus syndrome or second or third degree atrioventricular (AV) block]) unless already treated with a permanent pacemaker
9. Coronary-artery bypass grafting in the past 5 years
10. Known severe liver disease (e.g. ascites or signs of coagulopathy)
11. Renal failure requiring dialysis or anticipated need for dialysis during the course of the study
12. Pregnancy or lactation
13. Life expectancy < 1 year
14. Any condition which in the opinion of the Investigator would make it unsafe or unsuitable for the patient to participate in this study (e.g., active malignancy other than squamous cell or basal cell skin cancer)
15. Concern for inability of the patient to comply with study procedures and/or follow up (e.g., alcohol or drug abuse)
16. Participation in previous study with ticagrelor if treated with ticagrelor, or previous randomization in the present study
17. Involvement in the planning and/or conduct of the study (applied to both AstraZeneca staff and/or staff at the study site)
18. Participation in another clinical study with an investigational product during the preceding 30 days.

*See Protocol Changes, section 5.3.1.12

5.3.1.6 Study Treatments

According to the PEGUSUS study protocol, at visit 2 (Randomization), eligible subjects were randomly assigned to 1 of 3 treatment groups in a 1:1:1 ratio: ticagrelor 90 mg bd,

ticagrelor 60 mg bd, or placebo bd. The two ticagrelor tablets to be administered in the study have different sizes. All patients therefore needed to take two tablets bd to guarantee the blinding: (1) ticagrelor 90 mg and ticagrelor 60 mg placebo, (2) ticagrelor 90 mg placebo and ticagrelor 60 mg, or (3) ticagrelor 90 mg placebo and ticagrelor 60 mg placebo.

5.3.1.7 Concomitant Medications

ADP receptor blockers (e.g., clopidogrel, prasugrel, ticlopidine), dipyridamole, and cilostazol: Use of any of these drugs was an exclusion criterion to enrollment. Patients who developed a medial indication for ADP receptor blockade once in the study were candidates for the modified dosing algorithm (see Trial Design, section 5.3.1.4 above).

Non-ASA Non-Steroidal Anti-Inflammatory Drugs (non-ASA NSAIDs): Allowed during the study at the investigator's discretion, though the potential for increased GI-bleeding with non-selective NSAIDs was addressed and concomitant acid suppression and/or alternative therapy was recommended. Caution was likewise advised for concomitant use of selective cycloxygenase-2 inhibitors.

Parenteral anticoagulants: Short-term treatment with approved parenteral anticoagulants (e.g. unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), bivalirudin, fondaparinux]) was allowed, though long-term treatment with LMWH in outpatients (at venous thrombosis treatment doses) in combination with study medication was not allowed.

GPIIb/IIIa receptor antagonists: Allowed during PEGASUS.

Oral anticoagulants: Use of oral anticoagulant drugs was not permitted during the trial. If treatment with oral anticoagulant drugs is considered essential during the study, study medication had to be discontinued, but could have been resumed if anticoagulant therapy was stopped.

> *Reviewer's comment: the risk-benefit profile of DAPT with ASA-ticagrelor in subjects with atrial fibrillation who have a medical indication for oral anticoagulation is not addressed in PEGASUS, though other studies in progress with several of the NOACs may shed light on the optimal antithrombotic therapy combination following PCI (the PLATO indication, not the PEGASUS indication).*

Fibrinolytics: caution was advised due to lack of experience with the combination of these drugs with ticagrelor. It was recommended that study drug be discontinued and restarted no earlier than 24 hours after completion of the fibrinolytic therapy and when the risk of bleeding was deemed low in the judgment of the investigator.

Digoxin: Ticagrelor is a weak inhibitor of P-glycoprotein (P-gp), of which digoxin is a substrate, resulting in modest increases in digoxin levels when the two are used concomitantly. The recommendation was made for digoxin level monitoring.

Strong CYP3A4 inhibitors: may substantially increase ticagrelor levels, so concomitant use of these therapies required study drug interruption (with re-start after the CYP3A inhibitor was no long required).

CYP3A substrates or inducers: Concomitant therapy with simvastatin or lovastatin at doses higher than 40 mg daily was not permitted. There are no restrictions to other statin therapies. Co-administration of ticagrelor with CYP3A substrates with a narrow therapeutic index, and co-administration of ticagrelor with strong inducers of CYP3A was not allowed and necessitated study drug interruption during the period of time that these drugs were in use.

CYP2C19 inhibitors: Ticagrelor is not metabolized via CYP2C19. However, for patients who were being treated with modified study medication which could include clopidogrel (see Trial Design, section 5.3.1.4 above), or open-label clopidogrel, it was recommended to avoid concomitant use of drugs that inhibit CYP2C19, according to the clopidogrel label.

5.3.1.8 Concomitant Aspirin

All patients were to take open label ASA (75 – 150 mg once daily) throughout the study, and were responsible for their own ASA supply. Temporary use of higher doses (>150 mg daily) was allowed in the event that a patient developed a medical indication (e.g. ACS or PCI) for the duration of that indication, with subsequent reduction to a dose between 75-150 mg once daily. ASA use for pain relief was discouraged (acetaminophen was encouraged as an alternative).

5.3.1.9 Interruption of Medication

Disallowed con-meds: For concomitant medications requiring drug interruption, see section 5.3.1.7 (Concomitant Medications) above.

Surgery and other invasive non-cardiovascular procedures: The PEGASUS protocol recommended that elective major surgery (i.e., surgery that in the opinion of the Investigator poses a risk for clinically major bleeding, which typically includes cardiothoracic, abdominal, pelvic, spinal, and cranial surgery) not be performed until more than 5 days after stopping study medication to avoid excessive bleeding. It was noted that for urgent major surgery that needed to be performed within 5 days, the effect on platelet function caused by ticagrelor would have largely dissipated in most individuals by approximately 72 hours after discontinuation.

Severe thrombocytopenia (platelet count <50,000/uL): study medication could restart once resolved.

Major bleeding: required at least temporary discontinuation.

Permanent discontinuation from study medication was required for pregnancy and per physician and/or patient discretion. This did not result in discontinuation of follow-up in person or by phone.

All planned prescribed stops and unplanned non-prescribed temporary stops (>48 hours) were to be recorded in the eCRF.

5.3.1.10 Discontinued Subjects and Consent Withdrawal

Subjects permanently discontinuing medication were to do the End of Treatment (EoT) Visit and Follow-up Visit 2-4 weeks after discontinuation, followed by the regularly scheduled study visits every 4 to 6 months, with data collection and procedures continuing per the study protocol (except for blood clinical chemistry blood draws) until study closure. Patients not agreeing to this option were encouraged to participate in a modified, regularly scheduled telephonic contact or contact at study closure, and to attend the final study visit in person. The approach taken for following up these patients was recorded in the eCRF, medical records, and ICF.

Withdrawal of consent was documented in the eCRF, ICF, and medical records. Withdrawn subjects were asked about their reasons for withdrawal and the presence of adverse events. The EoT Visit was encouraged. Attempts to ascertain vital status on these subjects at study closure were made from publicly available sources at study closure.

For all subjects, at EoT, decisions regarding ongoing antiplatelet therapy were at the discretion of the treating physicians.

5.3.1.11 Adjudication of Clinical Endpoints

A blinded, independent clinical endpoints committee (CEC) adjudicated all potential efficacy and safety event of interest. Adjudicated efficacy events included death, cardiac ischemic events (MI, urgent coronary revascularization, unstable angina, and stent thrombosis), and cerebrovascular events (stroke and TIA).

Adjudicated bleeding events included all bleeding events that, in the opinion of the investigator, necessitated reporting as an adverse event, minimal bleeding events, and

non-minimal bleeding events according to the following bleeding definitions sets: TIMI, PLATO, GUSTO, and ISTH.

5.3.1.12 Protocol Changes

There was one global amendment effective 9 March 2011 which changed the exclusion for ischemic stroke within the prior 14 days to an exclusion of patients with:

- Any history of stroke
- Any history of central nervous system tumor or intracranial vascular abnormality
- Intracranial or spinal cord surgery within the prior 5 years.

At the time of the global amendment, all patients were reassessed and those meeting the new exclusion criteria were discontinued from the PEGASUS trial, but followed as premature discontinuations of study drug. This amendment impacted 102 subjects.

The only change to the analysis plan originally stipulated in the PEGASUS protocol was the deletion of two planned subgroup analyses – one for subjects by moderate CYP3A inhibitor usage at randomization (too few subjects expected for meaningful analysis), and one for subjects by cardiovascular risk score (lack of established definition). This change was made prior to unblinding of study data.

5.3.1.13 Treatment Compliance

Patient compliance was assessed by the investigator and recorded in the eCRF based on a pill count done at a patient level and recorded in the eCRF, as well as a dispensing log completed the study site personnel.

5.3.1.14 Analysis Plan

<u>Population sets</u>

- Full Analysis Set – all randomized subjects, analyzed according to their randomized drug regardless of whether an endpoint event occurred before or following discontinuation of study drug.

- Safety Analysis Set – all subjects who received one dose of study drug, for whom post-dose data are available, accounted for in their actual treatment group, including data from the final visit following the common study end date (CSED).

Interim analysis

AT least one interim analysis was planned at 50% achieved with the possibility of additional interim analyses as advised by the IDMC. Following the interim analysis performed 8/31/13 the IDMC did not recommend and early stop for PEGASUS.

Censoring rules

The CSED was the censoring date for event-free patients in the efficacy analyses. Efficacy analyses included events that occurred on or before the CSED. Event-free patients who did not have complete follow-up of endpoints after the CSED were censored at the last time point when a clinical event assessment was performed. Patients who withdrew consent were censored at the date of withdrawal, except in the analysis of all-cause mortality as a single endpoint. Patients lost to follow-up were censored at the last study contact where study endpoints were assessed. Death was a censoring event for all non-death endpoints.

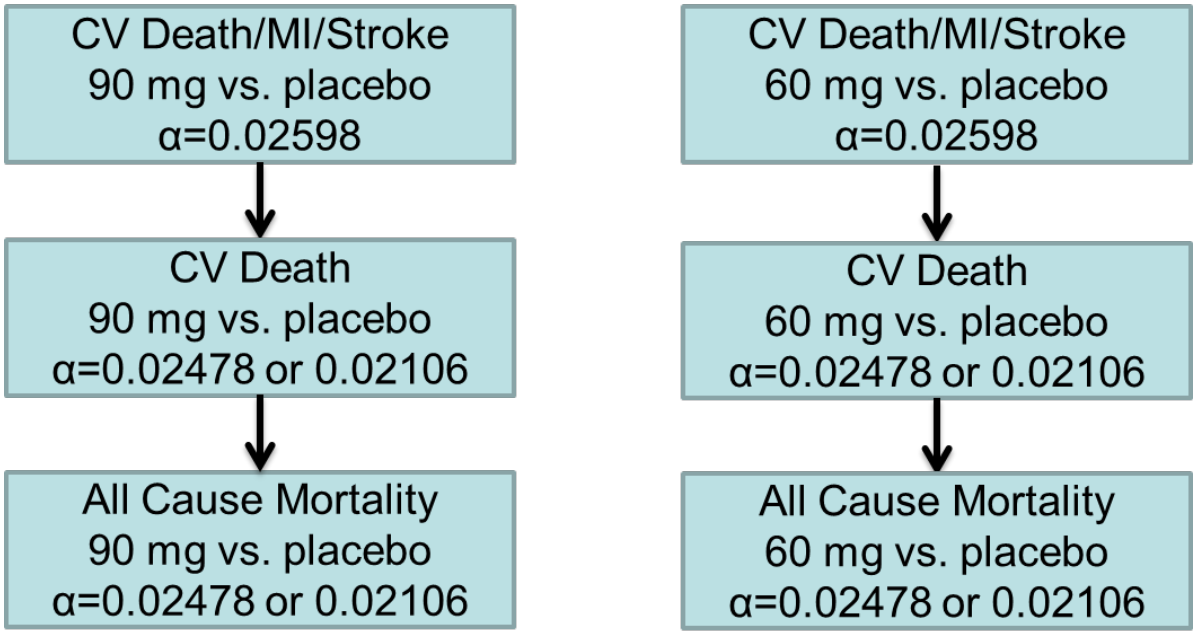
Efficacy analysis

The efficacy analysis was performed on the Full Analysis Set. Primary and secondary efficacy variables were analyzed by the Cox proportional hazards model with a factor for treatment group for the 90 mg bd and the 60 mg bd doses separately, for the following outcomes in the following hierarchical order:

1. Primary composite endpoint (time to first CV death, non-fatal stroke, or non-fatal MI)
2. CV death
3. All-cause mortality.

Family-wise error was controlled at 5%, with a two-sided significance level for each dose-placebo comparison of the primary endpoint in the final analysis of 0.02598. Significance levels for the CV death outcomes were set at 0.02478 and 0.02106 if both primary endpoints were significant (i.e. both doses reached significance on their primary endpoint) versus only one primary endpoint reaching significance, respectively. Significance levels for the all-cause mortality outcome were then set at 0.02478 and 0.02106 if both CV death endpoints were significant (i.e. both doses reached significance for CV death) as opposed to only one of the CV death endpoints being significant, respectively. This multiple testing procedure is displayed in the following figure:

Figure 6. PEGASUS multiple testing procedure



5.3.1.15 PEGASUS Schedule of Procedures

The PEGASUS schedule of procedures is shown in the following table:

Table 8. PEGASUS schedule of procedures, protocol edition 09 September 2010

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visits 6-9[b]	EoT Visit[c]	Follow-up Visit
Assessment	Enrollment ≤ 14 d prior to rando-mization	Randomization[a] (Day 0)	4 months ± 10d	8 months ±10d	12 months ±10d	18,24,30,36 months ±10d	≈38 months	14 – 28 days after EoT Visit
Biomarker sample[i]	√		√					
Genetics sample[j]	√							
PK Sampling[k]			√	√	√			
Serum & urine pregnancy test[l]	√							
Urinalysis	√				√			√
Dispense Study Medication		√	√	√	√	√		
Return Study Medication			√	√	√	√	√	
Compliance/drug accountability			√	√	√	√	√	
Current Medications	√		√	√	√	√	√	√
AEs, SAEs, and Endpoints	√[m]	√[n]	√	√	√	√	√	√

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visits 6-9[b]	EoT Visit[c]	Follow-up Visit
Assessment	Enrollment ≤ 14 d prior to rando-mization	Randomization[a] (Day 0)	4 months ± 10d	8 months ±10d	12 months ±10d	18,24,30,36 months ±10d	≈38 months	14 – 28 days after EoT Visit
Contact verification, retention risk assessment						*To be performed 3 months after each Study Visit after month 12 (eg 15, 21, 27, and 33 months) through study completion[o]		

a Randomization can be done immediately after enrollment or up to 14 days later
b If study continues >38 months, visits will continue every six months
c The study is event driven and number of visits will depend on when the pre-estimated number of primary events has been reached and all patients have been treated for a minimum of 12 months. This visit can occur before a study duration of ≈ 38 months if a randomized patient prematurely and permanently discontinues treatment, see section 3
d Only in participating countries, see appendix E for further details
e Laboratory samples will be analyzed at Central lab
f Serum creatinine only except annual visits (12, 24 and 36 months) which will also include haemoglobin. Only in patients on study drug.
g Analytes same as baseline (except serum ApoB and ApoA, see section 6.4.7)
h Serum creatinine and uric acid only
i Only in participating countries, see Appendix D for further details
j Only in participating countries, see Appendix E for further details. The genetic sample should be taken at visit 1 but can be taken at a later visit if necessary.
k Only in participating countries, see section 6.6 for further details
l Only in women of child-bearing potential, see section 4.1
m SAEs will be recorded from the time of informed consent.
n AEs and endpoints will be collected from time of randomization, see section 6.4.3 for details how to collect AEs in patients that have discontinued treatment.
o Contact verification can be through SMS services for patients who have consented to this form of contact. All patients who are not successfully contacted via SMS services or who have not agreed to SMS contact should be contacted by telephone to verify contact information and continued compliance with study procedures. See section 6.2.1

Safety Evaluation

The safety objective of this study was to assess the safety and tolerability of long-term therapy with ticagrelor compared with placebo on a background of ASA in patients with history of MI (1 to 3 years prior to randomization) and at high-risk of an atherothrombotic event, with specific focus was on:

- Time to first TIMI Major bleeding event following the first dose of study drug, Time to first TIMI Major or Minor bleeding event
- Discontinuation due to bleeding.
- Evaluation of AEs

6 Review of Efficacy

Efficacy Summary

The optimal duration of DAPT in patients following acute myocardial infarction is unknown (see section 2.2). In the PLATO trial, compared to clopidogrel 75 mg once daily, a 180 mg loading dose followed by 90 mg bd of ticagrelor added to a background of low-dose ASA for up to 12 months was shown to reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndromes (ACS) (unstable angina, non-ST elevation myocardial infarction, or ST elevation myocardial infarction), and to reduce the rate of stent thrombosis. Consequently, ticagrelor was approved in the United States in 2011 for this indication (NDA 22433).

This is an efficacy supplement to NDA 22433 based on a single large study, PEGASUS TIMI-54 (Trial D5132C00001), which is described in detail in section 5.3. The primary objective of the PEGASUS trial was to compare the effect of long-term treatment with ticagrelor vs. placebo on a background of low dose ASA on the event rate of the MACE composite of cardiovascular death, non-fatal MI, or non-fatal stroke in patients with a history of MI who are at high-risk of developing subsequent atherothrombotic events. Subjects enrolled into PEGASUS were required to have experienced their most recent spontaneous (not procedure-related) MI 1 to 3 years prior to randomization and to have had at least one of the following five conditions identifying them to be at high-risk for developing subsequent atherothrombotic events:

- Age ≥65 years
- Diabetes mellitus requiring medication
- Documented history of a second prior presumed spontaneous MI (>1 year ago)
- Angiographic evidence of multivessel coronary artery disease (CAD) (stenosis ≥50% in two major coronary artery territories [i.e., left anterior descending, ramus intermedius, left circumflex, right coronary artery] involving the main vessel, a major branch, or a bypass graft)
- Chronic, non-end stage renal dysfunction (creatinine clearance calculated by Cockcroft Gault equation <60 mL/min).

The primary efficacy variable in PEGASUS was time to first occurrence of CV death, non-fatal MI, or non-fatal stroke following randomization. Key secondary efficacy variables were the occurrence of any CV death and the occurrence of all-cause mortality through the common study end date (CSED).

Of note, in discussions regarding a special protocol assessment (SPA) for PEGASUS with the sponsor in 2010 (which resulted in no agreement), the Division communicated concern regarding the plan to test only the 90 mg bd dose of ticagrelor in PEGASUS, strongly advising that more than one dose of ticagrelor be tested to determine the

relationships of clinical outcomes with dose. AstraZeneca subsequently proposed adding a third arm to PEGASUS in which subjects would receive 60 mg bd. In a meeting with the sponsor on July 1, 2010, the Division reiterated support for testing more than one dose of ticagrelor in PEGASUS, but remained skeptical regarding the choice of 60 mg bd as the additional dose because:

- It was the Division's belief that there is only 40% between-patient variability in exposure between the 60 mg bd and the 90 mg bd doses, and
- The Division did not understand the rationale of choosing a ticagrelor dose on the basis of the level of IPA in the subgroup of subjects with prior MI administered Plavix in CHARISMA, given that clopidogrel had not been demonstrated to be effective in this clinical situation.

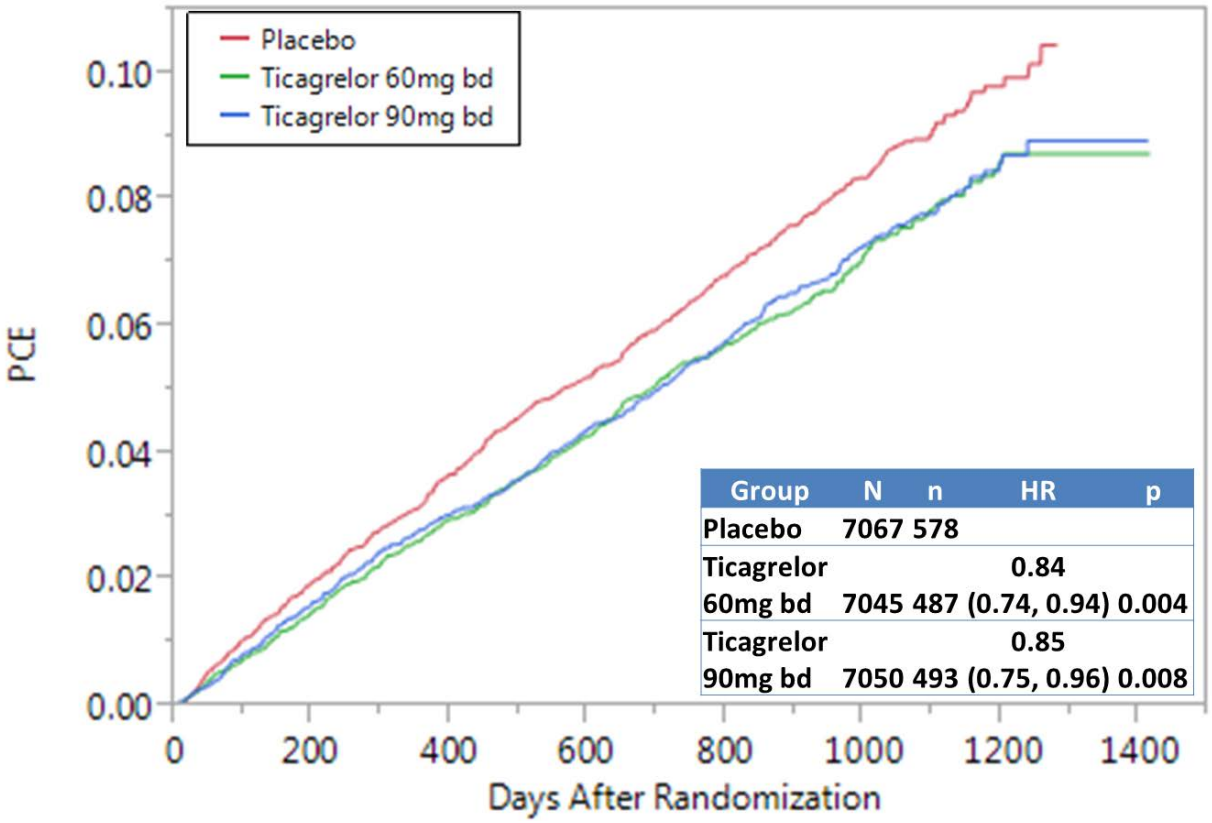
Understanding the Division's reservation regarding dose selection, PEGASUS proceeded as a three-arm study randomizing subjects 1:1:1 to ticagrelor 90 mg bd, ticagrelor 60 mg bd, or placebo according to the following timeline and disposition of subjects:

Table 9. Overall PEGASUS trial timeline and subject dispositions (source: adapted from the PEGASUS Final Study Report (FSR))

Original Protocol	9 Sept 2010
First patient enrolled	29 October 2010
Global amendment	9 March 2011
CSED	14 September 2014
Last visit of last patient	3 December 2014
Study sites	1164
Countries	31
Targeted number of primary events	1360
Primary events through CSED	1558
Total enrolled	21,326
Patients randomized	21,162 (99.2%)
Took One Dose of Study Medication	20,942 (98.2%)
Completed Study*	20,998 (98.5%)
Follow-up for all primary endpoints events (Randomization to death or CSED)	20,892 (98.7%)
Withdrew consent	N=154
Lost to follow-up**	N=10
Study duration	47 months
Maximum duration of exposure	48 months
Minimum follow-up (did not withdraw through CSED)	16 months
Median follow-up (to CSED)	33 months

Per the Clinical Efficacy Reviewer's analysis, PEGASUS convincingly achieved significance as defined in the analytical plan (see section 5.3.1.14) for both doses of ticagrelor versus placebo in reducing the composite of first occurrence of CV death, MI, or stroke, as shown in the following Kaplan-Meier (KM)-plot of the primary efficacy endpoint:

Figure 7. PEGASUS Primary Composite Endpoint (PCE): Time to First Occurrence of MI, Stoke, or CV Death, FAS to CSED (Sources: FDA Clinical Efficacy Reviewer, ADTTE and RSYB)



The identical performance of the two ticagrelor doses tested is noted and reflects the concerns expressed by the Division during the SPA review process.

The sponsor's plan for PCE component analyses in the event of statistically significant outcomes for the PCE itself was to assess the time to any occurrence of CV death, MI, or stroke, counting patients multiple times that had multiple PCE component events at different time points. The FDA Clinical Efficacy and Statistical Reviewers confirmed these sponsor-reported time to "any event" analyses, but also performed time to first component event analyses as well which were subsequently corroborated by the

sponsor. The Cox proportional hazards analyses using a factor for treatment group for both analysis types (time to first and time to any PCE component events), are shown in the following summary table:

Table 10. PEGASUS component outcomes of the primary composite endpoint, FAS to CSED (Sources: FDA Clinical Efficacy Reviewer, ADTTE and RSYB)

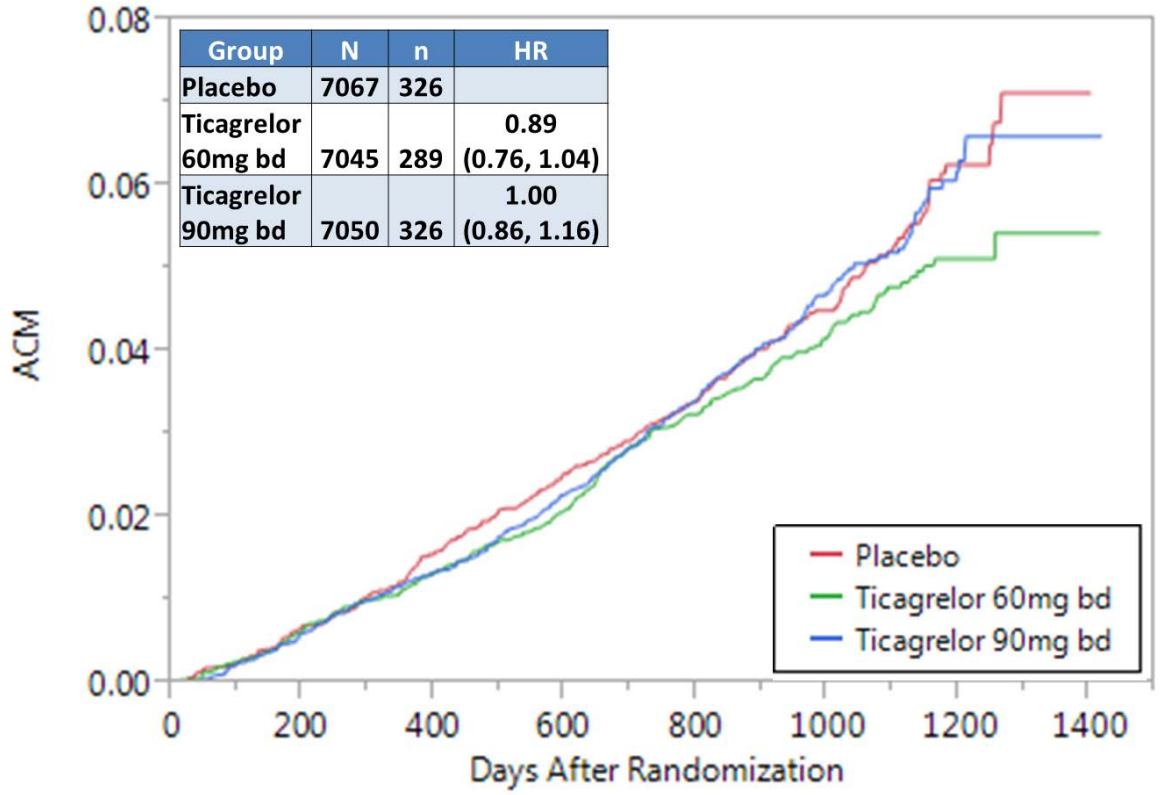
Endpoint	Placebo (N = 7067) n (%)	Brilinta 60 mg bd (N = 7045) n (%) HR (95% CI) p-value	Brilinta 90 mg bd (N = 7050) n (%) HR (95% CI) p-value
Primary composite endpoint: CV Death, MI, Stroke	578 (8.2)	487 (6.9) HR=0.84 (0.74, 0.94) p=0.004	493 (7.0) HR=0.85 (0.75, 0.96) P=0.008
First CV Deaths	128	116 HR=0.90 (0.70, 1.16)	127 HR=0.99 (0.77, 1.26)
First MI's	336	283 HR=0.84 (0.72, 0.98)	272 HR=0.81 (0.69, 0.95)
First Strokes	114	88 HR=0.77 (0.58, 1.01)	94 HR=0.82 (0.63, 1.08)
Subjects with events at any time			
Any CV Deaths	210	174 HR=0.83 (0.68, 1.01)	182 HR=0.87 (0.71, 1.06)
Any MI's	338	285 HR=0.84 (0.72, 0.98)	275 HR=0.81 (0.69, 0.95)
Any Strokes	122	91 HR=0.75 (0.57, 0.98)	100 HR=0.82 (0.63, 1.07)

Both time to first and time to any PCE component event analyses were directionally the same (favoring ticagrelor) and of similar magnitude for all three PCE components, though the point estimate for the HR of first CV deaths in patients randomized to the ticagrelor 90 mg bd arm was numerically higher than for the ticagrelor 60 mg bd dose, and higher than the point estimate for the HR of any CV death for the 90 mg bd dose.

Importantly, the first pre-specified secondary endpoint was the time to occurrence of any CV Death. This analysis for the ticagrelor 90 mg bd dose demonstrated a numerical decrease in the occurrence of any CV death compared to placebo that was not statistically significant (13% RRR, HR 0.87 [95% CI 0.71, 1.06], p=0.1547). A similar non-significant decrease in time to occurrence of any CV death was shown for the ticagrelor 60 mg bd dose compared with placebo (17% RRR, HR 0.83 [95% CI 0.68, 1.01], p=0.0676). Per section 5.3.1.14 of this review (Analysis Plan), the failure of this endpoint to attain its statistical hurdle for either dose of ticagrelor resulted in the termination of the hierarchical testing procedure, and the sponsor appropriately pointed out that any other p-values reported on other safety and/or efficacy endpoints were nominal.

The second secondary endpoint, time to occurrence of all-cause mortality, was not different for the 90 mg bd dose of ticagrelor compared to placebo, but there was a non-significant lean in favor of the 60 mg bd dose of ticagrelor compared to placebo, as shown in the figure for the analysis of ACM by the Clinical Efficacy Reviewer below:

Figure 8. PEGASUS time to All-cause Mortality, FAS to CSED (Sources: FDA Clinical Efficacy Reviewer, ADTTE and RSYB)



Subgroups of the PCE Analysis

Time from qualifying MI and time from prior ADP receptor blocker therapy

The estimate for the HR of the PCE in PEGASUS for subjects taking the 60 mg bd dose was approximately unity for subjects whose index (qualifying) MI occurred greater than or equal to 2 years prior to randomization, in contrast to those whose index MI had occurred less than 2 years preceding randomization who demonstrated nominally significant reduction of PCE outcomes (HR = 0.97 versus 0.77, respectively, see section 6.1.7). Results for the ticagrelor 90 mg bd dose were not convincingly different in this regard. However, both doses demonstrated a lack of effect in subjects whose last ADP receptor blocker therapy was greater than 12 months prior to randomization. These two subgroups suggest that subjects more than 2 years out from a prior MI and/or more than 12 months out from prior ADP receptor blockade do not benefit for restarting ADP receptor blockade with ticagrelor. This finding has biological plausibility in that these subjects may in fact represent survivors of discontinuation of prior ADP therapy and/or long-term MI survivors.

Age, Gender, Race, and Body Mass Index

Analyses from PLATO and PEGASUS suggest that lack of efficacy of the 60 mg bd dose of ticagrelor in these subgroups is likely a chance finding (see section 6.1.7).

Stent Thrombosis

There were two different timings for stent implants in PEGASUS: stents that were already in place at randomization, and stents that were placed during the study for medical cause. Because patients receiving a stent during PEGASUS for medical cause were either treated with open label DAPT during a study drug interruption per the discretion of the investigator, or with PLATO-type blinded dosing of either ticagrelor (90 mg bd) or clopidogrel (75 mg od) per the modified dosing algorithm (see section 5.3.1.4, Trial Design), it was the opinion of this reviewer that the more relevant analysis was for the occurrence of stent thrombosis in patients taking the PEGASUS dose of ticagrelor compared to placebo involving stents that were in place at the time of randomization. The Clinical Efficacy Reviewer's reanalysis of this population demonstrated that all but five patients experiencing stent thrombosis during PEGASUS fell into this category (i.e. stents in place at randomization).

The analysis of stent thrombosis in stents already in place at the time of randomization in PEGASUS involved a small number of subjects, but suggests a ticagrelor dose-responsive decrease in stent thrombosis during the trial (see section 6.1.6), with a HR (CI) for stent thrombosis for the ticagrelor 60 mg bd dose and the 90 mg bd dose being

0.83 (0.54, 1.26) and 0.63 (0.39, 0.98) respectively, in sample sizes that were only 30-48 subjects in each of the three comparison arms.

Patients Requiring Anticoagulation

The need for chronic oral anticoagulant therapy or chronic low-molecular-weight heparin (at venous thrombosis treatment not prophylaxis doses) were exclusions to enrollment in PEGASUS. Accordingly, the benefit-risk assessment of this review cannot be extrapolated to patients with a history of MI that occurred at least one year ago, who are at high-risk for recurrent atherothrombotic events, and who require oral anticoagulation or chronic low-molecular-weight heparin for the treatment of atrial fibrillation or venous thromboembolic events (deep venous thrombosis and/or pulmonary emboli).

Patients having major bleeding on DAPT in the year following MI

Patients who previously had ADP receptor blockade discontinued due to bleeding were effectively screened out of PEGASUS by its exclusion criteria (see section 6.1.10). Accordingly, the benefit-risk assessment of this review cannot be extrapolated to patients with a history of bleeding that was severe enough to warrant discontinuation of their prior ADP receptor blocker.

Efficacy Conclusions

- PEGASUS succeeded in meeting the statistical hurdle for its primary composite endpoint, which I agree was driven by numerically fewer first CV Deaths, first MIs, and first strokes in both treatment arms, with nominally significant reductions in first MIs for both ticagrelor doses. The results for first events of the PCE components, as well as any events of the PCE components, were directionally similar. Therefore, I agree with the sponsor's conclusion that both doses of ticagrelor reduce MACE events in subjects with spontaneous MI in the prior 1 to 3 years.
- KM analyses of the time to any CV death, any MI, or any stroke confirms that there is no time period during PEGASUS where Placebo is superior to either dose of ticagrelor for any of these three component outcomes (see Figure 11 and Figure 12 in section 6.1.4 below for KM analyses of time to any MI and to any stroke respectively, and Figure 13 in section 6.1.5 below for the KM analysis of time to any CV death).
- Likewise, there is never any time period during PEGASUS where the 90 mg dose is superior to the 60 mg dose for any of these component outcomes.
- The KM curves for time to any occurrence of any of the three components of the PCE in subjects on active ticagrelor treatment appear to continuously diverge

from the curve for placebo-treated subjects during the entire follow period of PEGASUS.

- The all-cause mortality analysis demonstrates a late, non-significant lean in favor of the 60 mg bd dose of ticagrelor compared to placebo and to the 90 mg bd dose of ticagrelor
- High-risk patients who are more than two years away from their prior MI, and subjects who are more than 12 months away from a prior discontinuation of ADP receptor block therapy did not demonstrate benefit from 60 mg bd ticagrelor in subgroup analyses. This finding has biological plausibility.
- High-risk subjects who are aged 65-75, female, non-Caucasian, of or a high body mass index did not demonstrate benefit from 60 mg bd ticagrelor in subgroup analyses. This appears to be a chance finding (see section 6.1.7, Subpopulations).
- PEGASUS effectively screened out subjects who had previously discontinued ADP receptor therapy due to bleeding events, so the benefit-risk assessment of this review does not apply to that subpopulation of patients.
- PEGASUS excluded patients on full dose anticoagulation. Therefore, the benefit-risk assessment of this review does not apply to subjects with atrial fibrillation, deep venous thrombosis, pulmonary embolus, or other conditions requiring full anticoagulation with oral, subcutaneous, or intravenous agents.

6.1 Indication (Proposed)

(b) (4)

6.1.1 Methods

This is an efficacy supplement based on a single large study, PEGASUS TIMI-54 (Trial D5132C00001), which is described in detail in section 5.3. Accordingly, there was no multiple-study integration for the efficacy analyses.

The primary endpoint of PEGASUS was the first occurrence of CV Death, MI, or Stroke. Component analyses were defined as all CV deaths, all MIs, and all Strokes, such that the sum of the component event occurrences was greater than the number of first primary composite events. Accordingly, efficacy outcomes are presented in this efficacy review by both methods, presenting:

1. Occurrences of all component events, the prespecified methodology in which the total number of component CV death, MI, and stroke events exceeds the number of primary composite events, and

2. Occurrences of only first component events, in which case only sum of the occurrences of first CV death, first MI, and first stroke events equals the number of primary composite endpoint events.

To begin our analysis, the FDA medical and statistical reviewers independently analyzed the adjudication database (RSYB) for YBTERMs of “CV Death, “Myocardial Infarction”, and “Stroke according to the protocol definition”. The FDA Clinical Efficacy Reviewer’s number of first primary composite events (PCE) was initially higher than the 1558 events reported by the sponsor. When this subset was corrected for events occurring only prior to the CSED (statistical reviewer), FDA identified 1567 events, an event count that was still 9 higher that the sponsor-reported 1558 events, per the following table:

Table 11. FDA Medical and Statistical Reviewers’ counts of PEGASUS primary efficacy events

	PBO			**60mg**			**90 mg**		
	Sponsor	**FDA**	**diff**	**Sponsor**	**FDA**	**diff**	**Sponsor**	**FDA**	**diff**
CV Death	128	134	+6	116	120	+4	127	131	+4
MI	336	336	0	283	284	+1	272	272	0
Stroke	114	113	-1	88	85	-3	94	92	-2

Source: Dataset RSYB and selected YBTERM only in 'CV Death', 'Myocardial Infarction', 'Stroke (CVA) according to protocol definition', sorted by usubjid and YBSTDY, selected first record by each subject (i.e. first occurring event), selected YBSTDTC < 9/15/2014 (CSED), then removing subject E5723027 who did not have a treatment code. Multiple component events occurring on the same day without documented timing were assumed to occur in the following order: MI occurs before stroke which occurs before CV death.

The additional 9 subjects identified by the medical and statistical reviewers were accounted for by the following 9 subjects who withdrew consent prior to the CSED, but were subsequently documented to have experienced CV death prior to the CSED as adjudicated by the ICEC (subjects E2312007, E2606012, E4301010, E6016012, E6212003, E6228020, E6703009, E7208006, E7880001). Five of these deaths occurred in the placebo arm, while the other four occurred on ticagrelor therapy. While these 9 subjects were counted in the all-cause mortality analysis, they were not, per the pre-specified censoring rules in PEGASUS, counted as CV deaths for the purpose of the PCE of the trial or the PCE component event counts.

Accordingly the total number of CV death, MI, and stroke events identified by FDA and the sponsor were in agreement, as were the numbers of first component events and primary composite endpoint events.

6.1.2 Demographics

Table 12. PEGASUS Demographics, FAS (FDA Clinical Efficacy Reviewer, dataset adsl_NB)

Demographic Parameters	Ticagrelor 60mg bd (n=7045) n (%)	Ticagrelor 90mg bd (n=7050) n (%)	Ticagrelor Combined (n=14095) n (%)	Placebo (n=7067) n (%)
Sex				
Male	5384 (76.4)	5368 (76.1)	10752 (76.3)	5350 (75.7)
Female	1661 (23.6)	1682 (23.9)	3343 (23.7)	1717 (24.3)
Age				
Mean years (SD)	65.2 (8.4)	65.4 (8.4)	65.3 (8.4)	65.4 (8.3)
Median (years)	65	65	65	65
Min, Max (years)	49, 93	47, 93	47, 93	50, 95
Age Group				
<17 years	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
>=17 - <65 years	3283 (46.6)	3190 (45.2)	6473 (45.9)	3154 (44.6)
>=65 years	3762 (53.4)	3860 (54.8)	7622 (54.1)	3913 (55.4)
>=75 years	1018 (14.4)	1038 (14.7)	2056 (14.6)	1027 (14.5)
Race				
White	6077 (86.3)	6126 (86.9)	12203 (86.6)	6124 (86.7)
Black or African American	128 (1.8)	109 (1.5)	237 (1.7)	116 (1.6)
Asian	682 (9.7)	663 (9.4)	1345 (9.5)	676 (9.6)
American Indian or Alaska Native	18 (0.3)	17 (0.2)	35 (0.2)	12 (0.2)
Native Hawaiian or Other Pacific Islander	86 (1.2)	85 (1.2)	171 (1.2)	89 (1.3)
Other	54 (0.8)	50 (0.7)	104 (0.7)	50 (0.7)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ethnicity				
Hispanic or Latino	836 (11.9)	868 (12.3)	1704 (12.1)	860 (12.2)
Not Hispanic or Latino	5983 (84.9)	5962 (84.6)	11945 (84.7)	5986 (84.7)
Missing	226 (3.2)	220 (3.1)	446 (3.2)	221 (3.1)
Region				
United States	863 (12.2)	866 (12.3)	1729 (12.3)	872 (12.3)
Rest of World	6182 (87.8)	6184 (87.7)	12366 (87.7)	6195 (87.7)
Canada	434 (6.2)	441 (6.3)	875 (6.2)	431 (6.1)
South America	814 (11.6)	822 (11.7)	1636 (11.6)	822 (11.6)
Europe	3572 (50.7)	3562 (50.5)	7134 (50.6)	3580 (50.7)
Asia	1034 (14.7)	1030 (14.6)	2064 (14.6)	1039 (14.7)
Africa	160 (2.3)	158 (2.2)	318 (2.3)	155 (2.2)
Other	168 (2.4)	171 (2.4)	339 (2.4)	168 (2.4)

As seen from the general patient demographics table above, there were no imbalances between the treatment groups with respect to important demographic characteristics. Both the mean and median ages of the randomized population was 65 years of age, approximately 87% were Caucasians, and approximately 76% were male. Approximately 12% identified as being of Hispanic ethnicity. Approximately 12% of subjects were randomized from the United States.

The efficacy results from PEGASUS appeared to be somewhat dependent on or influenced by the time from the subjects' prior myocardial infarctions, as well as the time from the subjects' prior treatments with an ADP receptor blocker. These two characteristics are likely not to be independent of each other given guideline recommendations for DAPT following NSTE ACS and STEMI (see section 2.2 for a summary of current ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline recommendations).

The following table demonstrates no important between-treatment differences in time from qualifying MI to randomization between the three treatment arms in PEGASUS:

Table 13. Time from index/qualifying MI to Randomization, FAS (Source: Sponsor Table 11.1.3.2.1, PEGASUS CSR 496/9148)

	Ticagrelor-90 bd (N=7050)	**Ticgrlor-60 bd (N=7045)**	**Placebo (N=7067)**
< 1 year	40 (0.6%)	54 (0.8%)	47 (0.7%)
≥1 to <2 years	4276 (60.7%)	4277 (60.7%)	4286 (60.6%)
≥2 to ≤3 years	2682 (38.0%)	2667 (37.9%)	2683 (38.0%)
>3 years	41 (0.6%)	35 (0.5%)	41 (0.6%)
Unknown	4 (0.1%)	2 (0.0%)	0 (0.0%)
No prior MI	7 (0.1%)	9 (0.1%)	10 (0.1%)
No info	0 (0.0%)	1 (0.0%)	0 (0.0%)

The timing of prior treatment with an ADP receptor blocker was also not different between the groups, with approximately a quarter of patients having been dosed with an ADP receptor blocker within 7 days of randomization, about a quarter having received their last dose more than 12 months before randomization, and about 11% apparently never having previously received an ADP receptor blocker, as shown in the following table:

Table 14. Treatment with ADP receptor blocker any time prior to randomization, FAS (Source: Sponsor Table 11.1.3.11.1, PEGASUS CSR 571/9148)

	Ticagrelor-90 bd (N=7050)	**Ticgrlor-60 bd (N=7045)**	**Placebo (N=7067)**
Ongoing, stopped	4 (0.1%)	6 (0.1%)	10 (0.1%)
Ongoing, after dose	14 (0.2%)	23 (0.3%)	12 (0.2%)
0-7 days	1826 (25.9%)	1816 (25.8%)	1828 (25.9%)
8-90 days	1243 (17.6%)	1257 (17.8%)	1243 (17.6%)
3-12 months	1498 (21.2%)	1520 (21.6%)	1540 (21.8%)
>12 months	1676 (23.8%)	1661 (23.6%)	1645 (23.3%)
Unknown	10 (0.1%)	6 (0.1%)	7 (0.1%)

6.1.3 Subject Disposition

The overall timeline of the conduct of PEGASUS, together with dates of various study periods, patient numbers enrolled, dosed, and followed, and ranges of exposure times are shown in the following summary table:

Table 15. PEGASUS trial timeline and subject dispositions (adapted from the PEGASUS FSR)

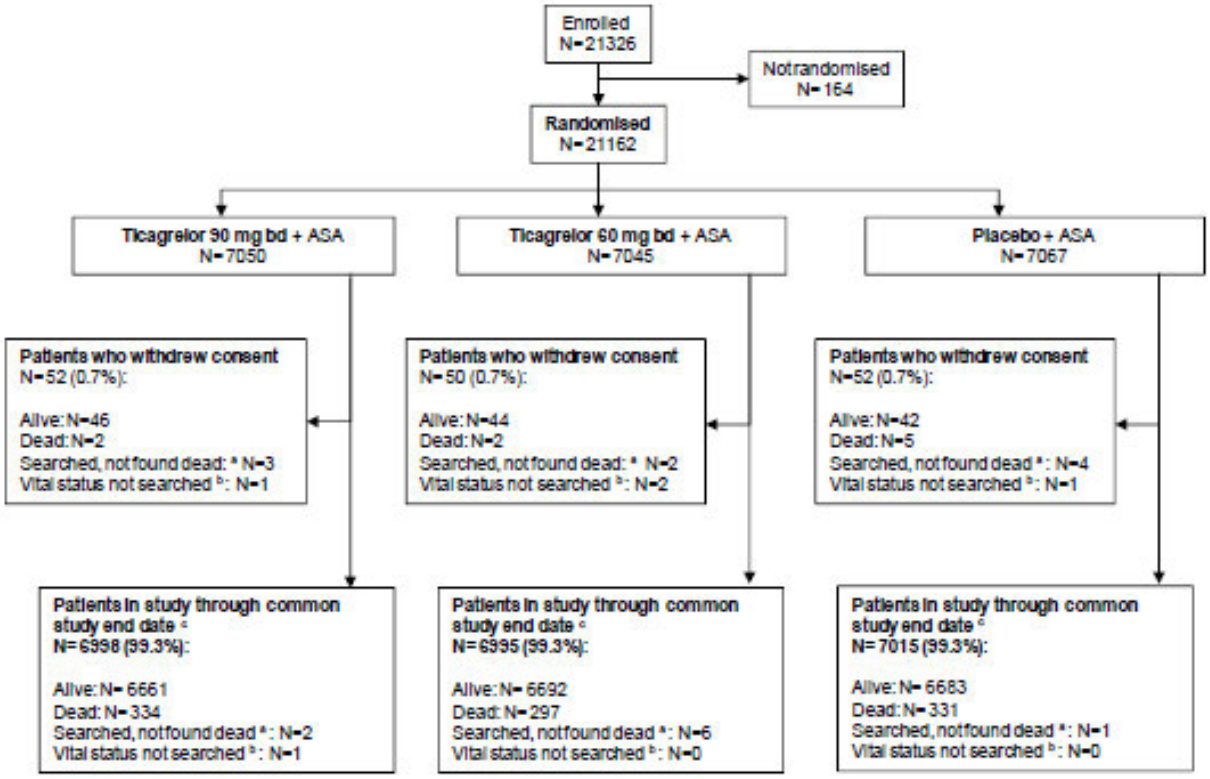
Original Protocol	9 Sept 2010
First patient enrolled	29 October 2010
Global amendment	9 March 2011
CSED	14 September 2014
Last visit of last patient	3 December 2014
Study sites	1164
Countries	31
Targeted number of primary events	1360
Primary events through CSED	1558
Total enrolled	21,326
Patients randomized	21,162 (99.2%)
Took One Dose of Study Medication	20,942 (98.2%)
Completed Study*	20,998 (98.5%)
Follow-up for all primary endpoints events (Randomization to death or CSED)	20,892 (98.7%)
Withdrew consent	N=154
Lost to follow-up**	N=10
Study duration	47 months
Maximum duration of exposure	48 months
Minimum follow-up (did not withdraw through CSED)	16 months
Median follow-up (to CSED)	33 months

*Study completers – randomized patients who did not withdraw consent and not lost to follow-up;
**Lost to follow-up – unknown vital status after CSED ('searched not found dead' and 'not searched')

Reference ID: 3804604

As seen above, the follow-up of subjects in PEGASUS was excellent, with 98.7% of subjects being followed for all primary endpoint events from randomization to either death or the CSED. Only 154 subjects withdrew consent, and only 10 were lost to follow-up. The minimal follow-up time of a subject that did not prematurely withdraw was 16 months through the CSED, and the median follow-up duration to the CSED was 33 months. The sponsor reports KM percentages of efficacy endpoint events at 36 months due to the high rate of drop-off in subject numbers being followed between months 36 and 48. This reviewer will present incidence rates of events (n/N) rather than selecting an arbitrary time point to quote KM percentage occurrences. A summary diagram of study participation and vital status of those subjects from the FAS is reproduced from the sponsor's CSR as follows:

Figure 9. PEGASUS Study Participation and Vital Status, FAS (Source: PEGASUS FSR)



Source: Table 11.1.1.1.1

[a] Publicly available sources searched, but vital status not confirmed (eg, patients not listed as dead in death registry)

[b] Search for vital status prohibited in some countries.

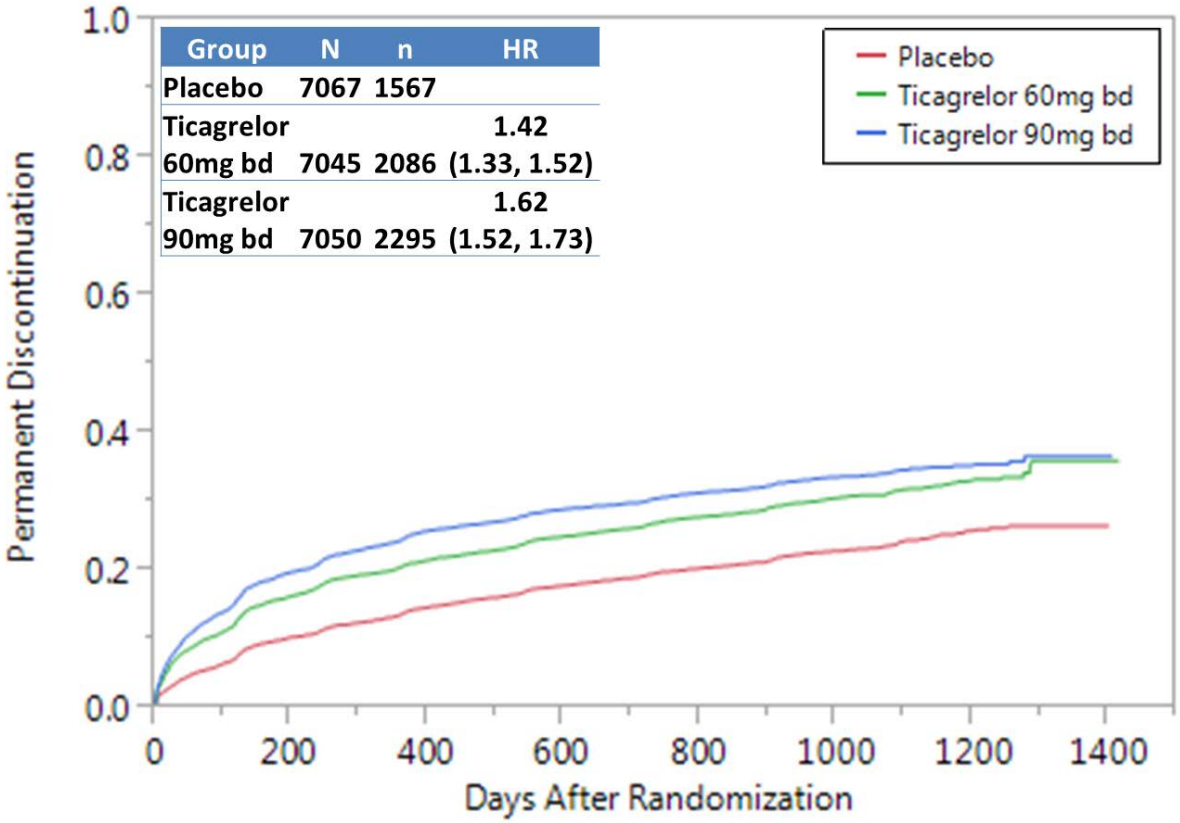
[c] Patients who did not withdraw consent, including patients who died during follow-up. The common study end date was the censoring date for efficacy analyses.

ASA Acetylsalicylic acid; bd Twice daily; N Number of patients in treatment group

Reviewer's note: The 102 subjects with a prior history of stroke, who were withdrawn due to Amendment 1, are represented in this figure. The sponsor states that these 102 subjects were followed through the end of the study for outcome events, and that some of these subjects experienced outcome events.

Drop-out rates were highest in all three treatment arms during the first approximately three months of therapy in all three treatment arms, with significantly higher rates of permanent discontinuation in the two ticagrelor arms in a dose-responsive pattern, as seen in the time to discontinuation figure below:

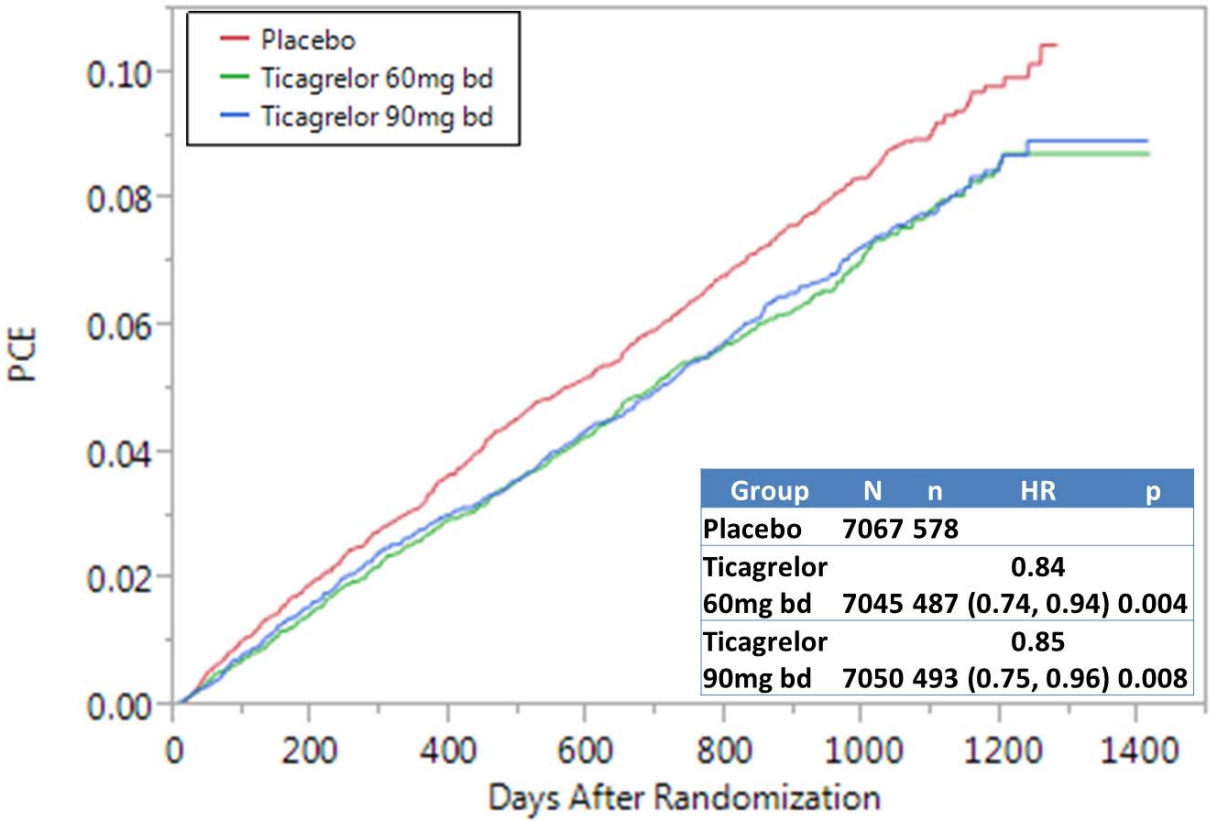
Figure 10. PEGASUS time to permanent discontinuations of study drug, FAS to CSED (Source: FDA Clinical Efficacy Reviewer, ADTTE)



6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoint of PEGASUS was the time for first occurrence of CV death, non-fatal MI, or non-fatal stroke, with an analysis of the components of the composite that would count any and all components events (as opposed to first CV death, first MI, and first stroke). This reviewer performed the analyses both ways using the ADTTE and RSYB datasets. PEGASUS convincingly achieved significance as defined in the analytical plan (see section 5.3.1.14) for both doses of ticagrelor versus placebo in reducing the composite of first occurrence of CV death, MI, or stroke, as shown in the following KM-plot of the PCE:

Figure 11. PEGASUS primary composite efficacy endpoint (time to first occurrence of CV Death, MI, or stroke). FAS to CSED (FDA Clinical Efficacy Reviewer, ADTTE and RSYB)



Reviewer's comment – identical primary efficacy outcomes for the 60 bd and 90 bd doses of ticagrelor, substantiating FDA's concern in the design phase of this

trial that the two doses were likely not sufficiently different to demonstrate a measurable dose-response or exposure-response relationship with respect to efficacy outcomes. The PCE KM curves for placebo-treated patients versus ticagrelor-treated subjects continue to diverge throughout the duration of follow-up.

PEGASUS success in meeting its statistical hurdle for its PCE was driven by numerically fewer first CV Deaths, first MIs, and first strokes in both treatment arms, with nominally significant reductions in first MIs for both ticagrelor doses, as seen in the following table:

Table 16. PEGASUS first occurrences of component outcomes of the primary composite endpoint, FAS to CSED (Sources: FDA Clinical Efficacy Reviewer, ADTTE and RSYB)

Endpoint	Placebo (N = 7067) n (%)	Brilinta 60 mg bd (N = 7045) n (%) HR (95% CI) p-value	Brilinta 90 mg bd (N = 7050) n (%) HR (95% CI) p-value
Primary composite endpoint: CV Death, MI, Stroke	578 (8.2)	487 (6.9) HR=0.84 (0.74, 0.94) p=0.004	493 (7.0) HR=0.85 (0.75, 0.96) P=0.008
First CV Deaths	128	116 HR=0.90 (0.70, 1.16)	127 HR=0.99 (0.77, 1.26)
First MI's	336	283 HR=0.84 (0.72, 0.98)	272 HR=0.81 (0.69, 0.95)
First Strokes	114	88 HR=0.77 (0.58, 1.01)	94 HR=0.82 (0.63, 1.08)

The PEGASUS protocol stipulated that if the PCE analysis met its statistical hurdle for a dose of ticagrelor, that the component events would by analyzed for any occurrence (i.e., the incidence and time to occurrence of any CV death, any MI, and any stroke), given that some patients suffered more than one of these outcomes. This analysis for the occurrence of any component events was consistent with the overall results of the occurrence of first events, as seen in the following table:

Table 17. PEGASUS any occurrences of component outcomes of the primary composite endpoint, FAS to CSED (Sources: FDA Clinical Efficacy Reviewer, ADTTE and RSYB)

Endpoint	Placebo (N = 7067) n (%)	Brilinta 60 mg bd (N = 7045) n (%) HR (95% CI) p-value	Brilinta 90 mg bd (N = 7050) n (%) HR (95% CI) p-value
Subjects with events at any time			
Any CV Deaths	210	174 HR=0.83 (0.68, 1.01)	182 HR=0.87 (0.71, 1.06)
Any MI's	338	285 HR=0.84 (0.72, 0.98)	275 HR=0.81 (0.69, 0.95)
Any Strokes	122	91 HR=0.75 (0.57, 0.98)	100 HR=0.82 (0.63, 1.07)

KM analyses of the time to any CV death, any MI, or any stroke confirms that there is no time period during PEGASUS where Placebo is superior to either dose of ticagrelor for any of these three outcomes (see Figure 12 and Figure 13 immediately below for KM analyses of time to any MI and to any stroke respectively, and Figure 14 in section 6.1.5 below (analysis of secondary endpoints) for the KM analysis of time to any CV death). Likewise, there is never any time period during PEGASUS where the 90 mg dose is superior to the 60 mg dose for any of these outcomes. The KM curves for time to any occurrence of any of the three components of the PCE in subjects on active ticagrelor treatment appear to continuously diverge from the curve for placebo-treated subjects during the entire follow-up period of PEGASUS.

Figure 12. PEGASUS time to any MI, FAS to CSED (Sources: FDA Clinical Efficacy Reviewer, ADTTE and RSYB)

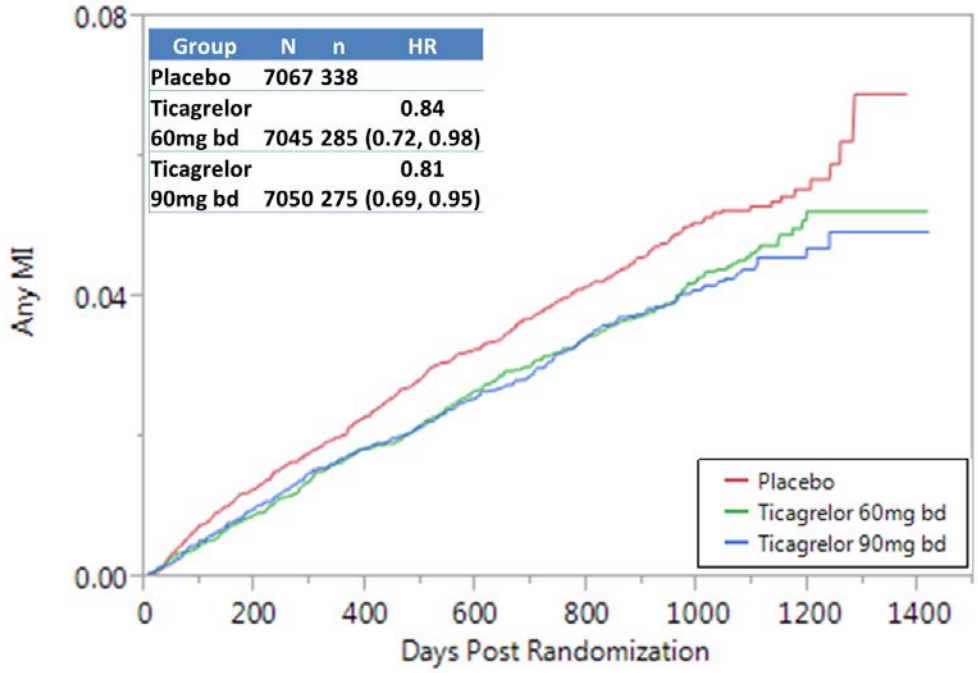
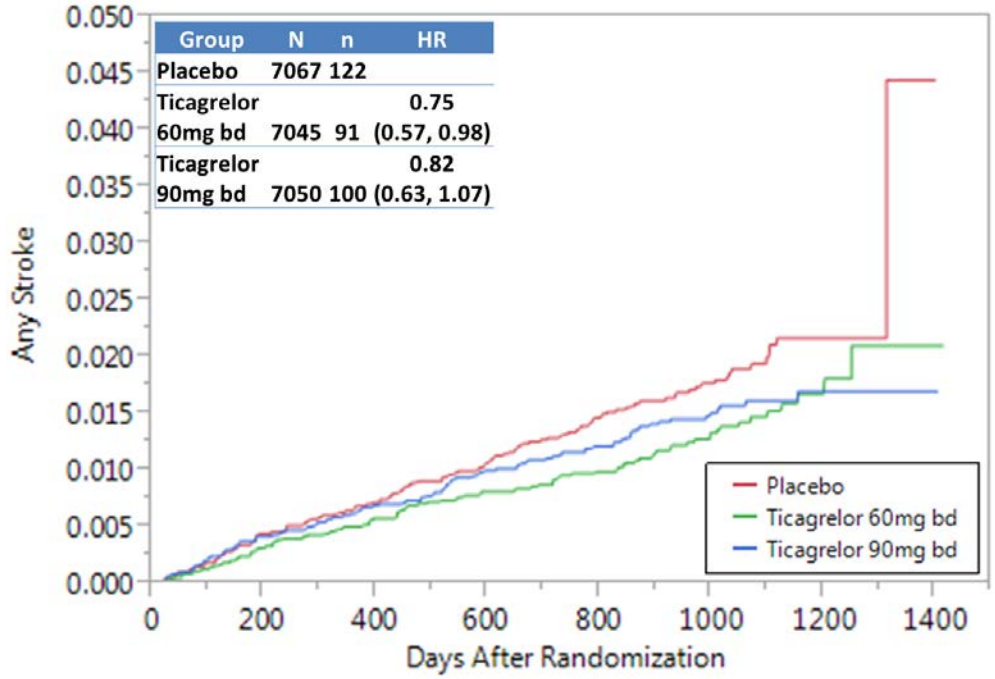


Figure 13. PEGASUS time to any stroke, FAS to CSED (Sources: FDA Clinical Efficacy Reviewer, ADTTE and RSYB)

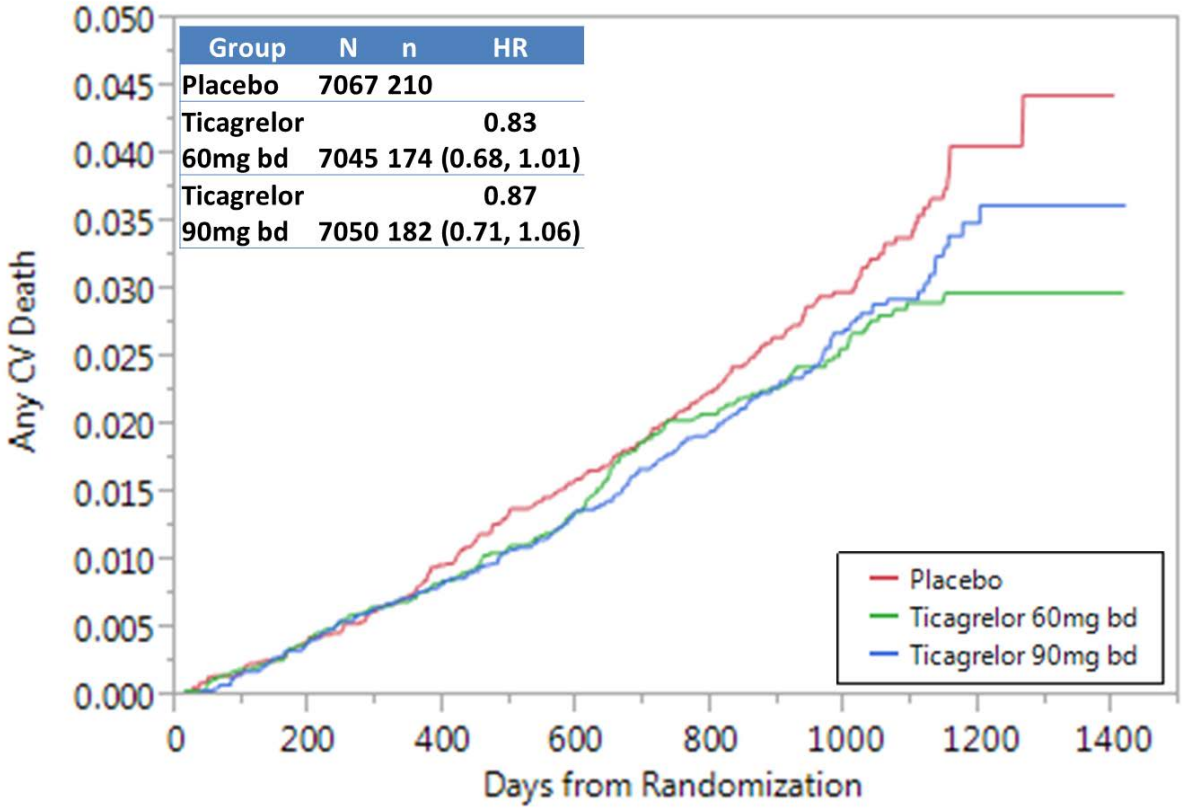


6.1.5 Analysis of Secondary Endpoints(s)

First Secondary Endpoint:

The first pre-specified secondary endpoint was the time to occurrence of any CV Death. This analysis for the ticagrelor 90 mg bd dose demonstrated a numerical decrease in the occurrence of any CV death compared to placebo that was not statistically significant (13% RRR, HR 0.87 [95% CI 0.71, 1.06], p=0.1547). A similar non-significant decrease in time to occurrence of any CV death was shown for the ticagrelor 60 mg bd dose compared with placebo(17% RRR, HR 0.83 [95% CI 0.68, 1.01], p=0.0676). The KM result by the FDA Clinical Efficacy Reviewer shown below for this outcome is in agreement with the results reported by the sponsor:

Figure 14. PEGASUS time to Any CV Death, FAS to CSED (Sources: FDA Clinical Efficacy Reviewer, ADTTE and RSYB)

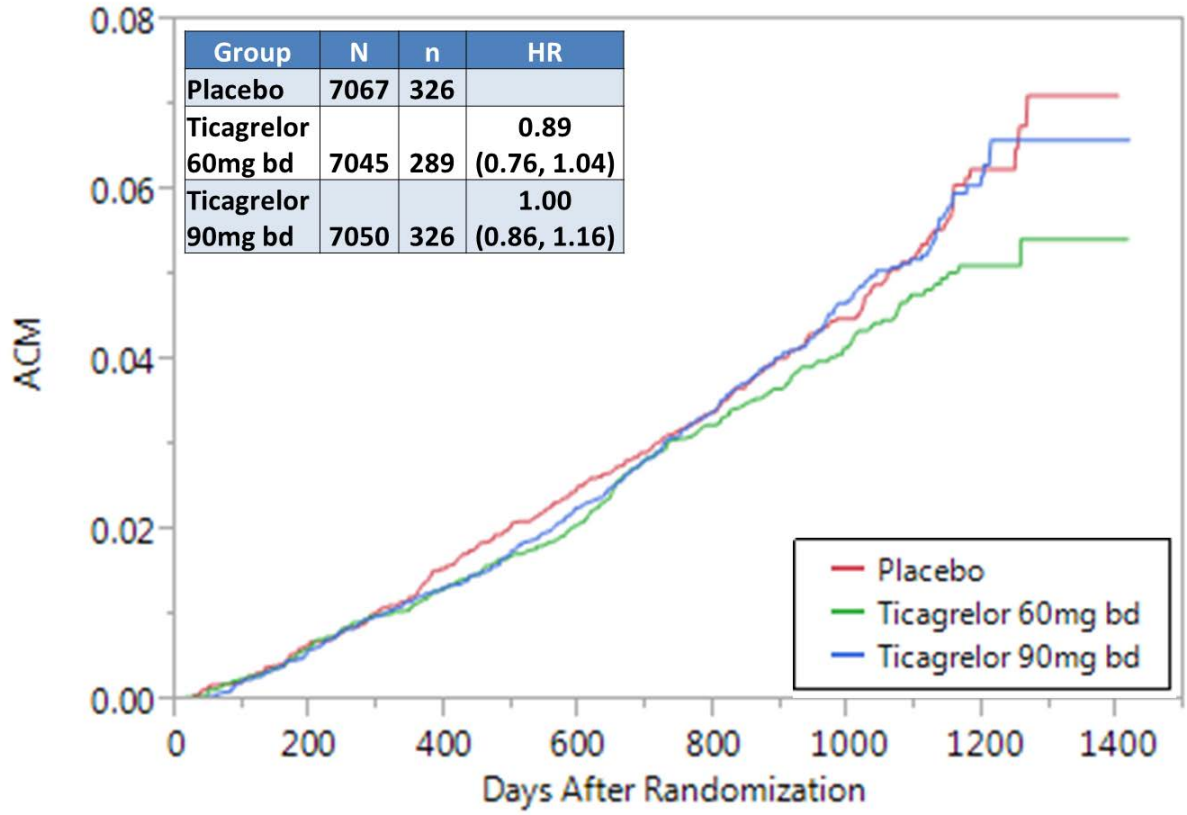


Per section 5.3.1.14 of this review (Analysis Plan), the failure of this endpoint to attain its statistical hurdle for either dose of ticagrelor resulted in the termination of the hierarchical testing procedure, and the sponsor appropriately pointed out that any other p-values reported on other safety and/or efficacy endpoints were nominal.

Second Secondary Endpoint:

The second secondary endpoint, time to occurrence of all-cause mortality, was not different for the 90 mg bd dose of ticagrelor compared to placebo, but there was a non-significant lean in favor of the 60 mg bd dose of ticagrelor compared to placebo, as shown in the figure for the analysis of ACM by the Clinical Efficacy Reviewer below:

Figure 15. PEGASUS time to all-cause mortality, FAS to CSED (Sources: FDA Clinical Efficacy Reviewer, ADTTE and RSYB)



Reviewer's comment: these 941 deaths in the RSYB dataset all occurred before or on the CSED. 30 additional deaths occurred in the FAS following the CSED (total RSYB deaths = 971). These additional 30 cases were balanced across the three treatment arms, with ten in each treatment group. The thirty subjects that died for any reason following the CSED, by treatment group, are as follows:

Table 18. PEGASUS subjects who died following the CSED, FAS (Sources FDA Clinical Efficacy Reviewer, ADTTE and RSYB)

USUBJID	TRT01A	DEATH ADJ	CV SUBCLASS	NON-CV SUBCLASS	CEREBROVASC SUBCLASS
E1055037	Placebo	Non-CV Death		Malignancy	
E1323018	Placebo	Non-CV Death		Malignancy	
E1606050	Placebo	CV Death	Presumed Cardiovascular		
E1914096	Placebo	CV Death	Death due to an acute MI		
E3336013	Placebo	Non-CV Death		Infection (including sepsis)	
E6007010	Placebo	CV Death	Presumed Cardiovascular		
E6220012	Placebo	CV Death	Sudden cardiac death		
E6220023	Placebo	CV Death	Death due to an acute MI		
E6909018	Placebo	Non-CV Death		Infection (including sepsis)	
E8506001	Placebo	CV Death	Death due to Cerebrovascular event		Death due to intracranial hemorrhage
E0709004	T-60mg bd	CV Death	Sudden cardiac death		
E1616021	T-60mg bd	CV Death	Presumed Cardiovascular		
E2803009	T-60mg bd	Non-CV Death		Malignancy	
E5757071	T-60mg bd	Non-CV Death		Infection (including sepsis)	
E6009032	T-60mg bd	CV Death	Presumed Cardiovascular		
E6105020	T-60mg bd	CV Death	Sudden cardiac death		
E6920035	T-60mg bd	CV Death	Presumed Cardiovascular		
E7002016	T-60mg bd	CV Death	Death due to Cerebrovascular event		Death due to intracranial hemorrhage
E8131007	T-60mg bd	Non-CV Death		Hepatic Failure	
E8620002	T-60mg bd	Non-CV Death		Pulmonary Failure	
E0705023	T-90mg bd	CV Death	Death due to Cerebrovascular event		Death due to non-hemorrhagic stroke
E0737012	T-90mg bd	CV Death	Sudden cardiac death		
E1032018	T-90mg bd	CV Death	Death due to an acute MI		
E1617012	T-90mg bd	CV Death	Presumed Cardiovascular		
E3302034	T-90mg bd	CV Death	Death due to Cerebrovascular event		Death due to non-hemorrhagic stroke
E3312070	T-90mg bd	Non-CV Death		Malignancy	
E5520013	T-90mg bd	CV Death	Sudden cardiac death		
E5710019	T-90mg bd	Non-CV Death		Malignancy	
E6714004	T-90mg bd	Non-CV Death		Infection (including sepsis)	
E6920019	T-90mg bd	CV Death	Sudden cardiac death		

Of note, none of the 9 subjects who both withdrew consent and died are included in this table. All of those subjects are appropriately included in the 941 deaths that occurred prior to the CSED.

There appears to be a programming misnomer in the ADTTE dataset with respect to ACM. The ACM parameter subset of the ADTTE file demonstrates 21,162 rows, consistent with the FAS dataset, but encompasses only the 941 ACM events occurring prior to the CSED according to the RSYB raw adjudication data (it does not include the 30 cases in the table above that occurred following the CSED). The ADTTE parameter "time to all-cause mortality before or on the CSED demonstrates only 21,123 rows (as opposed to the 21,162 subjects in the FAS, a difference of 39 subjects, which equals the 9 subjects who withdrew consent and subsequently died before the CSED plus the 30 subjects that died after the CSED). There is no separate parameter in the ADTTE file for ACM occurring after the CSED. Thus, I interpret the ADTTE parameters as follows:

- *ACM: all-cause mortality to the CSED = 941*
- *ACM before or on the CSED: all-cause mortality to the CSED minus the 9 subjects who withdrew consent (they should be withheld from the CV death count, but not from the ACM count) = 932. The cases missing from that dataset include the 9 who withdrew consent then died before the CSED and the 30 who died following the CSED.*
- *ACM from randomization to the end of the study including the 30 additional cases that occurred following the CSED: not submitted in the ADTTE dataset=971.*
- *ACM between the day following the CSED and the last patient out: not submitted in the ADTTE dataset, but=30.*
- *Since most of the 30 deaths occurring after the CSED were CV per adjudication, (6/10 for placebo, 6/10 for t-60, and 6/10 for t-90), the outcomes are fairly well simulated by the KM analyses of CV death occurring after the CSED, the data for which is in the ADTTE data file, and so the unaccounted for deaths in the post-CSED period are balanced at only 4, 4, and 3 cases the for placebo, t-60, and t-90 respectively.*

6.1.6 Other Endpoints

Time to Stent Thrombosis

Stent thrombosis was defined according to Academic Research Consortium Definitions as follows:[5]

- Possible – all unexplained deaths occurring at least 30 days after the procedure
- Probable - unexplained deaths within 30 days after the procedure or acute myocardial infarction involving the target-vessel territory without angiographic confirmation
- Definite – acute coronary syndrome with angiographic or autopsy evidence of thrombus or occlusion

Stent thrombosis was adjudicated in PEGASUS, including angiographic images. Stent thrombosis was either attributed to either:

- A stent implanted before randomization – efficacy variable calculated from date of randomization

5 Mauri L, Hsieh WH, Massaro JM, Ho KK, D'Agostino R, Cutlip DE. Stent thrombosis in randomized clinical trials of drug-eluting stents. N.Engl.J.Med. 2007; 356(10):1020-1029.

- A stent implanted after randomization – time to stent thrombosis calculated from date of stent implantation.

For patients with more than one stent and stent thrombosis not attributable to a specific stent, it was assumed to have occurred in the most recently implanted stent.

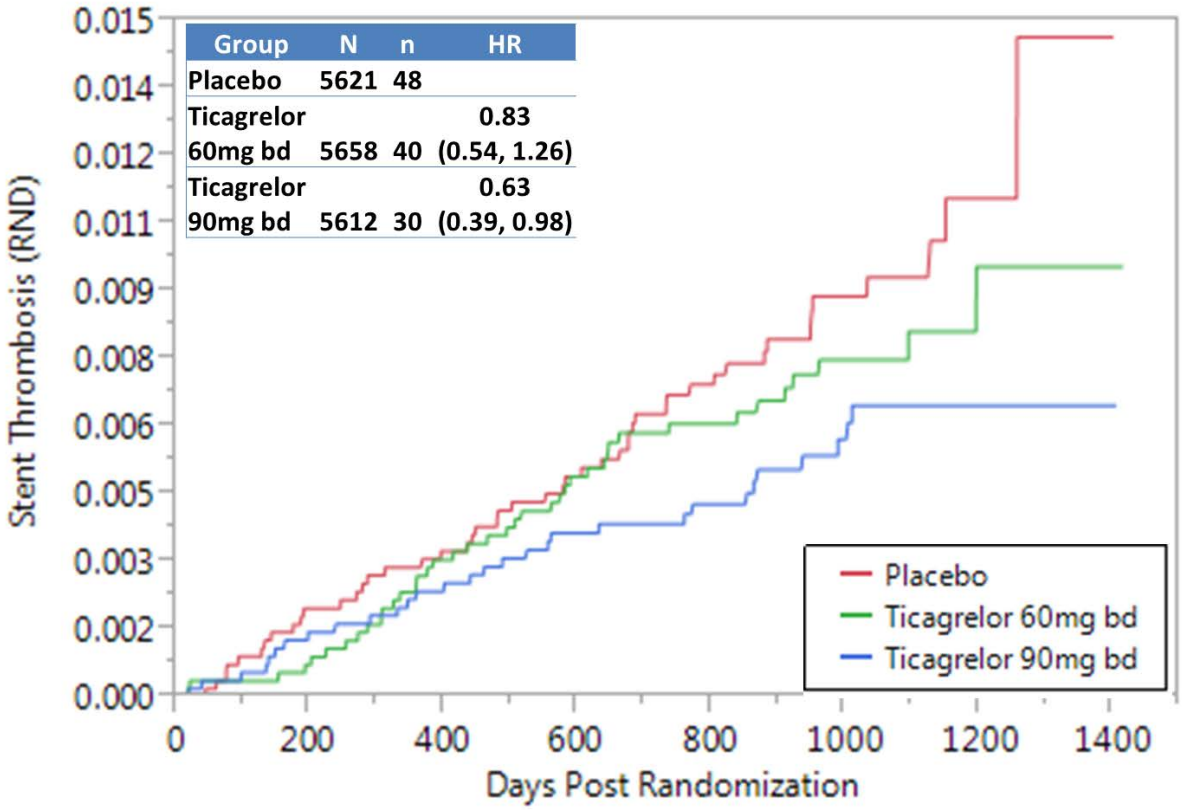
For the analysis of stent thrombosis results, the sponsor reports the combined results for pre-existing stents at randomization and newly placed stents: a numerical reduction in the rate of coronary stent thrombosis for both ticagrelor doses compared with placebo: 36% RRR, HR 0.64 (95% CI 0.41, 1.00) for 90 mg, and 18% RRR, HR 0.82 (95% CI 0.54, 1.23) for 60 mg, per the sponsor's table below:

Table 19. Sponsor analysis of time to first stent thrombosis (all stents, FAS, PEGASUS CSR 133/9148)

	Ticagrelor 90 mg bd N = 7050				Ticagrelor 60 mg bd N = 7045				Placebo N= 7067	
Characteristic	Patients (%) with events	KM %	HR (95% CI)	p-value	Patients (%) with events	KM %	HR (95% CI)	p-value	Patients (%) with events	KM %
Patients with a history of coronary stent implantation or receiving a stent during the study	5651				5695				5661	
Stent thrombosis	32 (0.6%)	0.6%	0.64 (0.41, 1.00)	0.0499	41 (0.7%)	0.8%	0.82 (0.54, 1.23)	0.3328	50 (0.9%)	0.9%

Because patients receiving a stent during PEGASUS were either treated with DAPT with a study drug interruption per the discretion of the investigator, or with PLATO-type blinded dosing of either ticagrelor (90 mg bd) or clopidogrel (75 mg od) per the modified dosing algorithm (see section 5.3.1.4, Trial Design), it was the opinion of this reviewer that the more relevant analysis was for the occurrence of stent thrombosis in patients taking the PEGASUS dose of ticagrelor compared to placebo involving stents that were in place at the time of randomization. The Clinical Efficacy Reviewer's reanalysis of this population demonstrated that all but five patients fell into this category (stents implanted before randomization), with a subject count difference of only 1 or 2 patients across the groups compared to the sponsor analysis, as shown in the figure below:

Figure 16. PEGASUS time to first stent thrombosis (stents already implanted at randomization, Sources: FDA Clinical Efficacy Reviewer, ADTTE)



In this small sample of patients, for stents in place at randomization, a non-significant numerical reduction in the rate of coronary stent thrombosis for the 90 mg bd dose of ticagrelor compared to the 60 mg bd dose of ticagrelor is suggested, with a 24% RRR, HR 0.76 (95% CI 0.47, 1.21) in favor of the higher ticagrelor dose.

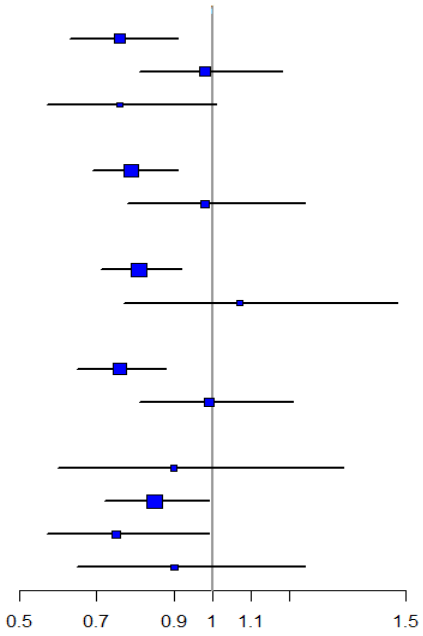
6.1.7 Subpopulations

Primary Efficacy Composite by gender, weight, race

Subgroup analyses generated by the FDA Statistical Reviewer confirmed the sponsor's finding that the point estimate for the HR of the PCE in PEGASUS for subjects taking the 60 mg bd dose was approximately unity for those between the ages of 65-75, females, non-Caucasians, and those with a BMI $\geq$ 30 kg/m^2 (HR = 0.98, 0.98, 1.07, and 0.99, respectively), per the following figure:

Table 20. PEGASUS PCE, demographic subgroups (60 mg vs. PBO) (Sources: FDA Statistical Reviewer, FAS to CSED)

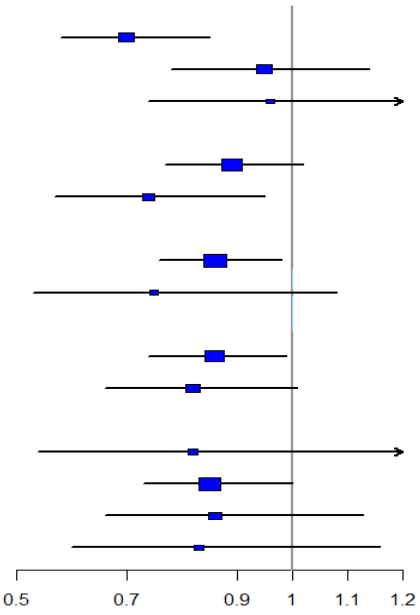
	HR	95% CI	Ticag60	Pbo
Age				
<65	0.76	(0.63, 0.91)	195/3283	243/3154
65-75	0.98	(0.81, 1.18)	209/2913	225/3074
>75	0.76	(0.57, 1.01)	83/849	110/839
Sex				
Male	0.79	(0.69, 0.91)	351/5384	435/5350
Female	0.98	(0.78, 1.24)	136/1661	143/1717
Race				
White	0.81	(0.71, 0.92)	411/6077	509/6124
Not White	1.07	(0.77, 1.48)	76/968	69/943
BMI				
<30	0.76	(0.65, 0.88)	290/4692	391/4827
>=30	0.99	(0.81, 1.21)	194/2335	186/2223
Region				
Asia/Australia	0.9	(0.60, 1.34)	46/788	51/788
Europe/S Afr	0.85	(0.72, 0.99)	286/4146	336/4154
N America	0.75	(0.57, 0.99)	87/1297	115/1303
S America	0.9	(0.65, 1.24)	68/814	76/822



The results for these four subgroups appeared to be somewhat better for the 90 mg ticagrelor dose, with point estimates for the HR of the composite primary endpoint for those aged 65-75, females, non-Caucasians, and those with a BMI $\geq$ 30 kg/m^2 trending lower (HR = 0.95, 0. 74, 0.75, and 0.82, respectively), per the following figure:

Table 21. PEGASUS PCE, demographic subgroups (90 mg vs. PBO) (Sources: FDA Statistical Reviewer, FAS to CSED)

	HR	95% CI	Ticag90	Pbo
Age				
<65	0.7	(0.58, 0.85)	174/3190	243/3154
65-75	0.95	(0.78, 1.14)	206/2977	225/3074
>75	0.96	(0.74, 1.25)	113/883	110/839
Sex				
Male	0.89	(0.77, 1.02)	389/5368	435/5350
Female	0.74	(0.57, 0.95)	104/1682	143/1717
Race				
White	0.86	(0.76, 0.98)	442/6126	509/6124
Not White	0.75	(0.53, 1.08)	51/924	69/943
BMI				
<30	0.86	(0.74, 0.99)	330/4731	391/4827
>=30	0.82	(0.66, 1.01)	160/2307	186/2223
Region				
Asia/Australia	0.82	(0.54, 1.23)	42/793	51/788
Europe/S Afr	0.85	(0.73, 1.00)	287/4128	336/4154
N America	0.86	(0.66, 1.13)	100/1307	115/1303
S America	0.83	(0.60, 1.16)	64/822	76/822



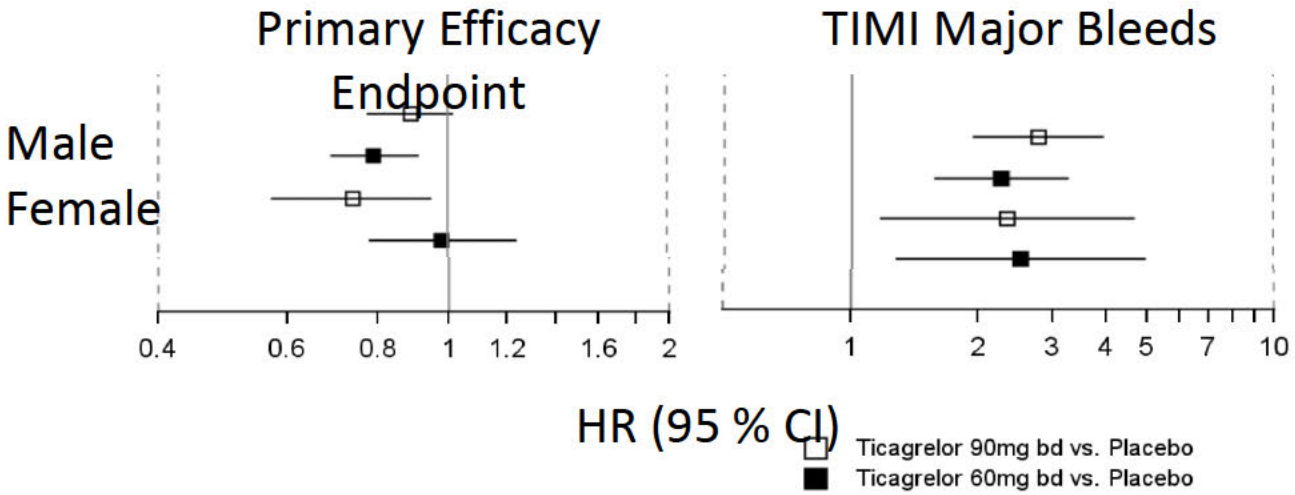
It should be noted that for age 65-75, non-Caucasian race, and high BMI, the confidence intervals for the point estimate of the HR for the treatment effect of 90 mg bd ticagrelor on the PCE results of PEGASUS continue to cross unity, and there is an asolute reversal of the relative treatment effect between men and women compared to the 60 mg bd ticagrlor dose. This pattern of findings in an analysis with no control for multiplicity suggests that these results may be chance findings, so the review team began to explore elements of these results in detail to see if other explanations might be found to suggest otherwise. To begin, baseline patient characteristics were examined as a function of sex and dose group, which were in fact balanced, as seen in the table below:

Table 22. PEGASUS subject characteristics by dose and sex (Sources: FDA clinical pharmacology reviewer, Exposure-Response set to CSED)

	F60 (N=1639)	F90 (N=1664)	M60 (N=5321)	M90 (N=5326)
Age in years (SD)	67.9 (8.4)	68.0 (8.2)	64.3 (8.2)	64.5 (8.3)
BW in Kg (SD)	73.1 (16.4)	73.4 (16.5)	84.7 (16.6)	84.5 (17.1)
BMI in Kg/m^2 (SD)	28.9 (5.8)	28.8 (7.9)	28.2 (7.0)	28.1 (6.7)
Asians (%)	8.6	8.3	11.6	11.2
Current Smokers (%)	13.2	12.8	18.3	18.2
Former Smokers (%)	27.2	29.2	55.0	54.3
Never Smoked (%)	59.5	57.9	26.7	27.5
Hypertension (%)	84.2	85.8	75.4	74.9
History of MI (%)	15.3	14.6	16.9	16.7
Diabetes (%)	37.0	37.3	31.5	30.0
PAD (%)	5.6	4.7	5.1	5.4
Unstable angina (%)	36.6	35.3	30.2	29.2
STEMI (%)	48.4	47.4	54.9	55.3

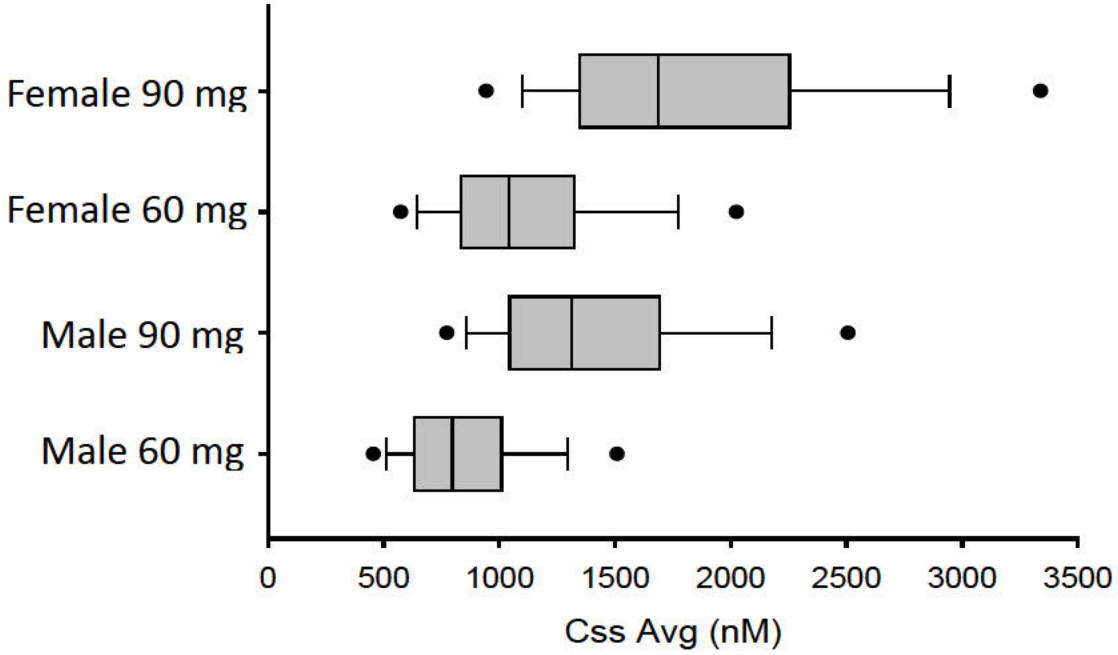
As an additional clinical/PD assessment, the occurrence of major bleeding by sex and by dose, was examined to assess whether female patients taking the lower 60 mg dose of ticagrelor demonstrated lessor pharmacodynamic impact, compared to the 90 mg bd dose, with respect to the occurrence of TIMI major bleeding events. This was in fact not the case, as female subjects given ticagrelor 60 mg bd experienced a TIMI major bleeding rate that was equal to, if not higher than female patients assigned to receive ticagrelor 90 mg bd, as shown in the figure below:

Figure 17. Pre-specified TIMI major bleeding analysis by sex and dose (sponsor analysis, SS)



Examination of average steady state concentrations of ticagrelor plus its active metabolite by dose and sex demonstrates the female subjects demonstrate higher average C_{ss} values than do their male counterparts for both doses of ticagrelor, as shown in the figure below:

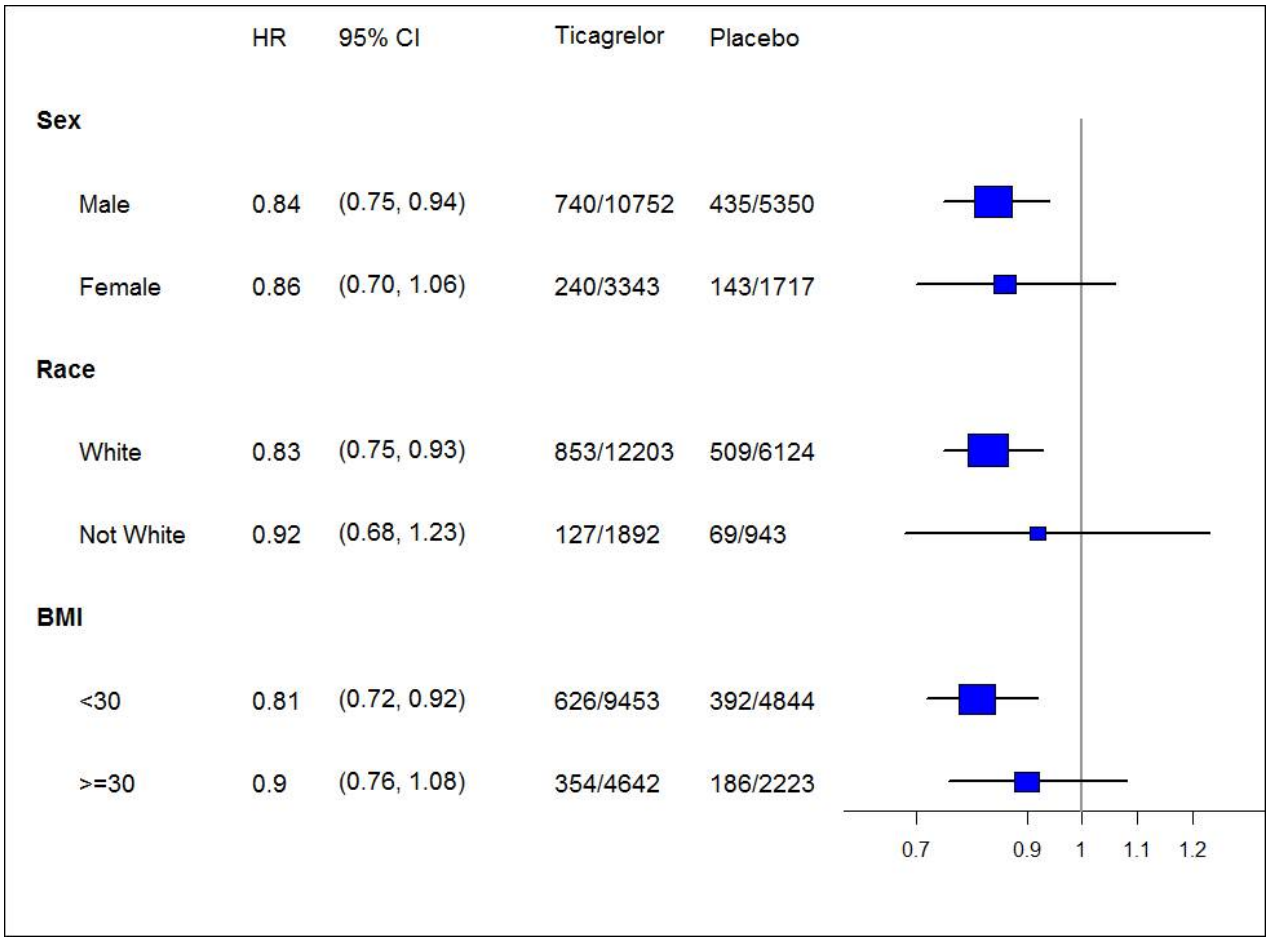
Figure 18. Observed avg Css of ticagrelor and its active metabolite by dose and by sex (Source: FDA Clinical Pharmacology)



Group	M60	M90	F60	F90
Median C_{ss} (nM)	796	1314	1040	1688
Avg BW (kg)	87	86	76	75
Avg Age (yrs)	64	64	67	67

Finally, a combined all-ticagrelor versus placebo analysis from PEGASUS demonstrates similar responses comparing male and female subjects, Caucasian and non-Caucasian subjects, and those with BMIs less than or greater than or equal to 30 kg/m^2, as shown in the figure below:

Figure 19. All ticagrelor versus placebo for the PEGASUS PCE (Source: FDA Statistical Reviewer, FAS to CSED)



Reviewer's comment: These analyses suggest that the subgroup findings in question are in fact chance findings among multiple sub-group analyses that are not controlled for multiplicity.

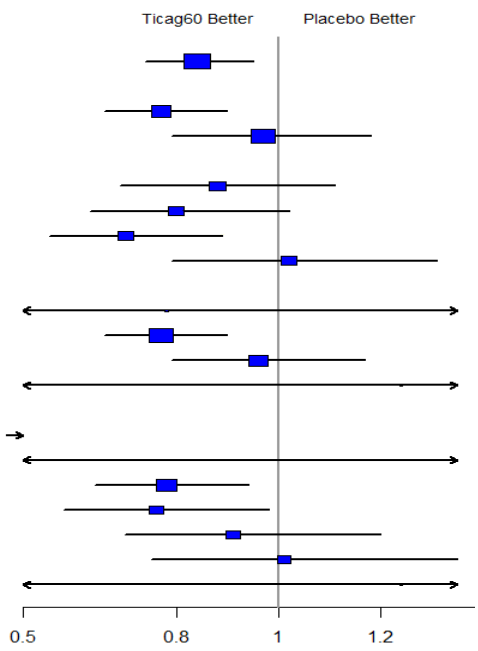
Primary efficacy composite by time from index myocardial infarction:

Subgroup analyses generated by the FDA Statistical Reviewer confirmed the sponsor's finding that the point estimate for the HR of the PCE in PEGASUS for subjects taking the 60 mg bd dose was approximately unity for subjects whose index (qualifying) MI occurred greater than or equal to 2 years prior to randomization in PEGASUS, in

contrast to those whose index MI had occurred less than 2 years preceding randomization who demonstrated nominally significant reduction of PCE outcomes (HR = 0.97 versus 0.77, respectively), a trend that was reproduced in quartile, annual, and semiannual time-cut analyses, per the figure below:

Figure 20. PEGASUS PCE, subgroups by Time from Qualifying MI (60 mg vs. PBO) (Sources: FDA Statistical Reviewer, FAS to CSED)

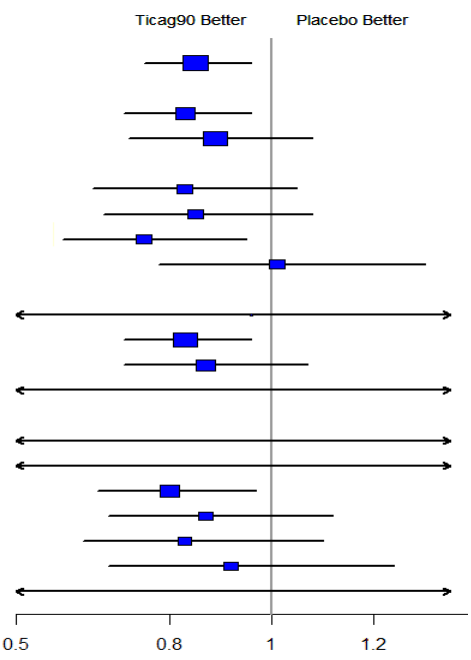
	HR	95% CI	Ticag60	Placebo
Overall	0.84	(0.74, 0.95)	487/7045	578/7067
by 2 years				
< 2 yrs	0.77	(0.66, 0.90)	292/4337	376/4338
>=2yrs	0.97	(0.79, 1.18)	195/2708	202/2729
by quartiles				
<=14.9 M	0.88	(0.69, 1.11)	129/1768	147/1777
14.9-20.6M	0.8	(0.63, 1.02)	126/1782	151/1718
20.6-28M	0.7	(0.55, 0.89)	111/1734	161/1800
>28M	1.02	(0.79, 1.31)	121/1761	119/1722
Annually				
<1yr	0.78	(0.29, 2.07)	8/66	8/57
1-2yrs	0.77	(0.66, 0.90)	285/4277	368/4286
2-3yrs	0.96	(0.79, 1.17)	192/2677	200/2683
>3yrs	1.24	(0.18, 8.84)	2/35	2/41
SemiAnn				
<6M	0	(0.00, 0.00)	0/18	2/16
6-12M	0.96	(0.33, 2.78)	8/48	6/41
12-18M	0.78	(0.64, 0.94)	188/2732	238/2708
18-24M	0.76	(0.58, 0.98)	97/1545	130/1578
24-30M	0.91	(0.70, 1.20)	98/1363	110/1391
30-36M	1.01	(0.75, 1.35)	94/1304	90/1292
>36M	1.24	(0.18, 8.84)	2/35	2/41



Results for the ticagrelor 90 mg bd dose were directionally similar but the magnitude of the difference of treatment effect between those with a prior MI less than two years before randomization and those whose MI was at least 2 years prior to randomization was less impressive, as seen in the figure below:

Figure 21. PEGASUS PCE, subgroups by Time from Qualifying MI (90 mg vs. PBO) (Sources: FDA Statistical Reviewer, FAS to CSED)

	HR	95% CI	Ticag90	Placebo
Overall	0.85	(0.75, 0.96)	493/7050	578/7067
by 2 years				
< 2 yrs	0.83	(0.71, 0.96)	313/4320	376/4338
>=2yrs	0.89	(0.72, 1.08)	180/2730	202/2729
by quartiles				
<=14.9 mon	0.83	(0.65, 1.05)	126/1819	147/1777
14.9-20.6 mon	0.85	(0.67, 1.08)	130/1720	151/1718
20.6-28 mon	0.75	(0.59, 0.95)	118/1743	161/1800
>28 mon	1.01	(0.78, 1.30)	119/1768	119/1722
Annually				
<1yr	0.96	(0.35, 2.64)	7/51	8/57
1-2yrs	0.83	(0.71, 0.96)	306/4276	368/4286
2-3yrs	0.87	(0.71, 1.07)	176/2682	200/2683
>3yrs	2.27	(0.42, 12.40)	4/41	2/41
SemiAnn				
<6M	1.83	(0.31, 10.96)	3/14	2/16
6-12M	0.68	(0.19, 2.42)	4/37	6/41
12-18M	0.8	(0.66, 0.97)	198/2773	238/2708
18-24M	0.87	(0.68, 1.12)	108/1503	130/1578
24-30M	0.83	(0.63, 1.10)	93/1397	110/1391
30-36M	0.92	(0.68, 1.24)	83/1285	90/1292
>36M	2.27	(0.42, 12.40)	4/41	2/41

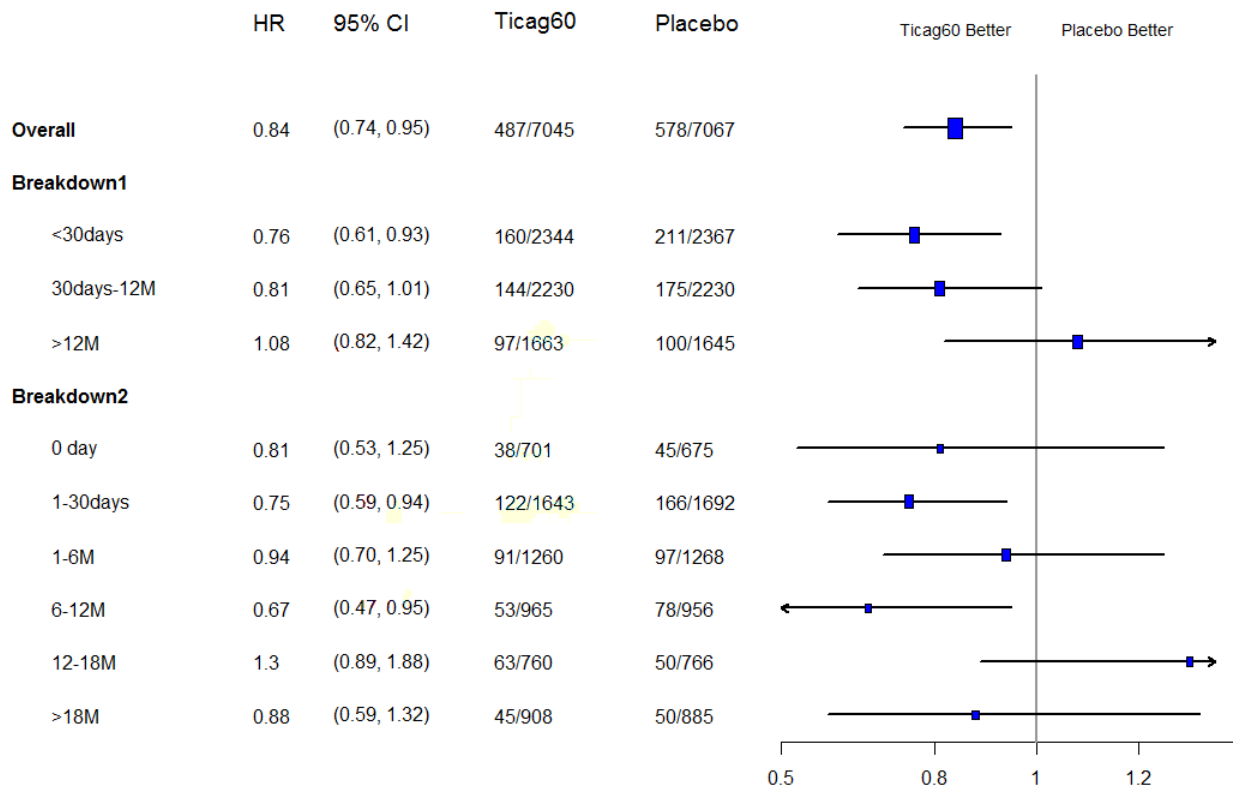


Reviewer's comment: this result suggests that those who are longer-term survivors from MI may not benefit from the addition of ticagrelor to daily aspirin therapy for the secondary prevention of MACE. Of note, the same conclusion cannot be applied to the subject who transitioned directly from DAPT to PEGASUS-indication dosing of ticagrelor for an additional year (total DAPT therapy 2 years) as rationale for stopping DAPT, as MACE events may occur in this population on discontinuing DAPT.

Efficacy by time since last ADP receptor blocker therapy:

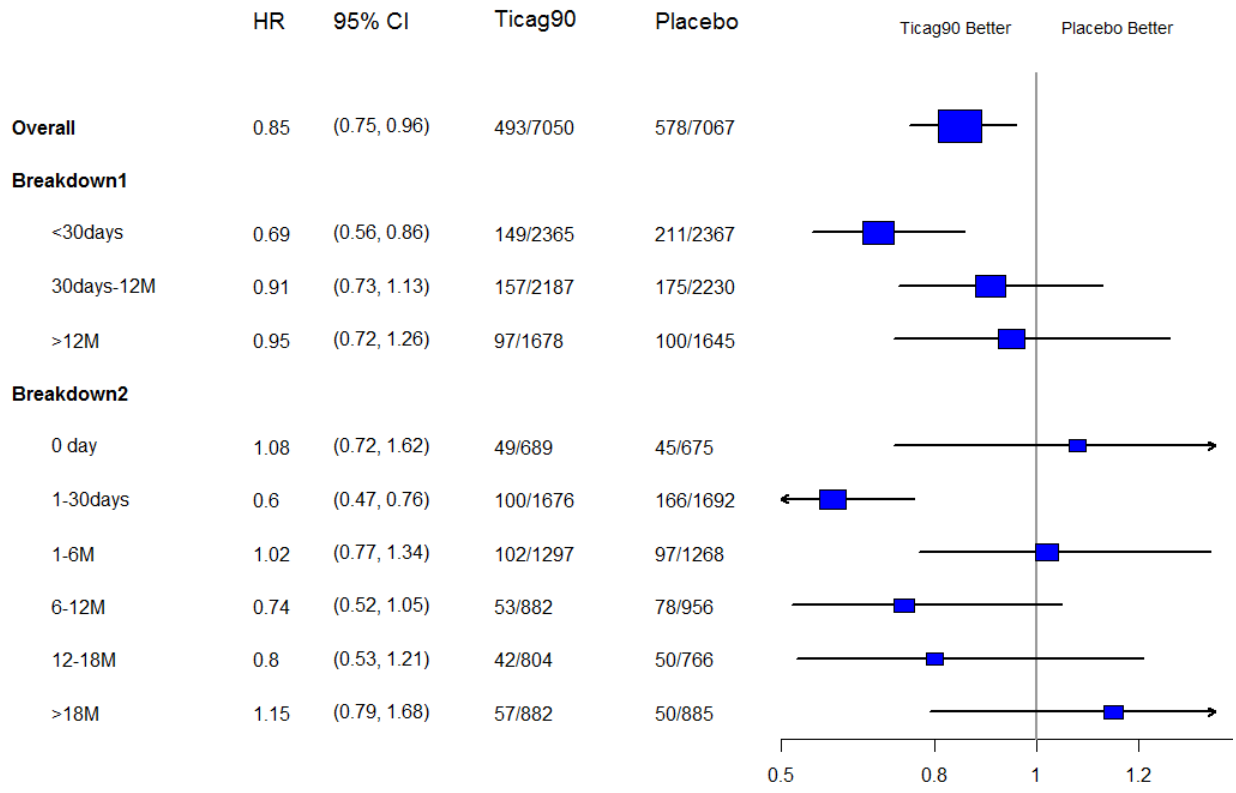
Subgroup analyses generated by the FDA Statistical Reviewer confirmed the sponsor's finding that the point estimate for the HR of the PCE in PEGASUS for subjects taking the 60 mg bd dose was greater than unity for subjects whose prior dosing with an ADP receptor blocker occurred more than 12 months prior to randomization in PEGASUS, in contrast to those whose last dose of ADP receptor blocker occurred within the prior 30 days to 12 months, or within the prior 30 days before randomization into PEGASUS (HR = 1.08, 0.81, 0.76, respectively).

Figure 22. PEGASUS PCE, subgroups by time since last ADP receptor blocker (60 mg vs. PBO) (Sources: FDA Statistical Reviewer, FAS to CSED)



Of note, a similar finding is seen with the ticagrelor 90 mg bd dose, with even less impressive efficacy results for those whose last ADP receptor blocker dose was taken between 30 days and 12 months prior to randomization into PEGASUS, as seen in the figure below:

Figure 23. PEGASUS PCE, subgroups by time since last ADP receptor blocker (90 mg vs. PBO) (Sources: FDA Statistical Reviewer, FAS to CSED)



Reviewer's comment: this finding supports and is supported by the finding that increasing time from the index MI results in diminished efficacy trends with respect to MACE reduction with PEGASUS-dosing of ticagrelor, because it is those patients with more distant MIs that will have the greatest duration of time elapse between their prior dose of ADP receptor blocker and randomization into PEGASUS.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

There is no demonstrable efficacy advantage of ticagrelor 90 mg bd for the sought indication as compared to the ticagrelor 60 mg bd dose.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

PEGASUS was in fact a trial of persistent efficacy in the secondary prevention of MACE events. Comparing 60 mg ticagrelor bd to placebo, the KM curves for the occurrence of

MACE, MACE components, and ACM appear to continue to separate over the duration of the trial.

6.1.10, Additional Efficacy Issues/Analyses

Atrial Fibrillation and Pulmonary Emboli

The Need for chronic oral anticoagulant therapy or chronic low-molecular-weight heparin (at venous thrombosis treatment not prophylaxis doses) were exclusions to enrollment in PEGASUS. Accordingly, the benefit-risk assessment of this review cannot be extrapolated to patients with a history of MI that occurred at least one year ago, who are at high-risk for recurrent atherothrombotic events, and who require oral, subcutaneous, or intravenous anticoagulation for the treatment of atrial fibrillation or venous thromboembolic events (deep venous thrombosis and/or pulmonary emboli).

Patients that have major bleeding on DAPT in the year following MI

Patients with a known bleeding diathesis or coagulation disorder, and patients with any condition which in the opinion of the investigator would have made enrollment into PEGASUS unsafe, were all excluded from PEGASUS. These exclusions very effectively kept patient out of PEGASUS who had previously stopped an ADP receptor blocker due to bleeding, per the table below (adapted from sponsor table:

Table 23. Reason prior ADP receptor blocker stopped (Sources: Sponsor FSR Table 17 p 98/9148, FAS)

Reason Stopped	Ticagrelor 90 bd N=7050	Ticagrelor 60 bd N=7045	Placebo N=7067
Bleeding	9 (0.1%)	9 (0.1%)	9 (0.1%)

Accordingly, the benefit-risk assessment of this review cannot be extrapolated to patients with a history of bleeding that was severe enough to warrant discontinuation of their prior ADP receptor blocker.

PEGASUS Results for the USA

The efficacy results for PEGASUS in the US population were similar directionally to the overall trial for the 60 mg bd dose group, the outcomes directionally favoring ticagrelor 60 mg bd relative to both placebo and ticagrelor 90 mg bd for the PCE, any CV death, any MI, and any stroke, as seen in the following four KM analyses for these four outcomes in the US population of PEGASUS:

Figure 24. USA-PEGASUS primary composite efficacy endpoint (time to first occurrence of CV Death, MI, or stroke). FAS to CSED (FDA Clinical Efficacy Reviewer, ADTTE-Efficacy Endpoints-Primary-Country-USA)

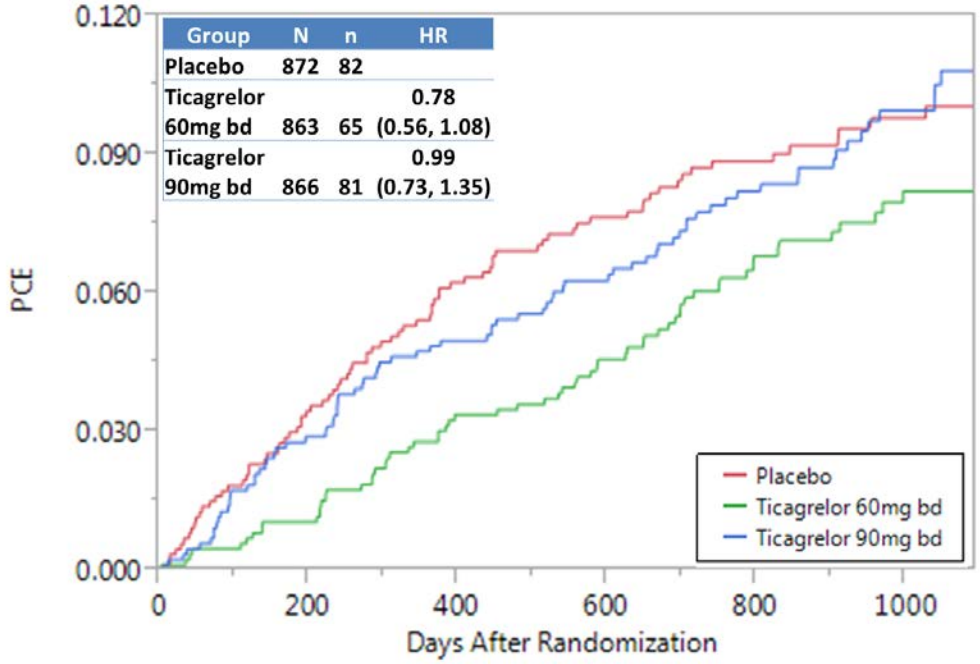


Figure 25. USA-PEGASUS Any CV Death. FAS to CSED (FDA Clinical Efficacy Reviewer, ADTTE-Efficacy Endpoints-CVDeath-Country-USA)

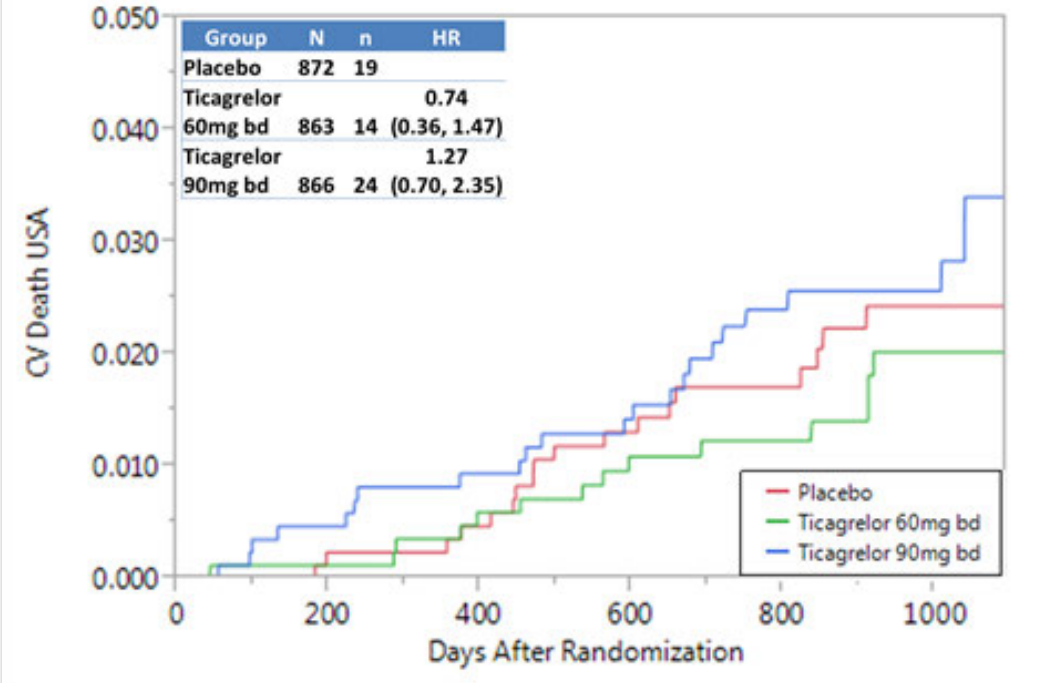


Figure 26. USA-PEGASUS Any MI. FAS to CSED (FDA Clinical Efficacy Reviewer, ADTTE-Efficacy Endpoints-MI-Country-USA)

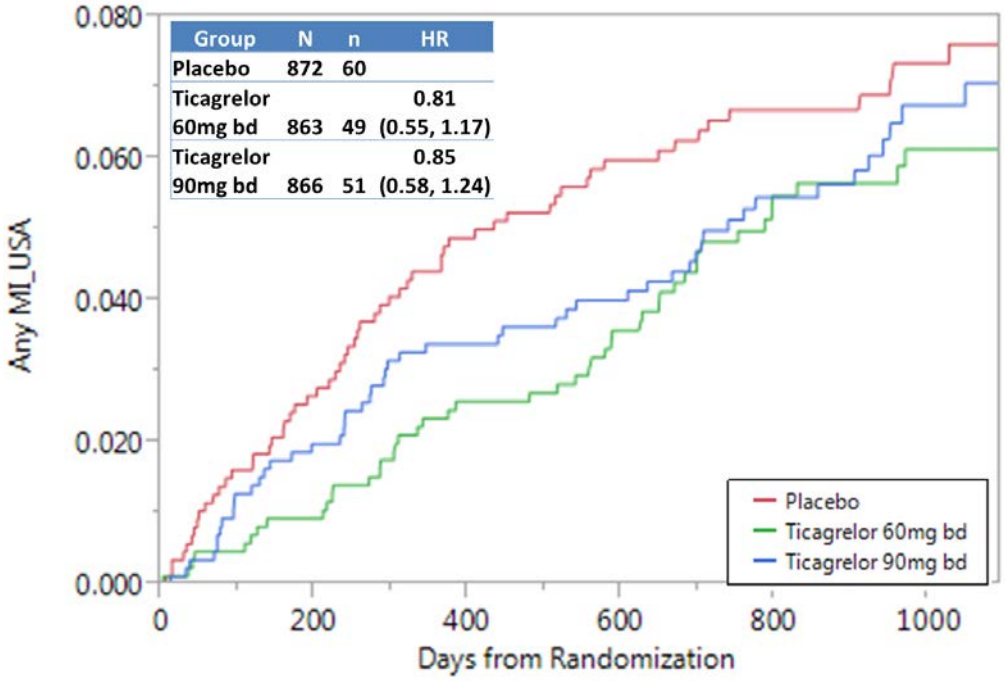
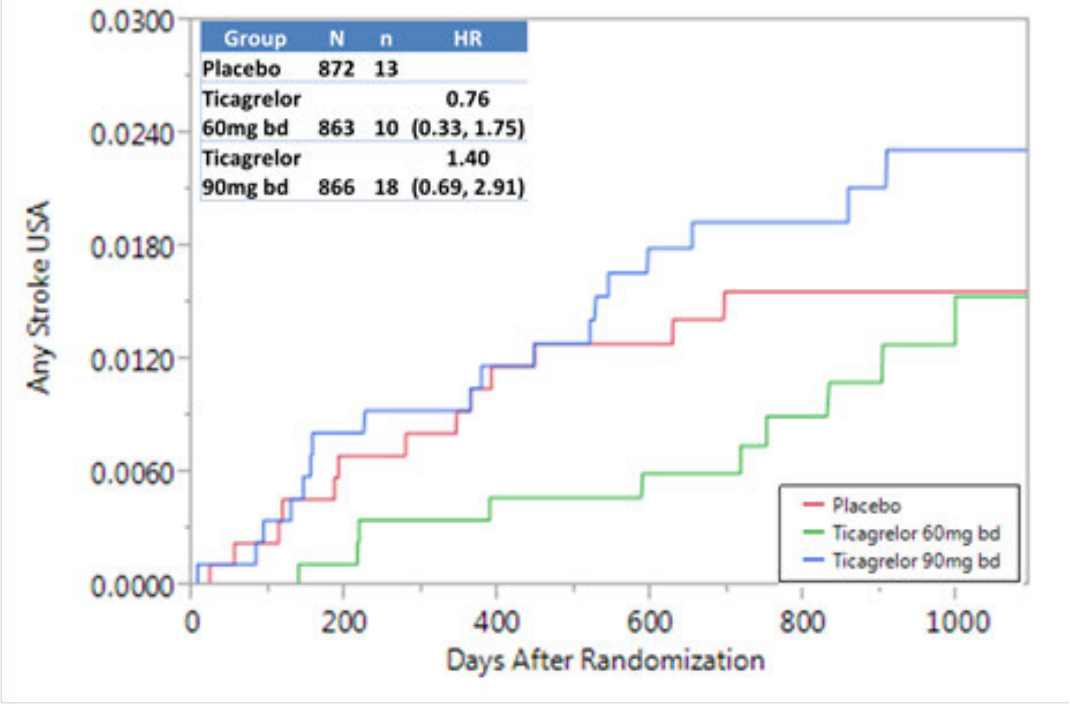


Figure 27. USA-PEGASUS Any Stroke. FAS to CSED (FDA Clinical Efficacy Reviewer, ADTTE-Efficacy Endpoints-Stroke-Country-USA)



PEGASUS results by premature discontinuation

To explore the effect of ticagrelor discontinuation on MACE, we did an exploratory analysis of MACE rate after premature discontinuation (during the trial and before the CSED) and after the CSED. In Table 24 one can see that there was little difference in MACE among the treatment groups if discontinuation occurred prematurely. If anything, the MACE rate remained lower for the ticagrelor groups than for the placebo group. This pattern changed for those subjects who discontinued treatment after the CSED. This might lead one to think that there could be a rebound effect, meaning increased MACE over what would occur if they had never been treated with ticagrelor. One argument against a rebound effect is that one would expect to see the same rebound effect during premature cessation of ticagrelor if there was a rebound effect. Limitations of the post-CSED analysis is that 1) it was a short period of observation (only 2 months maximum); and 2) the subjects were highly selected in that they had to have made it through the trial without an endpoint event. Perhaps these are the subjects who are benefitting most from the ticagrelor and taking them off of it makes them more susceptible to an event.

Table 24: MACE rate after treatment cessation during trial and after CSED (safety set)

	Placebo			Ticagrelor 60 mg bd			Ticagrelor 90 mg bd		
PERIOD	number of MACE events	Exp time in years	Event rate (%/yr)	Number of MACE events	Exp time in years	Event rate (%/yr)	Number of MACE events	Exp time in years	Event rate (%/yr)
All subjects with MACE During Trial (on Tx)	465	16072	2.9	337	14796	2.2	322	14070	2.3
Subjects who had events following premature discontinuation of study drug	136	2428	5.6	174	3702	4.7	198	4400	4.5
After CSED (off Tx)	10	263.9	3.8	17	237.4	7.2	14	226.4	6.2

Source: Reviewer's analysis: RSYB dataset.

7 Review of Safety

Safety Summary

In PEGASUS, a total of 20942 subjects (99% of randomized subjects) received at least 1 dose of randomized study drug (ticagrelor or placebo) on a background of ASA: 6988, 6958, and 6996 in the ticagrelor 90 mg, ticagrelor 60 mg, and placebo groups, respectively. The majority of subjects were treated for at least 24 months, with a maximum duration of exposure of 48 months. The mean age of patients was ~65 years and ~ ¾ of the enrolled population was male. Treatment groups were evenly matched for baseline demographic features. The length of exposure and numbers of patients exposed to ticagrelor at the doses or larger than the doses that the applicant is planning to market for this new indication provides confidence about the reliability of the results of the safety analysis.

There were more discontinuations in the ticagrelor groups than in the placebo groups which resulted in slightly lower exposure to ticagrelor than to placebo. For the ticagrelor 90 mg, ticagrelor 60 mg, and placebo groups, mean total duration of exposure to study drug (first dose to last dose) was 23.9, 25.3, and 27.3 months. Total duration of exposure to ticagrelor (from first dose to last dose) ranged from 0 to a maximum of 48.0 months. The increased rate of discontinuation of study drug was mostly because of AEs. Very few patients withdrew consent. Therefore, most were followed for the duration of the study for purposes of capturing endpoint events and AEs. The most commonly reported AEs that resulted in discontinuation were dyspnea and increased tendency to bruise and epistaxis.

As with other antiplatelet therapies, the major risk of ticagrelor is bleeding. Other risks were relatively rare and are discussed in sections 7.34 and 7.3.5. TIMI major bleeding, the primary safety endpoint, defined as any intracranial bleeding or clinically overt signs of hemorrhage associated with a fall in Hb ≥ 5 g/dL or fatal bleeding (major bleed resulting in death within 7 days) is the only risk of treatment that is included in the benefit-risk analysis.

TIMI Major bleeding occurred in 1.8%, 1.7% and 0.8% of subjects on ticagrelor 90 mg, ticagrelor 60 mg and placebo (aspirin alone), respectively. KM percentages for TIMI Major bleeding were 2.6%, 2.3% and 1.1%, respectively. Most notably, the incidence of fatal bleeding was similar among treatment groups; 0.1%, 0.2% and 0.2% of subjects, respectively. KM percentages for fatal TIMI major bleeding were 0.1%, 0.3% and 0.3%, respectively. The nearly 2% reduction in MACE (less hemorrhagic infarct) in the ticagrelor arms puts the 1% increase in TIMI Major bleeding into better perspective, particularly because the fatal bleeding rate was no higher in the ticagrelor arms than

with placebo. Gastrointestinal bleeding was the most common type of TIMI Major bleeding.

The bleeding profile of ticagrelor 60 mg was consistent across multiple subgroups with the exception of a few outlier subgroups with small numbers. See Section 1.2, as well as Table 35 and Table 36.

Altogether there were 961 deaths in the safety population (those subjects who received at least one dose of their actual treatment), including 30 that occurred after the CSED. All-cause mortality trended toward being improved in the ticagrelor 60 mg bd group compared to placebo (safety set). CV death favored ticagrelor 60 mg bd in the safety set (shown for the 60 mg bd dose in Figure 28). There was a trend favoring CV death for the 90 mg bd dose (APPENDIX 3, Figure 47).

There was a favorable trend for all-cause mortality for the 60 mg ticagrelor dose, but there was no trend favoring all-cause mortality for the 90 mg ticagrelor dose. In fact, there was a trend for more non-CV deaths in the 90 mg ticagrelor group. In all there were 115, 116 and 145 non-CV deaths in the placebo, ticagrelor 60 mg and ticagrelor 90 mg treatment groups, respectively. Malignancy and infection were the most common causes for the excess mortality in the ticagrelor 90 mg bd arm, both common causes for death in the elderly. Malignancy deaths were higher in both ticagrelor arms, and this accounts for most of the non-CV deaths. In fact, there were nominally statistically significant more neoplasm deaths in the ticagrelor 90 mg bd arm than in the placebo arm. See APPENDIX 3 (Figure 49) for a K-M of the neoplasm-related deaths comparing ticagrelor 90 mg bd to placebo. The difference in the neoplasm-related deaths between the ticagrelor 60 mg bd and placebo was smaller and not statistically significant. This observation prompted analyses of neoplasms in both of the large ticagrelor trials, PEGASUS and PLATO. Excluding squamous cell carcinoma of the skin, the event rate for malignancy was 1.3%/yr for placebo, 1.5%/yr for ticagrelor 60 mg bd and 1.8%/yr for ticagrelor 90 mg bd. When excluding all non-melanoma skin cancers (basal cell carcinomas also) the average annual rate was 1.16%/year, 1.22%/year and 1.3%/year for the 3 groups, respectively.
In PLATO the event rate for malignancy excluding squamous cell carcinoma of the skin in both the ticagrelor 90 mg bd and clopidogrel 75 mg od arms were ~ 2.1%/yr and this was a much shorter study (average exposure time in PLATO and PEGASUS were ~ 9 months and 2 years, respectively).
The neoplasm signal is discussed in depth in section 7.3.5. In the end, this reviewer believes that the data do not convincingly support an exposure-mediated effect of ticagrelor on neoplastic potential/ carcinogenicity.

Other safety findings of interest are discussed in depth in section 7.3.4. As shown in PLATO, ticagrelor caused dyspnea in PEGASUS as well. However, on a reassuring note, as was shown in PLATO, dyspnea resolved upon discontinuation and there were

no increases in more serious dyspnea related serious adverse events such as cardiac arrest, respiratory failure, acute respiratory distress syndrome, postoperative respiratory failure, or hypoxia in PEGASUS.

Bradycardia was an AE of interest because it was reported in 4.3% of ticagrelor–exposed subjects in PLATO (4.0% in clopidogrel-exposed subjects). Many fewer in PEGASUS, 59 (0.8%), 71 (1.02%) and 57 (0.8%), had bradycardia AEs during the on-treatment period (up to 7 days post discontinuation) in the placebo, ticagrelor 60 mg and ticagrelor 90 mg treatment groups, respectively. The change from baseline of heart rate in PEGASUS was not apparently different in any of the treatment groups. As for bradycardia SAEs in PEGASUS, although the numbers are small, there were notably more events in the ticagrelor arms than in the placebo arm [14 (0.2%) for both of the ticagrelor arms and 6 (0.09%) for the placebo arm]. However, there was no greater incidence of sick sinus syndrome, sinus block or sleep apnea and just a minor increase in syncope and near-syncope [(119(1.7%), 105 (1.5%) and 87 (1.2%)] for ticagrelor 60 mg bd, ticagrelor 90 mg bd, and placebo, respectively. This is reassuring because bradycardia occurred commonly in PLATO and a Holter substudy in PLATO confirmed the increased frequency of ventricular pauses and other cardiac arrhythmias, particularly at night time raising the possibility that ticagrelor could worsen sleep apnea.

An important limitation of both the PLATO and PEGASUS studies is that patients with an increased risk of bradycardic events (e.g., those with a pacemaker and known sick sinus syndrome, second or third degree AV block or previous documented syncope suspected to be due to bradycardia unless treated with a pacemaker) were excluded from the studies. Therefore, it is not known if ticagrelor might cause worsening of these heart block conditions. After reviewing the current label I noted that there is no current warning in the label about the potential for worsening heart block in patients with baseline high degree heart block. A warning pertaining to patients with known high degree heart block should be added to the label.

Because ticagrelor 90 mg bd was associated with a >50% increase in serum creatinine levels in 7.4% of subjects compared to 5.9% of subjects who received clopidogrel in PLATO, renal impairment is an adverse event of interest. Treatment groups in PLATO did not differ for renal-related serious adverse events such as acute renal failure, chronic renal failure, toxic nephropathy or oliguria. In PEGASUS, the incidence of subjects developing elevations in creatinine > 50% from baseline were 3.5%, 3.9% and 4.2% in the placebo, ticagrelor 60 mg bd and ticagrelor 90 mg bd groups, respectively. Renal AEs (elevated BUN or creatinine, anuria, acute renal failure, chronic renal failure and/or oliguria) occurred in ~ 2.5% of subjects in each treatment group during the on-treatment period (up to 7 days post-discontinuation). The risk of serious renal-related AEs (acute renal failure, anuria) was about 0.2 to 0.3% in each treatment group. The balance among treatment groups of acute renal failure confirmed the absence of a relationship between ticagrelor and acute renal failure.

It was shown in PLATO that uric acid levels increased approximately 0.6 mg/dL from baseline in subjects who were on ticagrelor, compared to an increase of approximately 0.2 mg/dL on clopidogrel, but no difference in gout AEs between treatment groups. In PEGASUS there were 117(1.67%), 168(2.4%) and 184 (2.63%) gout AEs in the placebo, ticagrelor 60 mg bd and ticagrelor 90 mg bd treatment groups, respectively, suggesting a dose relationship and a causal relationship between ticagrelor and gout. Also, there were 3 serious gout AEs in the ticagrelor 90 mg bd treatment group compared to 1 in each of the placebo and ticagrelor 60 mg bd treatment groups. The new ticagrelor label should include verbiage about the higher incidence of gout in patients on ticagrelor.

In PLATO there was a numerical difference in reports of gynecomastia between the treatment arms (0.23% of men on ticagrelor compared with 0.05% on clopidogrel). In PEGASUS, the number of reported AEs of gynecomastia was low and evenly distributed across the treatment groups: 11, and 8, 10 male patients in the placebo, ticagrelor 60 mg bd, and ticagrelor 90 mg bd groups, respectively. It appears now that it is unlikely that there is a causal relationship between ticagrelor and gynecomastia. Therefore, the common adverse events section of the label can be changed to remove gynecomastia.

Erythema multiforme was reported for 2 patients, one in each of the ticagrelor treatment groups. Both events were non-serious AEs. One (the subject in ticagrelor 90 mg) was discontinued from study drug. The event was considered “severe” and it was attributed by the investigator to ticagrelor. It is possible that ticagrelor had a causal role in these 2 cases. Because erythema multiforme is a rare condition that is often the result of immune complexes and there is known hypersensitivity reactions with ticagrelor, there should be some mention of this AE in the label.

There were 15 pulmonary fibrosis AEs: 5 patients in each treatment group. However, the only SAEs for pulmonary fibrosis of which there were 5 were in subjects on ticagrelor. Only one case was likely to have been caused by another drug (methotrexate). Therefore, there may be a causal relationship between ticagrelor in at least 4 of the 5 severe cases of pulmonary fibrosis, 2 of which resulted in death. In PLATO, there were several cases of non-serious pulmonary fibrosis reported (~30, ~0.3%) in both the ticagrelor arm and the clopidogrel arm; none were SAEs. Interstitial pneumonitis is a listed postmarketing AE in the clopidogrel label. Pulmonary fibrosis should be a listed AE in the ticagrelor label.

7.1 Methods

I used a combination of methods to conduct my review including JMP analyses, MAED, Jreview, and review of the applicant's documents. When appropriate I compared safety findings between the initial ticagrelor trial that won it approval for acute coronary syndrome (PLATO) and the current pivotal trial, PEGASUS.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety data from PEGASUS were the primary data used to evaluate safety. Other trials, including PLATO and initial Holter studies will be referred to as needed. There was one other new trial included in this NDA, D5130L00012; a clinical pharmacology study in Hispanic patients. It was brief (up to 18 days) and only enrolled 40 patients. There were no deaths, SAEs or discontinuations due to adverse events reported. Because this study was small, brief and had no concerning adverse events, it did not contribute to our understanding of safety and it will not be discussed further in this review.

7.1.2 Categorization of Adverse Events

MedDRA 17.0 was used to categorize adverse events. I used an FDA renaming tool to reclassify adverse events to bring out adverse event differences between active drug and placebo that might be obscured by "lumping" like terms together or "splitting" like terms. The tool is a JMP file that one joins with AE and demographic data files. It automatically reclassifies AEs (preferred MedDRA terms) into 262 categories. For instance, gout is in the "gout" category as well as the "gout and high uric acid" category. This is helpful for teasing out if gout by itself was more common in ticagrelor. A signal of gout and high uric acid might have obscured that gout itself was also more common in the ticagrelor arms. Another example is that the tool has one category "CHF or pulmonary edema". Often these AEs will be split because the former is considered in the cardiovascular SOC whereas the latter is considered in the pulmonary SOC. Having each categorized separately and also together increases the likelihood of detecting a heart failure signal. The list of categories is located in APPENDIX 6.

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

There were no other trials which were appropriate for pooling of safety data with PEGASUS data. (PLATO used an active comparator, clopidogrel, and the population of subjects was different in that they were immediately post-MI and had no history of ADP-blocker use).

7.2 Adequacy of Safety Assessments

With ~ 29,000 patient-years of safety data in the active treatment arms, there are adequate data for an adequate safety assessment. All pertinent safety questions in the population of patients studied and for the length of time they were studied (mean of 26 months) could be addressed with the data that were accumulated in this study.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In PEGASUS, a total of 20942 subjects (99% of randomized subjects) received at least 1 dose of randomized study drug (ticagrelor or placebo) on a background of ASA: 6988, 6958, and 6996 in the ticagrelor 90 mg, ticagrelor 60 mg, and placebo groups, respectively. The majority of subjects were treated for at least 24 months, with a maximum duration of exposure of 48 months.

Mean duration of exposure was lower on both ticagrelor 90 mg (23.9 months) and 60 mg (25.3 months) compared with placebo (27.3 months), reflecting the higher proportion of subjects who prematurely discontinued from study drug in the ticagrelor groups compared to placebo. This will be discussed further in section 7.3.3.

The demographic and baseline characteristics of the subjects in the safety analysis set were balanced across the randomized treatment groups. The mean age of the safety population was 65.3 years and 12.1% were aged over 75 years. Males constituted the majority (76.1%) of subjects, and mean weight was 82.0 kg. The treatment groups were also balanced with respect to use of concomitant medications.

A total of 15214 subjects completed treatment with study drug; the remaining 5728 subjects (27.4% of those treated) prematurely and permanently discontinued study drug. Subjects who prematurely and permanently discontinued treatment with study drug, but did not withdraw from the study were to be followed for SAEs and study endpoint events through the CSED unless they explicitly withdrew consent for follow-up which occurred in only ~ 0.6% of subjects. See Table 27 for a tabular listing of numbers of subjects who discontinued study drug and withdrew from the study.

7.2.2 Explorations for Dose Response

Dose-related AEs are discussed in Sections 7.3-7.5.

7.2.3 Special Animal and/or In Vitro Testing

Because this is a supplement, there were no new animal or in vitro studies submitted.

7.2.4 Routine Clinical Testing

The testing was done in a central laboratory and appeared to be adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

These issues were thoroughly analyzed and discussed in the original NDA clinical pharmacology review.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Ticagrelor is the only marketed drug in its chemical class, cyclopentyltriazolopyrimidines. It is an oral, direct acting, selective, and reversibly binding P2Y12 receptor antagonist that prevents adenosine diphosphate (ADP)-mediated platelet activation and aggregation. Ticagrelor does not prevent ADP binding, but when bound to the P2Y12 receptor, prevents ADP-induced signal transduction. Since platelets participate in the initiation and/or evolution of thrombotic complications of atherosclerotic disease, inhibition of platelet function has been shown to reduce the risk of cardiovascular events such as death, MI, or stroke.

Ticagrelor also has an additional mechanism of action (Nylander et al 2013), increasing local endogenous adenosine levels by inhibiting equilibrative nucleoside transporter-1 (ENT-1), which transports adenosine from extracellular fluid into cells. Adenosine is formed locally at sites of hypoxia and tissue damage through degradation of released adenosine tri- and di-phosphate (ATP and ADP). As adenosine degradation is essentially restricted to the intracellular space, inhibition of ENT-1 by ticagrelor prolongs the half-life of adenosine and thereby increases its local extracellular concentration, providing enhanced local adenosine responses. Adenosine has been documented to have a number of effects that include: vasodilation, cardioprotection, platelet inhibition, modulation of inflammation, and induction of dyspnea, which may account for certain aspects of the clinical profile of ticagrelor.

While the adverse event profile for ticagrelor would be expected to be different from that of the other marketed antiplatelet drugs because of its different mechanism of action, bleeding which results from the down-stream effects of the antiplatelet activity is a risk factor in common to all antiplatelet drugs. Bleeding will be discussed in the next several sections.

Neoplasm is another potential safety concern that was explored. The reason for the concern is that there is a signal for neoplasm in prasugrel, another approved antiplatelet therapy. FDA reviewer, Dr. Thomas Marciniak, noticed a 62% increase in new or worsening non-squamous cell, non-basal cell, non-brain solid cancers from his review of TRITON-TIMI 38 which compared clopidogrel to prasugrel. Whether or not this finding

might reflect ascertainment bias because of increased bleeding in patients on prasugrel is unknown. Despite the absence of a neoplasm signal in PLATO, the comparator of ticagrelor in that trial was clopidogrel which could have its own attendant risks for neoplasm and which may have obscured any increased risk of neoplasm with ticagrelor. In an attempt to understand any ticagrelor-related increase in neoplasm risk, I did an analysis of the PEGASUS safety data in wherein I compared the incidence of neoplasm in placebo and ticagrelor treatment arms. This analysis is described in section 7.3.5.

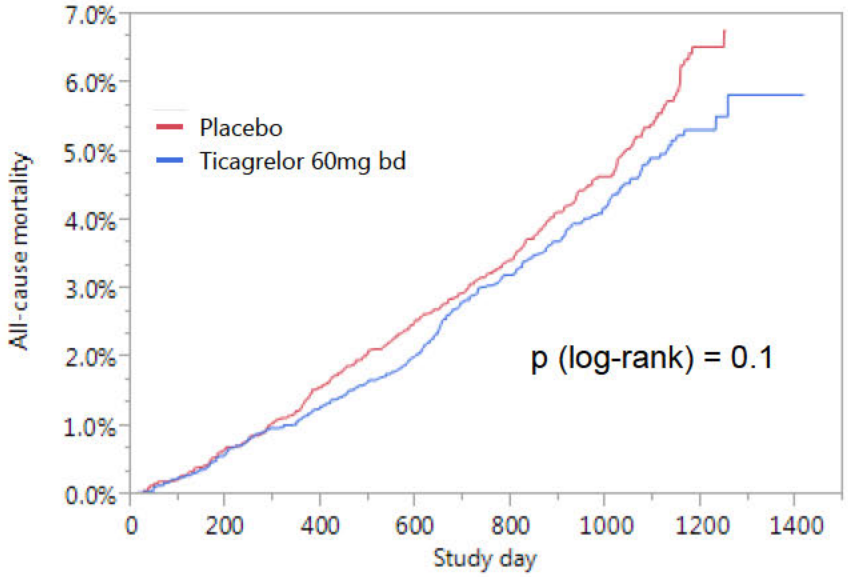
7.3 Major Safety Results

7.3.1 Deaths

Altogether there were 961 deaths in the safety population (those subjects who received at least one dose of their actual treatment), including 30 that occurred after the CSED.

When looking at the safety population, all-cause mortality trended toward being improved in the ticagrelor 60 mg bd group compared to placebo, similar to the finding in the ITT population (see Figure 14). There was a statistically significant improvement in CV mortality in the ticagrelor 60 mg bd safety set compared to the placebo safety set (Figure 28). The K-M curves for all-cause mortality for ticagrelor 90 mg bd and placebo were nearly superimposable (APPENDIX 3,
Figure 46). CV death favored ticagrelor 60 mg bd in the safety set (shown for the 60 mg bd dose in Figure 28). There was a trend favoring CV death for the 90 mg bd dose (APPENDIX 1, Figure 47).

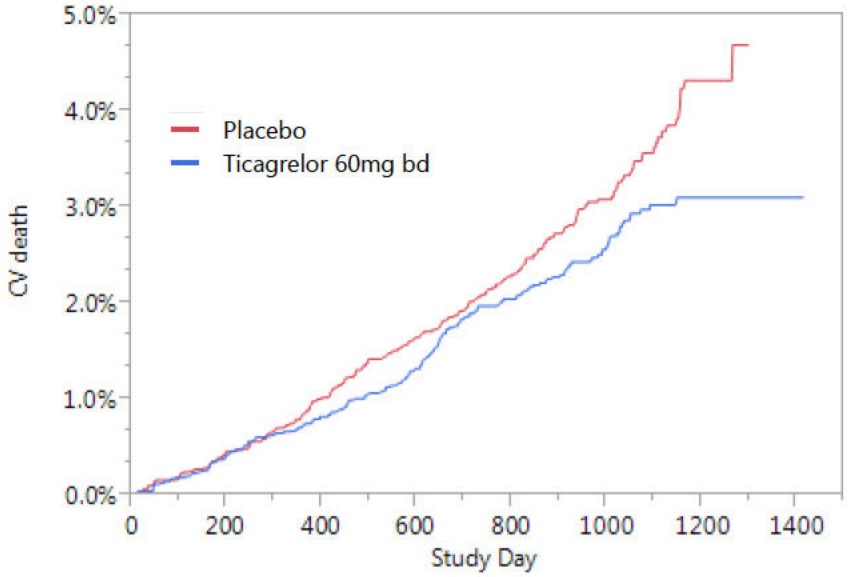
Figure 28: Kaplan-Meier time to event plot for all death (safety population, T60 mg bd vs. placebo), overall treatment period



Group	Number failed	Number censored	Mean		Std Error
Placebo	334	6662	1259.05	Biased	2.15165
Ticagrelor 60mg bd	292	6666	1223.5	Biased	1.88973
Combined	626	13328	1261.51	Biased	1.47399

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	2.7324	1	0.0983
Wilcoxon	1.6502	1	0.1989

Figure 29: Kaplan-Meier time to event plot for CV death (safety population, T60mg bd vs. placebo), overall treatment period



Group	Number failed	Number censored	Mean	Std Error
Placebo	219	6777	1272.4 Biased	1.7632
Ticagrelor 60mg bd	176	6782	1131.79 Biased	1.30184
Combined	395	13559	1274.76 Biased	1.19249

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	4.6078	1	0.0318*
Wilcoxon	2.5809	1	0.1082

The distribution of causes of death is presented in Table 25. There were numerically fewer CV deaths in the ticagrelor arms than in the placebo arm, but more non-CV deaths in the ticagrelor 90 mg bd arm. Since death is a common occurrence for patients of the age range enrolled in PEGASUS, it is reasonable to consider that the subjects spared a CV death in the 90 mg arm were more likely to die of another cause, thus appearing to increase the risk of other causes of mortality. Malignancy and infection were the most common causes for the excess mortality in the ticagrelor 90 mg bd arm, both common causes for death in the elderly. Malignancy deaths were higher in both ticagrelor arms, and this accounts for most of the non-CV deaths. In fact, there were nominally statistically significant more neoplasm deaths in the ticagrelor 90 mg bd arm than in the placebo arm. See APPENDIX 3 (Figure 49) for a K-M of the neoplasm-related deaths comparing ticagrelor 90 mg bd to placebo. The difference in the

neoplasm-related deaths between the ticagrelor 60 mg bd and placebo was smaller and not statistically significant. The neoplasm signal is discussed in depth in section 7.3.5.

Deaths from bleeding were no higher in the ticagrelor arms; a reassuring finding. In fact, there were more intracranial hemorrhage related deaths in the placebo arm than in the ticagrelor arms.

Table 25: CV death and non-CV death rates by treatment (FAS) overall treatment period*

CV death							
Treatment	Acute MI	HF or cardiogenic shock	Intracranial hemorrhage	Non-hemorrhagic stroke	Sudden cardiac death	Other/ probable or unclassified CV death	SUMS
	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)
Pbo	26 (0.4)	22 (0.3)	9 (0.1)	12 (0.2)	106 (1.5)	44 (0.6)	219 (3.1)
T60 mg bd	22 (0.3)	18 (0.3)	7 (0.1)	10 (0.1)	82 (1.2)	37 (0.5)	176 (2.5)
T90 mg bd	13 (0.2)	24 (0.3)	6 (0.1)	15 (0.2)	85 (1.2)	47 (0.7)	190 (2.7)
							585 (2.8)
Non-CV death							
	Malignancy	Infection (including sepsis)	Pulmonary Failure	Renal failure	Fatal Bleed	Other	SUMS
	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)
Pbo	53 (0.8)	24 (0.3)	9 (0.1)	4 (0.06)	5 (0.07)	20 (0.3)	115 (1.6)
T60 mg bd	63 (0.9)	25 (0.4)	9 (0.1)	4 (0.06)	5 (0.07)	10 (0.1)	116 (1.7)
T90 mg bd	77 (1.1)	31 (0.4)	10 (0.1)	2 (0.03)	6 (0.09)	19 (0.3)	145 (2.1)
							376 (1.8)
ALL-DEATH total							961 (4.6)

*Overall treatment period = from randomization to last follow-up day/
Source: RSADJ dataset, reviewer's analysis

7.3.2 Serious Adverse Events

To analyze serious adverse events (SAEs), I used an automated AE renaming tool, a JMP tool which captures AEs in groups and singly as a way to sort out if the applicant's categorization may be obscuring any important signals. (See APPENDIX 4). The source data for the analysis was the applicant's analysis adverse event dataset (RSAE) in the safety population. After renaming, I calculated the incidence rates per treatment group during the on-treatment period (during and 7 days post-discontinuation if discontinuation occurred prior to the CSED) and relative risk compared to placebo. The overall exposure time during the trial for subjects was 16072 years, 14796 and 14070 years for placebo, ticagrelor 60 mg bd, and ticagrelor 90 mg bd, respectively. The lower exposure time in the ticagrelor groups was a result of increased AEs/ SAEs. Because ticagrelor subjects were dropping out mostly for AEs/SAEs more often than placebo subjects, this may have slightly reduced other safety signal. However, because of the large size of the trial, this is not a significant concern and does not interfere with making conclusive statements about safety.

The most common SAEs that may have been drug related are listed in Table 26 along with other SAEs that I felt merited some discussion. The commonest SAEs were bleeding and dyspnea related which was expected given the PLATO experience and the platelet aggregation inhibiting properties of ticagrelor. The increased incidence of serious gastrointestinal events such as gastric, duodenal and jejunal ulcerations and complications thereof was possibly due to ascertainment bias (increased ascertainment because of antiplatelet properties of ticagrelor leading to increased bleeding).

There were also more bradycardia SAEs in PEGASUS (which was also expected because it was seen in PLATO). This is discussed in section 7.3.4.

The cases of pneumothorax (all cases were SAEs) were rare events and not dose related. The imbalance is probably a chance finding. There were also few cases of glaucoma/ high intraocular pressure. There were 13 non-serious AEs of glaucoma/high intraocular pressure in placebo, 17 in ticagrelor 60 mg and 18 in ticagrelor 90 mg. The imbalance here is probably a chance finding as well.

Table 26: Serious Adverse Events (safety population, on treatment) with relative risk (Ticagrelor 60 mg bd/ placebo ≥ 1.5)

	Pbo	T60 mg bd	T90 mg bd	RR	RR
	N= 6996	N=6958	N=6988	T60 mg bd	T90 mg bd
	n(%)	n(%)	n(%)	Pbo	Pbo
Epistaxis	2(0.03)	15(0.22)	19(0.27)	7.33	9
Pneumothorax	1(0.01)	5(0.07)	2(0.03)	7	3
Glaucoma, high intraocular pressure	1(0.01)	4(0.06)	2(0.03)	6	3
Ecchymosis, hematoma, bruise	5(0.07)	27(0.39)	19(0.27)	5.57	3.86
Dizziness, light-headedness	1(0.01)	3(0.04)	9(0.13)	4	13
Fe Deficiency	3(0.04)	11(0.16)	20(0.29)	4	7.25
Hemoptysis	1(0.01)	3(0.04)	4(0.06)	4	6
Constipation	1(0.01)	3(0.04)	2(0.03)	4	3
Bacteremia	3(0.04)	11(0.16)	8(0.11)	4	2.75
Dyspnea on exertion	1(0.01)	3(0.04)	1(0.01)	4	1
Nephritis, glomerulonephritis	1(0.01)	3(0.04)	1(0.01)	4	1
Seizure	1(0.01)	2(0.03)	2(0.03)	3	3
High K+	1(0.01)	2(0.03)	1(0.01)	3	1
Ligament rupture	1(0.01)	2(0.03)	0(0)	3	0
Dyspnea, SOB, respiratory distress	9(0.13)	25(0.36)	23(0.33)	2.77	2.54
Hematuria	3(0.04)	8(0.11)	9(0.13)	2.75	3.25
Shock, non-cardiogenic	3(0.04)	7(0.1)	9(0.13)	2.5	3.25
Encephalitis, encephalopathy	2(0.03)	5(0.07)	4(0.06)	2.33	2
GI bleed	34(0.49)	78(1.12)	89(1.27)	2.29	2.59
Anemia	14(0.2)	31(0.45)	43(0.62)	2.25	3.1
Bradycardia	6(0.09)	14(0.2)	14(0.2)	2.22	2.22
Gastric, duodenal, or jejunal ulcer, erosion, perforation	16(0.23)	33(0.47)	49(0.7)	2.04	3.04
Motor vehicle accident	2(0.03)	4(0.06)	2(0.03)	2	1
Hearing loss, deafness	2(0.03)	4(0.06)	1(0.01)	2	0.33
Bleeding	90(1.29)	168(2.41)	165(2.36)	1.87	1.83
Hernia, incarcerated, obstructive, gangrenous, or ruptured	3(0.04)	5(0.07)	5(0.07)	1.75	1.75
Pulmonary edema	4(0.06)	7(0.1)	3(0.04)	1.67	0.67
Asthenia, fatigue, malaise, weakness, narcolepsy	4(0.06)	7(0.1)	2(0.03)	1.67	0.5
UTI	16(0.23)	26(0.37)	40(0.57)	1.61	2.48
Stone, renal colic	14(0.2)	22(0.32)	32(0.46)	1.6	2.3
Hypotension	5(0.07)	8(0.11)	5(0.07)	1.57	1
Hernia	24(0.34)	37(0.53)	33(0.47)	1.56	1.38
Low LVEF, low cardiac output, cardiomyopathy, LV dysfunction	3(0.04)	4(0.06)	12(0.17)	1.5	4.25
Cranial neuropathy, palsy	3(0.04)	4(0.06)	2(0.03)	1.5	0.75
Ocular hemmorhage	3(0.04)	4(0.06)	2(0.03)	1.5	0.75
Cardiac thrombus	3(0.04)	4(0.06)	1(0.01)	1.5	0.25

Analysis using RSAE and ADSL datasets, on treatment (safety set) with renaming of MedDRA preferred terms (AEDECOD). The complete list of SAEs that occurred at least once is located in APPENDIX 4.

7.3.3 Dropouts and/or Discontinuations

There were more discontinuations in the ticagrelor groups than in the placebo groups which resulted in slightly lower exposure to ticagrelor than to placebo. For the ticagrelor

90 mg, ticagrelor 60 mg, and placebo groups, mean total duration of exposure to study drug (first dose to last dose) was 23.9, 25.3, and 27.3 months, respectively; median total duration of exposure was 28.3, 29.4, and 30.4 months, respectively. Total duration of exposure to ticagrelor (from first dose to last dose) ranged from 0 to a maximum of 48.0 months. The increased rate of discontinuation of study drug was mostly because of AEs and the breakdown of reasons for discontinuations is presented in Figure 29.

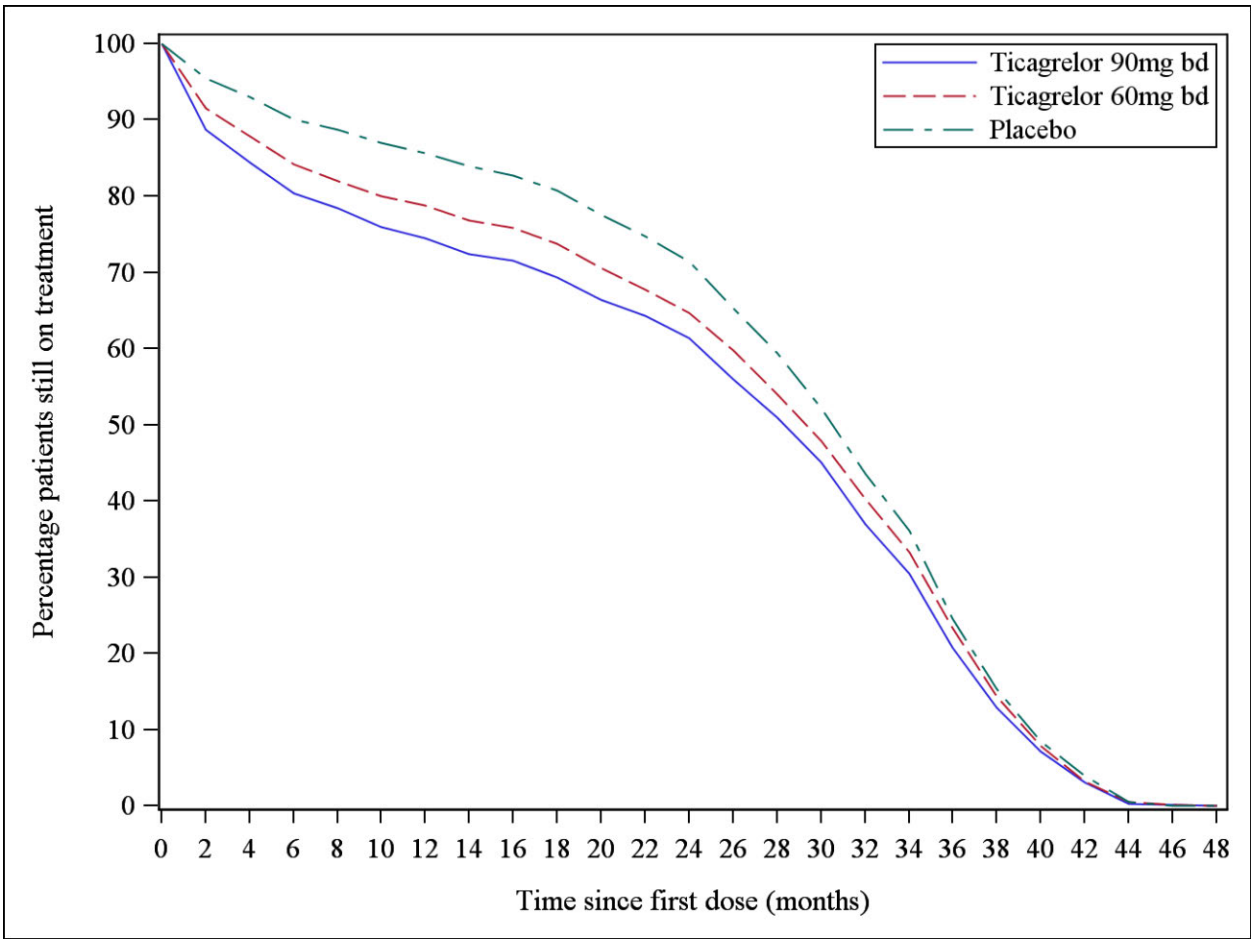
The precipitous drop off in study subjects between 24 months and 44 months is mostly because subjects reached the CSED or died as opposed to discontinuation. Most subjects completed the study on treatment or died (62.7% of subjects in the ticagrelor 90 mg bd group, 66.6% of subjects in the ticagrelor 60 mg bd group, and 73.3% of subjects in the placebo group). See Table 27 for a tabular listing of discontinuations, reasons for discontinuations, deaths prior to CSED and withdrawal of consent. Very few subjects withdrew consent and even fewer were lost to follow-up. Discontinuation for AE/SAEs was almost twice as common for the ticagrelor groups as for the placebo group.

Table 27: Discontinuations, Deaths and Drops-outs before CSED (safety set)

	Placebo	Ticagrelor 60 mg bd	Ticagrelor 90 mg bd
	N=6996	N=6958	N=6988
Discontinuation	1496 (21.4%)	1999 (28.7%)	2233 (32.0%)
AE/ SAE	784 (11.2%)	1257 (18.1%)	1434 (20.5%)
Patient decision	590 (8.4%)	635 (9.1%)	689 (9.9%)
Other	122 (1.7%)	107 (1.5%)	110 (1.6%)
Death before CSED	329 (4.7 %)	287 (4.1%)	330 (4.7%)
Drop-out (withdrawal)	40 (0.6%)	39 (0.6%)	46 (0.7%)
Patients with unknown vital status	6 (0.1%)	10 (0.1%)	7 (0.1%)

Source: Response to information request, supporting document182

Figure 30: Kaplan-Meier Time to Discontinuation Curve: % still on treatment over time (safety analysis set)



Source: Clinical Study Report, p. 141
At a given time t, the curve shows the percentage with exposure time > t.

Patients who discontinued prematurely who were on ticagrelor did not have an increased risk of MACE compared to placebo. However, those who discontinued after the CSED did have an increased risk of MACE. This is covered in section 6.1.10.

There were approximately 25% in each treatment group that had temporary interruptions of therapy.

The most commonly reported AEs that resulted in discontinuation were dyspnea and increased tendency to bruise and epistaxis. Dyspnea AEs resulting in discontinuation occurred in 6.0%, 4.0% and 0.7% of subjects on ticagrelor 90 mg, ticagrelor 60 mg and placebo, respectively. Bleeding AEs leading to discontinuation occurred in 6.2%, 5.1% and 1.3% of subjects on ticagrelor 90 mg, ticagrelor 60 mg and placebo, respectively.

This corresponds to a Kaplan-Meier percentage at 36 months of 7.8%, 6.2% and 1.5%. The most common bleeding AEs leading to discontinuation were increased tendency to bruise, epistaxis and spontaneous hematoma, more so-called nuisance bleeding than life-threatening bleeding. Nonetheless, there were some TIMI major bleeding events that led to discontinuation of study drug. See Table 28. Bruising AEs resulting in discontinuation occurred in 1.3%, 0.9% and 0.1% of subjects on ticagrelor 90 mg, ticagrelor 60 mg and placebo, respectively. Epistaxis AEs resulting in discontinuation occurred in 1.0%, 0.7% and 0.2% of subjects on ticagrelor 90 mg, ticagrelor 60 mg and placebo, respectively.

Table 28: TIMI Major Bleeding Leading to Discontinuation by System Organ Class

System organ class	Ticagrelor 90 mg	Ticagrelor 60 mg	Placebo
	N=6988	N=6958	N=6996
Infections and Infestations	0(0%)	1(0%)	0(0%)
Neoplasms	5(0%)	3(0%)	1(0%)
Blood and Lymphatic system disorders	1(0%)	1(0%)	0(0%)
Nervous system disorders (including hemorrhagic stroke)	8(0.1%)	5(0.1%)	12 (0.2%)
Eye disorders	0(0%)	1(0%)	0(0%)
Vascular disorders	1(0%)	0(0%)	0(0%)
Gastrointestinal disorders	25 (0.4%)	23 (0.3%)	9 (0.1%0
Renal and Urinary Disorders	1(0%)	1(0%)	0(0%)
Reproductive system and breast disorders	1(0%)	0(0%)	0(0%)
Injury, Poisoning, and Procedural Complications	18 (0.3%)	17 (0.2%)	6 (0.1%)

Source: CSR, p.1302-3.

7.3.4 Significant Adverse Events

Bleeding and Intracranial Hemorrhage

See section 7.3.5.

Dyspnea

As shown in PLATO, ticagrelor causes dyspnea. Approximately 17% of subjects on ticagrelor 90 mg bd and approximately 14% of subjects on ticagrelor 60 mg bd developed dyspnea, compared to only approximately 5% on placebo (see Table 34). There were also twice as many dyspnea SAEs in the ticagrelor groups compared to placebo [26 (0.4%) and 29 (0.4%) for ticagrelor 60 mg bd and ticagrelor 90 mg bd, respectively compared to 12 (0.2%) for placebo]. However, on a reassuring note, as was shown in PLATO, there were no increases in more serious dyspnea related serious adverse events such as cardiac arrest, respiratory failure, acute respiratory distress syndrome, postoperative respiratory failure, or hypoxia in PEGASUS.

In PEGASUS, dyspnea happened throughout the trial, but the median times to first dyspnea AE were 11, 29 and 240 days for subjects on ticagrelor 90 mg, ticagrelor 60 mg and placebo, respectively. See Table 29.

Table 29: Incidence of Dyspnea in PEGASUS (On-treatment, safety analysis set)

	Ticagrelor 90 mg bd (N=6988)	Ticagrelor 60 mg bd (N=6958)	Placebo (N=6996)
n	1204	986	382
Mean	116.2	168.4	326.7
SD	218.0	260.2	308.7
Median	11.0	29.0	240.0
Min	1	1	1
Max	1231	1258	1384
n (%)[a]			
1 - 3 days	421 (35.0%)	276 (28.0%)	31 (8.1%)
4 - 7 days	122 (10.1%)	73 (7.4%)	18 (4.7%)
8 - 30 days	194 (16.1%)	149 (15.1%)	27 (7.1%)
31 - 90 days	119 (9.9%)	97 (9.8%)	44 (11.5%)
91 - 180 days	110 (9.1%)	106 (10.8%)	38 (9.9%)
> 180 days	238 (19.8%)	285 (28.9%)	224 (58.6%)

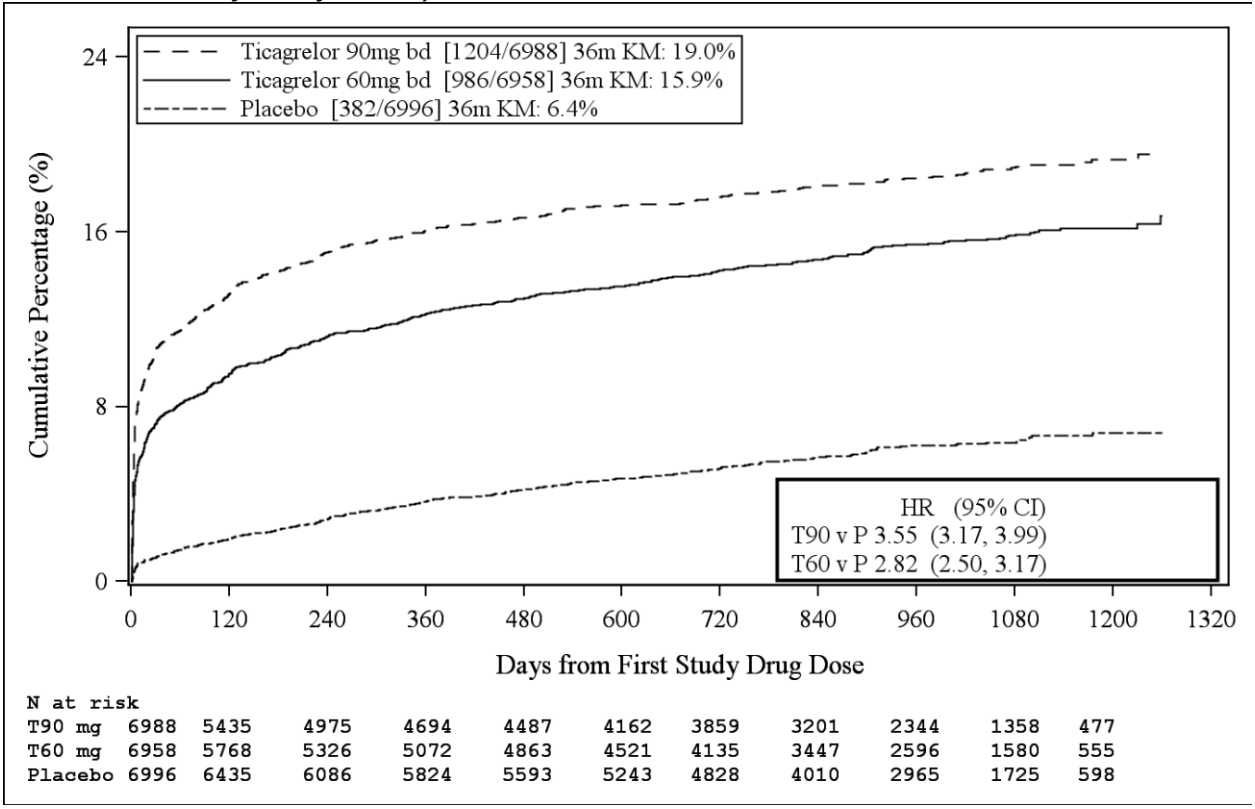
Source: Table 11.3.8.1.9.1
Dyspnoea events are 1 of the 5 PTs: dyspnoea, dyspnoea at rest, dyspnoea exertional, dyspnoea paroxysmal nocturnal, and nocturnal dyspnoea.
Includes events with onset date on or after the date of first dose and up to and including 7 days following date of last dose of study drug.
[a] Percentage of patients with an event.
AE adverse event; bd Twice daily; Max Maximum; Min Minimum; n Number of patients in category or analysis; N Number of patients in treatment group; SD Standard deviation.

Source: PEGASUS CSR

Reference ID: 3804604

The K-M plot of the cumulative percentage of patients with first dyspnea in PEGASUS is very similar to what was seen in PLATO, as shown in Figure 30 and Figure 32. After the first few weeks, the rate of new onset dyspnea is similar among all treatment groups, suggesting that ticagrelor-induced dyspnea happens early.

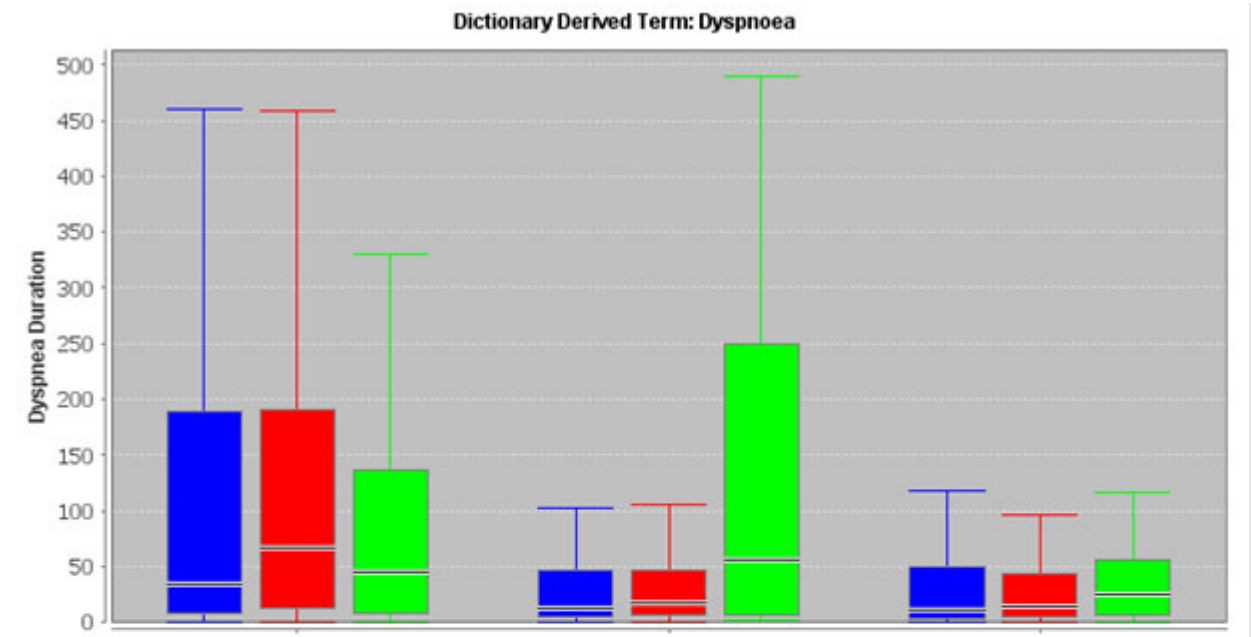
Figure 31: K-M plot of cumulative percentage of patients with first dyspnea (on treatment, Safety analysis set) in PEGASUS



Source: CSR, p. 191

Figure 31 shows that most dyspnea in PEGASUS lasts more than 50 days in Ticagrelor 60 mg if the dose isn't changed, but less than 50 days if drug is interrupted or withdrawn. Similarly, in PLATO, most of the dyspnea episodes were longer than 20 days – but discontinuing ticagrelor made most go away. In PLATO, 2/3 of the dyspnea cases resolved without discontinuation.

Figure 32: Dyspnea Duration Following Drug Interruption or Discontinuation (on-treatment, safety set) in PEGASUS



	DOSE NOT CHANGED			DRUG INTERRUPTED			DRUG WITHDRAWN		
	1	2	3	1	2	3	1	2	3
Mean	128.81	136.13	109.95	59.80	46.95	150.11	47.06	48.26	50.02
Median	34.50	67.00	45.00	12.00	17.50	55.50	11.00	14.00	24.50
Q1	8.00	12.00	8.00	5.00	6.00	7.00	4.00	5.00	6.00
Q3	189.00	191.00	137.00	47.00	46.50	250.00	50.00	44.00	56.00
N	520	424	193	188	134	18	405	278	48

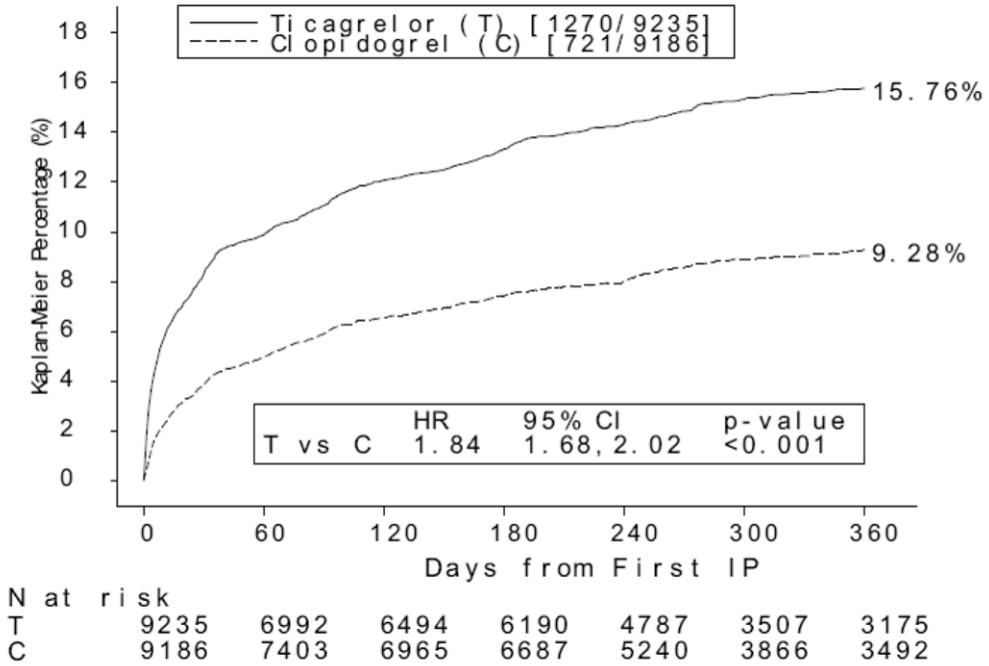
Source: Reviewer Analysis using safety set, DSAE and Jreview

Figure 32 is from PLATO. Here you can see that most dyspnea had early onset but that new cases occurred as long as subjects were on drug. The curve was not as steep for clopidogrel.

Cross-trial comparisons are difficult because the patients enrolled have different characteristics. Nevertheless, it is interesting to note that the clopidogrel dyspnea rates

in PLATO were at least twice as high as the dyspnea rates in the placebo group in PEGASUS.

Figure 33: K-M plot of cumulative % of dyspnea episodes in PLATO comparing T (ticagrelor 90 mg) to C (clopidogrel 75 mg)



Source: PLATO CSR

Bradyarrhythmias

Bradycardia was reported in 4.3% of ticagrelor –exposed subjects in PLATO (4.0% in clopidogrel-exposed subjects) and therefore is an adverse event of interest. Fifty-nine (0.84%) subjects exposed to placebo during the on-treatment period (up to 7 days post discontinuation) and 71 (1.02%) and 57 (0.82%) of subjects during the on-treatment period who were exposed to ticagrelor 60 mg bd and ticagrelor 90 mg bd, respectively, had bradycardia reported as an AE. The change from baseline of heart rate in PEGASUS was not apparently different in any of the treatment groups. As for bradycardia SAEs in PEGASUS, although the numbers are small, there were notably more events in the ticagrelor arms than in the placebo arm [14 (0.2%) for both of the ticagrelor arms and 6 (0.09%) for the placebo arm], shown in the SAE Table 26. However, there was no greater incidence of sick sinus syndrome, sinus block or sleep apnea and just a minor increase in syncope and near-syncope [(119(1.7%), 105 (1.5%)

and 87 (1.2%)] for ticagrelor 60 mg bd, ticagrelor 90 mg bd, and placebo, respectively. This is reassuring because bradycardia occurred commonly in PLATO and a Holter substudy in PLATO confirmed the increased frequency of ventricular pauses and other cardiac arrhythmias, particularly at night time raising the possibility that ticagrelor could worsen sleep apnea. Of note, in the Holter substudy of PLATO, the ticagrelor –treated patients had no greater frequency of symptomatic events.

An important limitation of both the PLATO and PEGASUS studies is that patients with an increased risk of bradycardic events (e.g., those with a pacemaker and known sick sinus syndrome, second or third degree AV block or previous documented syncope suspected to be due to bradycardia unless treated with a pacemaker) were excluded from the studies. Therefore, it is not known if ticagrelor might cause worsening of these heart block conditions.

Reviewer's Comment: There should be a warning in the label about not knowing if ticagrelor might worsen high degree heart block.

Renal Impairment
Because ticagrelor 90 mg bd was associated with a >50% increase in serum creatinine levels in 7.4% of subjects compared to 5.9% of subjects who received clopidogrel in PLATO, renal impairment is an adverse event of interest. Of note, the creatinine increases typically did not progress with ongoing treatment in PLATO (and often decreased with continued therapy). The increase in serum creatinine also diminished after discontinuation of ticagrelor. Treatment groups in PLATO did not differ for renal-related serious adverse events such as acute renal failure, chronic renal failure, toxic nephropathy or oliguria. In PEGASUS, fewer subjects than in PLATO had an increase in maximum serum creatinine > 50% from baseline despite over twice average exposure times. The incidence of subjects developing elevations in creatinine > 50% from baseline in PEGASUS were 3.5%, 3.9% and 4.2% in the placebo, ticagrelor 60 mg bd and ticagrelor 90 mg bd groups, respectively. Renal AEs (elevated BUN or creatinine, anuria, acute renal failure, chronic renal failure and/or oliguria) occurred in ~ 2.5% of subjects in each treatment group during the on-treatment period (up to 7 days post-discontinuation). The risk of serious renal-related AEs (acute renal failure, anuria) was about 0.2 to 0.3% in each treatment group. The balance among treatment groups of acute renal failure confirmed the absence of a relationship between ticagrelor and acute renal failure.

Gout and Hyperuricemia
In PLATO it was shown that uric acid levels increased approximately 0.6 mg/dL from baseline in subjects who were on ticagrelor, compared to an increase of approximately 0.2 mg/dL on clopidogrel, but no difference in gout AEs between treatment groups. In PEGASUS there were 117(1.67%), 168(2.4%) and 184 (2.63%) gout AEs in the placebo, ticagrelor 60 mg bd and ticagrelor 90 mg bd treatment groups, respectively,

suggesting a dose relationship and a causal relationship between ticagrelor and gout. Also, there were 3 serious gout AEs in the ticagrelor 90 mg bd treatment group compared to 1 in each of the placebo and ticagrelor 60 mg bd treatment groups. There was also a slight increase in renal stone/ renal colic AEs [61(0.9%), 77 (1.1%) and 92 (1.3%) in the placebo, ticagrelor 60 mg bd and ticagrelor 90 mg bd treatment groups, respectively] and SAEs [14(0.2%), 22 (0.3%) and 32 (0.5%) in the placebo, ticagrelor 60 mg bd and ticagrelor 90 mg bd treatment groups, respectively in PEGASUS]. The etiology of the dose-related stones/ renal colic is not known, but I mention it here because it might be a consequence of hyperuricemia.

Reviewer's comment: The new ticagrelor label should include verbiage about the higher incidence of gout in patients on ticagrelor.

Hepatic Events

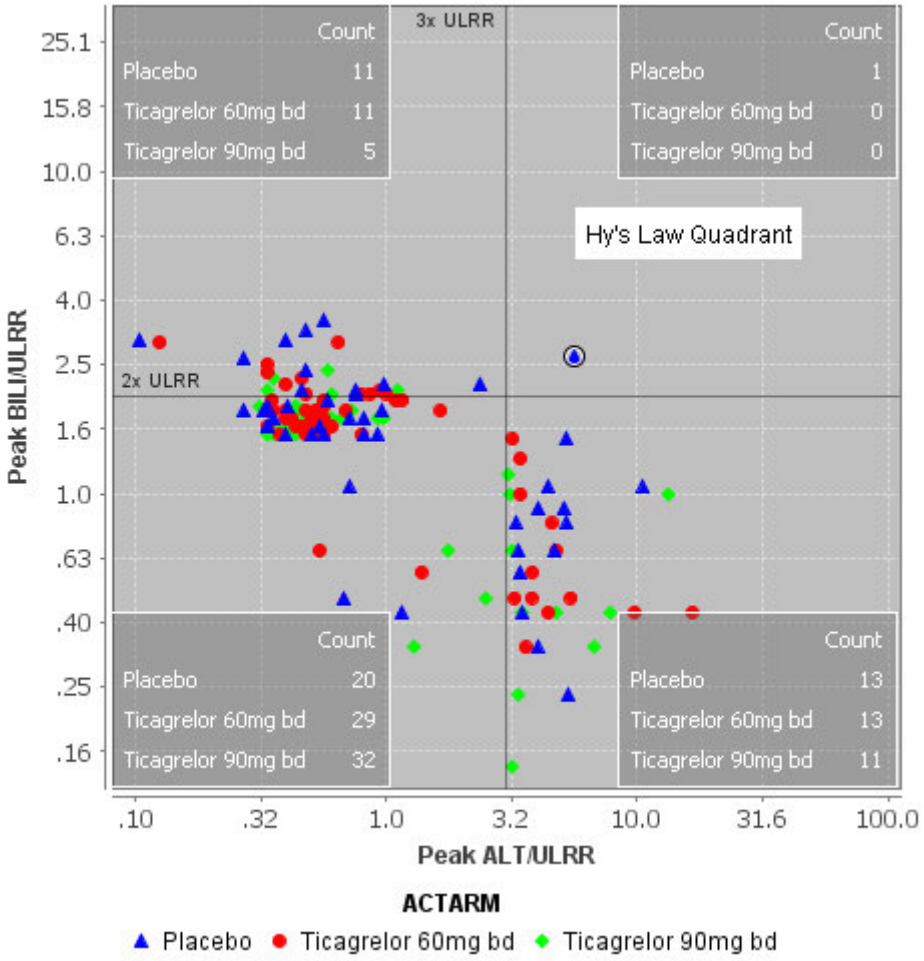
Patients with known severe liver disease at baseline were excluded from the study but patients with moderate liver disease as judged by the investigator were allowed to participate. According to the applicant, there was no evidence of drug-induced liver injury (DILI) from ticagrelor despite there being four patients for which DILI was reported, two on ticagrelor 60 mg bd and two on placebo. There were few hepatic-related SAEs (n=6) or discontinuations from hepatic AEs (n=3) and the frequencies were similar across treatment groups. There were no hepatic-related AEs in the ticagrelor treatment groups resulted in death.

As shown in Figure 33, there were no Hy's law cases in the ticagrelor treatment groups in PEGASUS identified using Jreview where the strict criteria for Hy's law case are as follows:

- ALT or AST >3x Upper limit of Normal
- BILI >2x Upper Limit of Normal (without respect to time course)
- ALP is <2xULN at any time point when the ALT/AST and BILI abnormalities meet Hy's Law criteria

My independent analyses and review of narratives of potential Hy's law cases (derived from less strict criteria) showed similar results to that of the applicant's (no ticagrelor-induced DILI).

Figure 34: Hy's Law Identification, Safety Set



Source: RSAE exploration with Jreview

Gynecomastia

In PLATO there was a nominal difference in reports of gynecomastia between the treatment arms (0.23% of men on ticagrelor compared with 0.05% on clopidogrel). In PEGASUS, the number of reported AEs of gynecomastia was low and evenly distributed across the treatment groups: 11, and 8, 10 male patients in the placebo, ticagrelor 60 mg bd, and ticagrelor 90 mg bd groups, respectively (~0.01% in each treatment group). Four patients discontinued study treatment due to gynecomastia; 2 on placebo and 2 on ticagrelor 60 mg bd.

One SAE of gynecomastia (right-sided tumor confirmed by histology as benign) was reported in the ticagrelor 90 mg bd treatment group.

Reviewer's Comment: It appears that the observation of increased gynecomastia in the ticagrelor arm in PLATO may have been a chance finding. It appears now that it is unlikely that there is a causal relationship between ticagrelor and gynecomastia. Therefore, the common adverse events section of the label can be changed to remove gynecomastia.

Thrombocytopenia

According to the applicant, there was a low number of thrombocytopenia AEs, evenly distributed across treatment groups: 17 (0.2%) on placebo, 17 (0.2%) ticagrelor 60 mg, and 20 patients (0.3%) on ticagrelor 90 mg. Three (0.04%) on placebo, 2 (0.2%) on ticagrelor 60 mg bd and 6 (0.9%) on ticagrelor 90 mg bd were serious. Reviewer analysis revealed very similar results. No cases of thrombocytopenia that were reported as AEs had a fatal outcome. Treatment with ticagrelor was unchanged in 3 cases, temporarily interrupted in 2 cases and permanently stopped in 3 patients. Four of the patients with SAEs on ticagrelor recovered from the thrombocytopenia event. Two patients with ongoing thrombocytopenia had other AEs with fatal outcome and 2 patients had not recovered by the end of the study. The subjects with thrombocytopenia SAEs had possible explanations for the thrombocytopenia such as malignancies, chemotherapy or other concomitant medications known to be associated with thrombocytopenia.

Reviewer's Comment: It does not appear that ticagrelor causes thrombocytopenia.

Pancytopenia/ Aplastic Anemia

There were 6 mild to moderate AEs of pancytopenia reported on treatment (1 on placebo, 2 on ticagrelor 60 mg bd and 3 on ticagrelor 90 mg bd. Three of these events were serious (2 on ticagrelor 60 mg bd and 1 on ticagrelor 90 mg bd). None of the severe cases of pancytopenia resulted in death but one died of an extradural spinal cord neoplasm and another died of a cardiac arrest a few days after the pancytopenia was discovered. A third did not die and etiology was attributed to a virus "or some other cause". Therefore, one or two cases of severe pancytopenia may be attributable to ticagrelor (the one who died of cardiac arrest and the one whose etiology was attributed to a virus "or some other cause"). Pancytopenia in the subject who died of an extradural spinal cord neoplasm may have been related to the underlying neoplasm.

One patient on ticagrelor 60 mg bd died of pneumococcal sepsis and had aplastic anemia at the time that she was diagnosed with sepsis. It is possible that the aplastic anemia resulted from the sepsis and that in this case ticagrelor was an "innocent bystander".

Reviewer's Comment: There were 2 cases of pancytopenia that appear to have been possibly caused by ticagrelor. Because the numbers of cases are so low and the possibility that a virus or another unreported illness caused them, instead of labeling

ticagrelor as possibly causing pancytopenia, at this time we should consider pancytopenia an AE of interest for post-marketing surveillance.

Rhabdomyolysis
There were few rhabdomyolysis AEs, evenly distributed across treatment groups: 3 subjects on ticagrelor 90 mg, 4 on ticagrelor 60 mg, and 3 on placebo. There was 1 SAE in each treatment group. A review of the rhabdomyolysis SAE narratives revealed that all subjects were on statins which are known to be associated with rhabdomyolysis.

Reviewer's Comment: Because of the presence of statins and the even distribution of rhabdomyolysis across treatment groups, it is unlikely that ticagrelor had a causal role in these AES.

Stevens-Johnson syndrome
Stevens-Johnson syndrome was reported for a single subject on ticagrelor 60 mg treatment. This subject was also on vancomycin which was the likely cause because it is known to cause Stevens-Johnson syndrome and after stopping it the subject recovered within one day.

Reviewer's Comment: Because the one case of reported Stevens-Johnson syndrome was in a subject who was also on vancomycin and this subject recovered after stopping vancomycin (and was only temporarily interrupted from study drug), it is unlikely that ticagrelor had a causal role in this AE.

Erythema multiforme
Erythema multiforme was reported for 2 patients, one in each of the ticagrelor treatment groups. Both events were non-serious AEs. One (the subject in ticagrelor 90 mg) was discontinued from study drug. The event was considered "severe" and it was attributed by the investigator to ticagrelor.

Reviewer's Comment: It is possible that ticagrelor had a causal role in these 2 cases. Because Erythema multiforme is a rare condition that is often the result of immune complexes and there is known hypersensitivity reactions with ticagrelor, there should be some mention of this AE in the label.

Vasculitis
One patient in each treatment group reported an AE of vasculitis. Only the AEs in the ticagrelor arms were reported as "hypersensitivity vasculitis". The subject in the ticagrelor 60 mg arm's event of vasculitis was reported as an SAE of hypersensitivity vasculitis. Histological examination showed chronic eczema. Treatment with ticagrelor was unchanged and the patient recovered.

Reviewer's Comment: Because the histological examination showed chronic eczema, it is unlikely that this SAE that occurred in a subject in the ticagrelor 60 mg arm was a true vasculitis.

Toxicity to various agents
There were 3 drug toxicity AEs, all in patients on ticagrelor 90 mg treatment. One SAE of metformin toxicity was reported. The patient also had lactic acidosis, renal failure and sepsis. Study drug and metformin were withdrawn. The patient recovered.

Reviewer's Comment: The metformin SAE may have been caused by metformin alone. Therefore, it does not seem reasonable to invoke a causal relationship between ticagrelor and metformin toxicity at this time.

Drug hypersensitivity
There were 31 drug hypersensitivity AEs, evenly distributed across treatment groups: 10 patients on ticagrelor 90 mg, 12 on ticagrelor 60 mg, and 9 on placebo. Two SAEs were reported, all in ticagrelor 60 mg. One of the 2 led to the discontinuation of the drug. One SAE occurred on Day 1 and the second occurred on Day 375. There were also 3 non-serious AEs leading to discontinuation of the drug, 2 on ticagrelor 90 mg and 1 on ticagrelor 60 mg. DAEs had onset days ranging from Day 2 to Day 126. All events resolved.

There were 3 subjects in ticagrelor 90 mg and 3 on placebo who reported anaphylactic shock AEs, two events in each treatment group were SAEs. None of the SAEs led to discontinuation. The non-SAE of anaphylaxis that occurred in the subject in the ticagrelor 90 mg group occurred on the first day and resulted in permanent discontinuation. This patient recovered the same day.

There were 17 subjects with angioedema AEs; 3 subjects on ticagrelor 90 mg, 8 on ticagrelor 60 mg and 6 on placebo. Of these 17, 6 SAEs were reported: 1 subject on ticagrelor 90 mg, 2 on ticagrelor 60 mg and 3 on placebo. There was one subject in the ticagrelor 60 mg group who had multiple SAEs of angioedema which ultimately led to discontinuation of the drug. There were also two non-serious AEs (1 subject in each of the ticagrelor arms) which led to discontinuation of study drug. All angioedema SAEs and AEs resolved.

There were 12 AEs of drug hypersensitivity /anaphylactic reactions identified as possibly related to study drug by investigators. Only one was an SAE. None of these AEs were classified as severe. Five of the nine subjects who were on ticagrelor had drug withdrawn, and 1 had drug interrupted. Only 3 of these subjects had their reactions within 2 days of starting study drug. The rest ranged from day 16 to day 253. The one AE classified as anaphylaxis occurred on day 1 (5420015).

Reviewer's Comment: The hypersensitivity + allergic reactions SAEs identified by this reviewer's analysis were balanced across treatment groups. After reviewing the individual distribution of cases, it appears that ticagrelor causes hypersensitivity reactions in some patients. This is implied in the label because there is a contraindication against use in patients with known hypersensitivity to ticagrelor.

Guillain-Barre
Three SAEs of Guillain-Barre were reported; 2 patients on ticagrelor 90 mg, and 1 on placebo. Both SAEs in the subjects on ticagrelor were reported as moderate intensity and the SAE in the subject on placebo was reported as severe. For one event in the ticagrelor 90 mg group, the SAE resolved with no change to treatment. For the other subject in the ticagrelor 90 mg group, the Guillain-Barre SAE was reported as ongoing at time of the study report and ticagrelor was continued following an interruption for an unrelated AE (tooth abscess).

Reviewer's Comment: It is possible that ticagrelor played a role in one subject's Guillain-Barre syndrome SAE. However, if the investigator had thought so s/he would have discontinued it. The fact that s/he didn't discontinue study drug in the face of Guillain-Barre suggests that the investigator did not believe that ticagrelor caused it.

Myasthenic syndrome
A single AE was reported in the placebo treatment group.

Reviewer's Comment: There is no signal for myasthenia gravis.

Convulsions
There were few convulsion AEs, evenly distributed across treatment groups: 2 patients on ticagrelor 90 mg, 3 on ticagrelor 60 mg, and 3 on placebo. A single SAE in a patient on ticagrelor 60 mg was reported. A review of the convulsion SAE narrative showed that the patient had a medical history of seizures.

Reviewer's Comment: There is no signal for seizures

Pancreatitis, pancreatitis acute
There were 44 pancreatitis AEs: 16 patients on ticagrelor 90 mg, 14 patients on ticagrelor 60 mg and 14 on placebo. Thirty-five SAEs were reported: 11 patients on ticagrelor 90 mg, 11 on ticagrelor 60 mg, and 13 on placebo. Cholelithiasis and alcohol overconsumption were found among concomitant medical conditions.

Reviewer's Comment: There is no signal for pancreatitis

Pulmonary hypertension

There were 8 pulmonary hypertension AEs: 3 patients on ticagrelor 90 mg and 5 patients on ticagrelor 60 mg. Three SAEs were reported: 2 patients on ticagrelor 90 mg and 1 on ticagrelor 60. However, all SAEs were associated with congestive heart failure, a likely cause of pulmonary hypertension.

Reviewer's Comment: On a background of CHF it would be hard to attribute the causality of pulmonary hypertension to ticagrelor.

Pulmonary fibrosis
There were 15 pulmonary fibrosis AEs: 5 patients in each treatment group. Five SAEs were reported, all in subjects on ticagrelor: 3 on ticagrelor 90 mg and 2 on ticagrelor 60 mg. One of the SAEs on ticagrelor 90 mg was fatal. Another subject died after receiving a diagnosis of pulmonary fibrosis but cause of death was not reported to the registry office after patient was lost to follow-up. One subject on ticagrelor 60 mg with an SAE was on concomitant medication known to be associated with pulmonary fibrosis (methotrexate).

The AE of "interstitial lung disease" which represents a broad spectrum of non-obstructive pulmonary diseases was more balanced. There were 10 AEs of interstitial lung disease: 3 subjects on ticagrelor 90 mg, 1 on ticagrelor 60 mg and 6 on placebo. Five SAEs were reported; 2 on ticagrelor 90 mg and 3 on placebo. One of the SAEs on placebo was fatal.

Table 30: Tabular Description of Subjects with Pulmonary Fibrosis SAEs

Subject Description	Treatment Arm	Day at which subject developed PF	Action/ outcome
63 y/o white male with no h/o pulmonary fibrosis, heart failure or COPD	Ticagrelor 90 mg	~140	None. Ticagrelor discontinued at ~day 300 because patient had an MI. followed past day 700. Unresolved.
64 y/o white male with "flare-up" of idiopathic pulmonary fibrosis	Ticagrelor 90 mg	~325	None. Outcome recovered/ resolved at ~ day 800.
68 y/o white male with no h/o pulmonary fibrosis but on methotrexate (known to cause pulmonary fibrosis)	Ticagrelor 60 mg	~450	Methotrexate stopped. Ticagrelor temporarily interrupted. Outcome not recovered/ not resolved at day ~950.
73 y/o white male	Ticagrelor 90 mg	~720	Ticagrelor stopped at time of pulmonary investigations. Fatal at around day 950
76 y/o white male	Ticagrelor 60 mg	~800	None. Lost to follow-up but letter was sent to registry office explaining that patient died at ~ day 975, cause of death not provided.

Reviewer's Comment: There may be a causal relationship between ticagrelor and at least 4 of these 5 severe cases of pulmonary fibrosis. In order to explore further, narrative of subjects with interstitial lung disease were read, reviewed and documented in table below (Table 31). There were 4 placebo subjects and 6 ticagrelor subjects who were documented with interstitial lung disease during PEGASUS. None of these were nonconfounded as they were all smokers, former smokers, had CHF or were on a concomitant medication known to cause interstitial lung disease. These cases do not

support the signal of pulmonary fibrosis, but they do not detract from it. In PLATO, there was only one subject in the ticagrelor group who had a reported SAE of pulmonary fibrosis (none for SAE of interstitial lung disease) and there were 30 (0.3%) subjects with pulmonary fibrosis non-serious AEs. There was one subject in the clopidogrel group who had a reported SAE of interstitial lung disease (none for SAE of pulmonary fibrosis) and there were 27 (0.3%) subjects with pulmonary fibrosis non-serious AEs. In the postmarketing section of the clopidogrel, interstitial pneumonitis is listed. I think it would be reasonable to include a short discussion about the incidence of pulmonary fibrosis in the ticagrelor label.

Table 31: Cases of interstitial Pneumonia lung disease (all subjects with background of smoking and/or CHF or other medication known to cause interstitial lung disease)

Subject Description	Treatment Arm	Day at which subject developed ILD	Action/ outcome
79 y/o Asian former smoker male with h/o COPD	Placebo	688	Drug discontinuation 13 days later followed by respiratory arrest 4 days later, followed by Death (attributed to ILD)
76 y/o white former smoker male	Ticagrelor 60 mg	646	None. Did not resolve. Died 25 days later of ventricular tachycardia. That was attributed to pneumonia (bilateral interstitial lung disease pneumonia/pneumonitis) diagnosed as acute interstitial pneumonia on bronchoscopy.
68 y/o white Hispanic female – no smoking by history	Ticagrelor 90 mg	793	None. Recovered 17 days later. Died of CV death ~ 2 months later.
64 y/o Asian male former smoker	Ticagrelor 90 mg	935	Stopped Ticagrelor at day 767 after SAE of hemoptysis. Not recovered or resolved.
63 y/o Asian male, current smoker	Placebo	234	Drug withdrawn. Not recovered
55 y/o white female, current smoker	Ticagrelor 90 mg	1097	Drug interrupted. Recovered. Drug restarted ~1 month later and continued until CSED. Biopsy: "Sections of peripheral pulmonary parenchyma with disseminated fields of non-specific interstitial cellular pneumonia and signs of bronchiolitis with peri-bronchiolar fibrosis"
53 y/o white female, current smoker	Placebo	1087	Drug interrupted and recommenced on the next day after the event was considered as

			resolved by the investigator.
64 y/o white male, former smoker	Ticagrelor 90 mg	172	Drug temporarily interrupted. SOB started prior to study. Biopsy 6 months after study drug started showed interstitial lung disease. (2 months before starting study drug, CT showed fibrotic changes in upper lobe; 1 month after starting drug, Angio CT showed interstitial lung disease).
80 y/o Asian male, former smoker	Ticagrelor 90 mg	618	None (drug had been stopped at day 320 after diagnosis of gall bladder cancer). Interstitial Lung disease was considered to be resolved at ~60 days after onset. Investigator thought that a concomitant medication known to be associated with interstitial pneumonitis, gemcitabine, which had been started ~ 4 months prior to and discontinued ~ 2 weeks prior to diagnosis of interstitial lung disease, was the causative agent.
71 y/o white male non-smoker	Placebo	1081	None (discontinued for severe allergic reaction to unknown substance on day 59). Biopsy: “usual interstitial pneumonia”. Not recovered or resolved. Patient with h/o CHF.

Source: Independent review of applicant-provided narratives

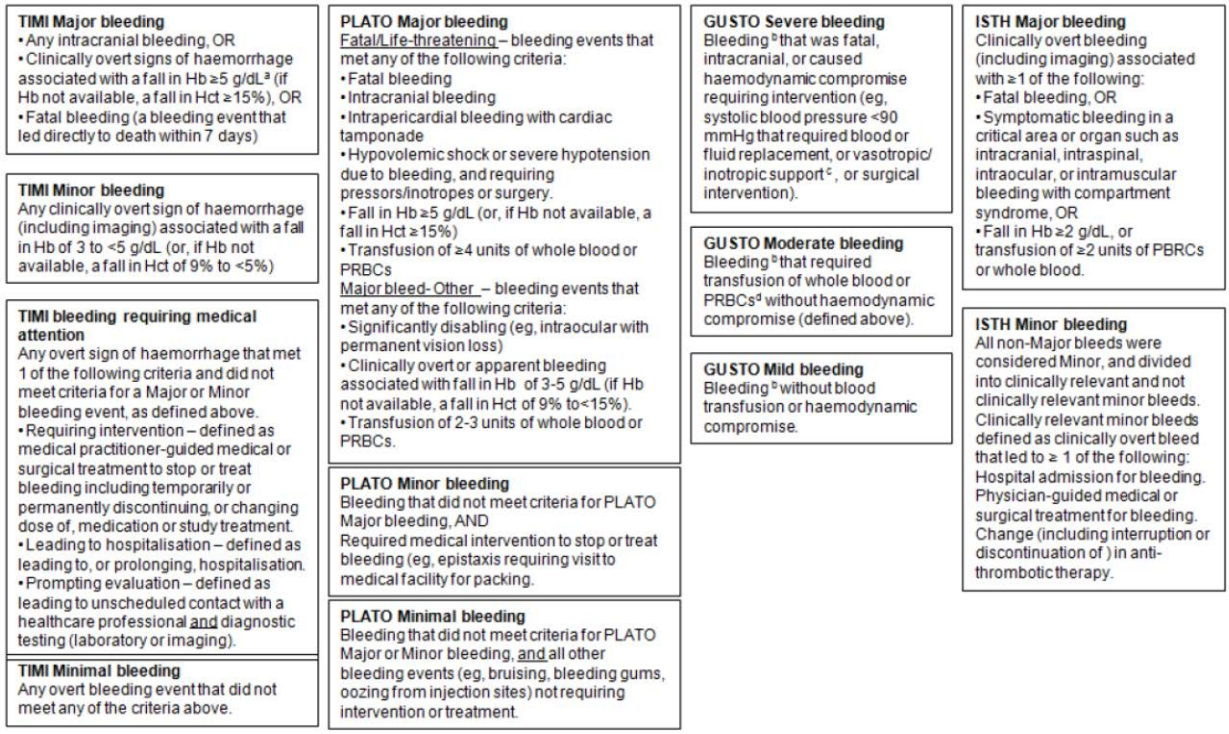
7.3.5 Submission Specific Primary Safety Concerns

Bleeding

Bleeding is an expected side effect of antiplatelet therapy, due to the mechanism of action. It is the most common and clinically important safety concern with ticagrelor, and is therefore an important component of the benefit risk analysis.

Bleeding events were classified by the CEC using the TIMI, PLATO, GUSTO, and ISTH definitions. See Figure 34 for a listing of these definitions. TIMI major bleeding was the primary safety endpoint and therefore, this reviewer has used this definition of major bleeding to analyze more severe bleeding and calculate the risk-benefit differences. TIMI major bleeding criteria are: any intracranial bleeding or clinically overt signs of hemorrhage associated with a fall in Hb ≥ 5 g/dL or fatal bleeding (resulting in death within 7 days). TIMI major bleeding differs from PLATO major bleeding mostly in that PLATO major bleeding includes transfusion as a sole criterion and TIMI major bleeding does not. GUSTO severe bleeding requires that the bleed be fatal, intracranial or causing hemodynamic compromise and does not include the sole criterion of clinically overt hemorrhage associated with a fall in Hb >= 5 g/dL which is included in the definition of a TIMI major bleed. ISTH major bleeding does include a criterion for Hb but it is much less than what is required to meet the criteria of a TIMI major bleed (fall in Hb of >= 2 g/dL or transfusion of >= 2 units of blood).

Figure 35: Bleeding Definitions



Source: p. 20 Summary of Clinical Safety

[a] To account for transfusions, haemoglobin (Hb) measurements were adjusted for any packed red blood cells (PRBCs) or whole blood given between baseline and post-transfusion measurements. Transfusion of 1 unit of blood was assumed to result in an increase by 1 gm/dL in Hb. Thus, to calculate the true change in Hb, if there had been an intervening transfusion between 2 blood measurements, the following calculations were performed: Δ Hb = [Baseline Hb - Post transfusion Hb]+[# transfused units];
Δ Haematocrit (Hct) = [Baseline Hct – post transfusion Hct] + [number of transfused units x 3].
[b] In all cases, bleeding had to be clinically overt
[c] Need for vasopressor/inotropic support for haemodynamic compromise, even if blood pressure was >90 mm Hg with treatment.
[d] Does not include cell-saver transfusion during coronary artery bypass graft.

The TIMI major bleeding comparisons among treatment groups are presented in Table 32 and Figure 35. Clearly there is more TIMI major bleeding in the ticagrelor treatment groups than in the placebo (aspirin only) treatment group and this is statistically significant. There is also a dose-relationship with slightly more TIMI major bleeding in the ticagrelor 90 mg group than in the ticagrelor 60 mg group (2.6%, 2.3% and 1.1% K-M rates in ticagrelor 90 mg, 60 mg and placebo, respectively). Most of the difference is in the “other major” bleeding category, which means clinically overt signs of hemorrhage associated with a fall in Hb ≥ 5 g/dL (2.0%, 1.6% and 0.3% K-M rates in ticagrelor 90 mg, 60 mg and placebo, respectively). Most of the “other major” bleeding was gastrointestinal bleeding. Of note, there was no increase in fatal bleeding in the ticagrelor 60 mg group compared to placebo, and ICH rates were similar (0.4% event rates in ticagrelor groups and 0.3% event rates in placebo). There was also an increase in TIMI minor bleeding (fall in Hb ≥ 3 g/dL but < 5 g/dL) (1.3%, 1.1% and 0.3% K-M rates in ticagrelor 90 mg, 60 mg and placebo, respectively). Spontaneous and traumatic

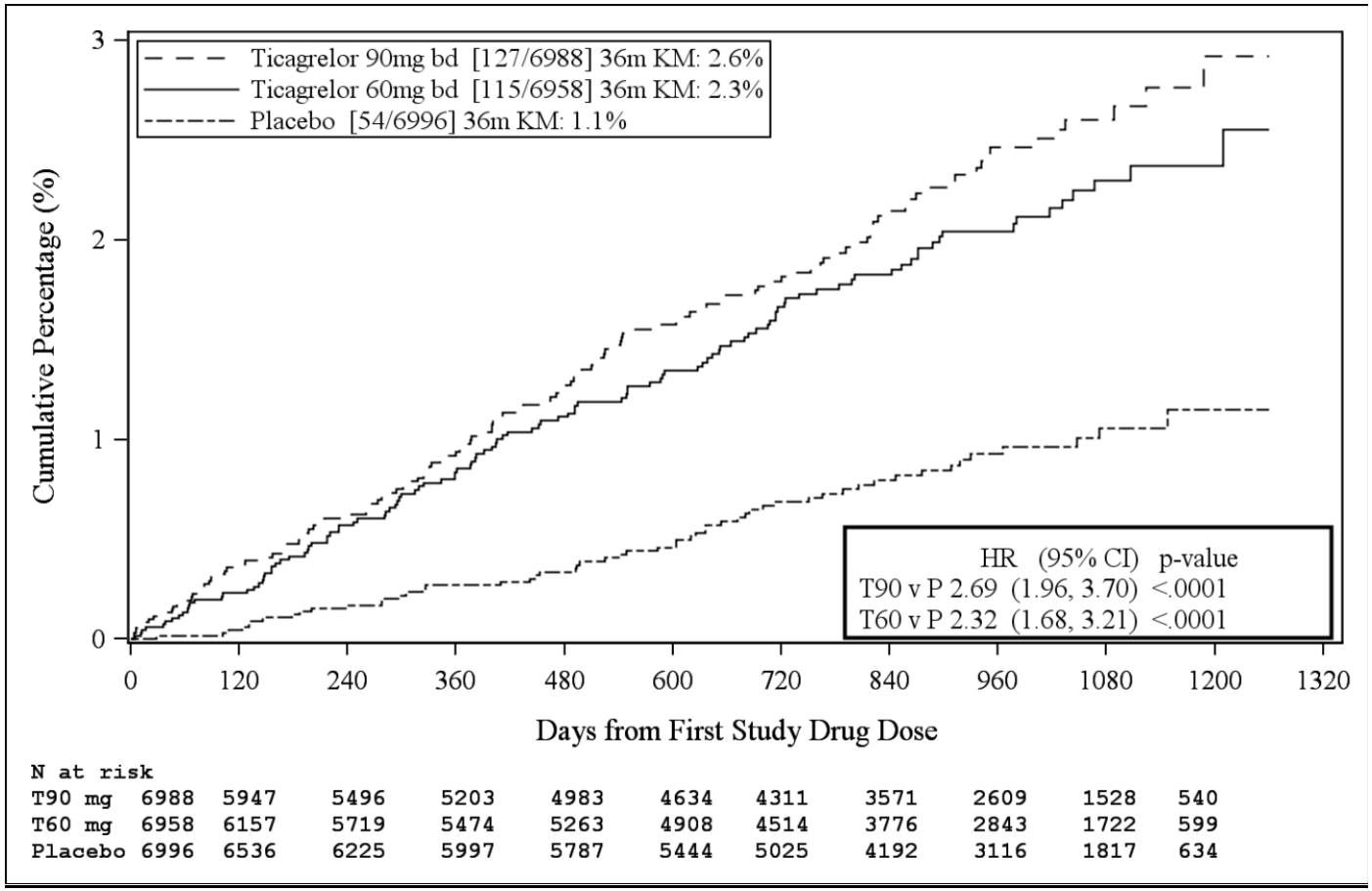
TIMI major bleeds appeared to be more common in the ticagrelor groups, but this was not true for the procedural bleeds but numbers were small and thus, it is difficult to assess.

TIMI Major or Minor bleeding or bleeding that required medical attention (not shown in table) occurred in 16.6% of subjects on ticagrelor 60 mg on a background of aspirin compared to 7.0% of subjects on aspirin alone.

Table 32: Analyses of bleeding events using TIMI definitions (on treatment –safety analysis set, Source: Summary of Clinic Safety, p. 56, 57)

	Ticagrelor 90 mg bd (N=6988)				Ticagrelor 60 mg bd (N=6958)				Placebo (N=6996)	
Characteristic	**Patients (%) with events**	**KM%**	**HR (95% CI)**	**p-value**	**Patients with events (%) with events**	**KM%**	**HR (95% CI)**	**p-value**	**Patients (%) with events**	**KM%**
TIMI Major	127(1.8%)	2.6%	2.69 (1.96, 3.70)	<.0001	115 (1.7%)	2.3%	2.32 (1.68, 3.21)	<.0001	54 (0.8%)	1.1%
Fatal	6 (0.1%)	0.1%	0.58 (0.22, 1.54)	0.27	11 (0.2%)	0.3%	1.00 (0.44, 2.27)	1.00	12 (0.2%)	0.3%
ICH	29 (0.4%)	0.6%	1.44 (0.83, 2.49)	0.19	28 (0.4%)	0.6%	1.33 (0.77, 2.31)	0.31	23 (0.3%)	0.5%
Other Major	95 (1.4%)	2.0%	4.34 (2.79, 6.74)	<.0001	83 (1.2%)	1.6%	3.61 (2.31, 5.65)	<.0001	25 (0.4%)	0.5%
TIMI Major or Minor	192 (2.7%)	3.9%	3.05 (2.32, 4.00)	<.0001	168 (2.4%)	3.4%	2.54 (1.93, 3.35)	<.0001	72 (1.0%)	1.4%
TIMI Major Subcategories										
Spontaneous	88 (1.3%)	1.8%	2.96 (1.99, 4.40)	<.0001	83 (1.2%)	1.7%	2.66 (1.79, 3.97)	<.0001	34 (0.5%)	0.7%
Procedural	16 (0.2%)	0.3%	1.66 (0.77, 3.58)	0.19	14 (0.2%)	0.3%	1.39 (0.63, 3.05)	0.42	11(0.2%)	0.2%
Traumatic	23 (0.3%)	0.5%	2.91 (1.35, 6.29)	< 0.01	17 (0.2%)	0.4%	2.06 (0.92,4.62) 4.62)	0.08	9 (0.1%)	0.2%

Figure 36: Kaplan-Meier plot of the cumulative percentage of patients with TIMI major bleeding events- on treatment (safety set)



Source: Summary of Clinical Safety, p. 61

The benefit-risk table in APPENDIX 1 (Table 35) shows that the relative risk of TIMI-major bleeding in females was the same as males and the absolute risk was even slightly less. This was an unexpected finding because usually females have higher bleeding rates in trials of antiplatelet drugs.

GI bleeding was the most common type of TIMI major bleed. There were 57 subjects (0.8%) in the ticagrelor 90 mg group, 52 subjects (0.8%) in the ticagrelor 60 mg group and 15 subjects (0.2%) in the placebo group with TIMI major bleeding with a gastrointestinal disorder etiology. Traumatic intracranial hemorrhage was the next most common type of TIMI major bleeding with 16 subjects (0.2%) in the ticagrelor 90 mg group, 14 subjects (0.2%) in the ticagrelor 60 mg group and 9 (0.1%) subjects in the placebo group having this event.

Bleeding AEs leading to discontinuation were reported for 454, 355, and 88 patients on ticagrelor 90 mg, ticagrelor 60 mg, and placebo, respectively, corresponding to Kaplan-Meier percentages at 36 months of 7.8%, 6.2%, and 1.5%: HR 5.67 (95% CI 4.51, 7.12), p <0.0001 for ticagrelor 90 mg, and HR 4.31 (95% CI 3.41, 5.45), p<0.0001 for ticagrelor 60 mg. There was an increased risk of discontinuations due to bleeding from the start of treatment with ticagrelor, which is most pronounced during the first months of treatment, but similar to placebo (aspirin only) after that. The most common bleeding AEs leading to discontinuation by PT were increased tendency to bruise, epistaxis, and spontaneous hematoma.

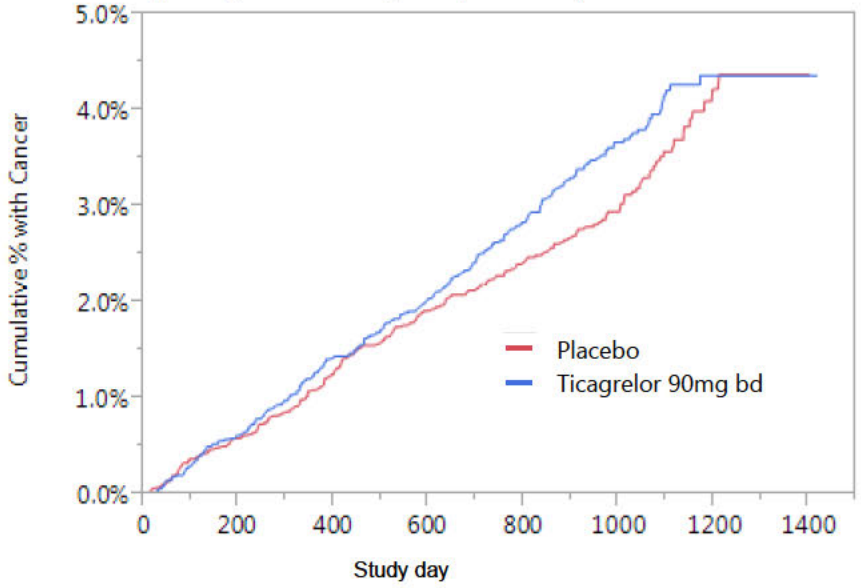
Neoplasm

A malignant neoplasm signal for the 90 mg dose of ticagrelor was detected upon reviewing the AE data for PEGASUS. It was noticed that for all malignancy excluding squamous cell carcinoma of the skin, the incidence was 3.1% for placebo, 3.1% for ticagrelor 60 mg bd and 3.7% for ticagrelor 90 mg bd. This equates to 1.3%/year for placebo, 1.5%/year for ticagrelor 60 mg bd and 1.8%/year for ticagrelor 90 mg bd. In PLATO the event rates for malignancy excluding squamous cell carcinoma of the skin in both the ticagrelor 90 mg bd and clopidogrel 75 mg od arms were ~ 2.1%/year and this was a much shorter study (average exposure time in PLATO and PEGASUS were ~ 9 months and 2 years, respectively). For the purpose of this review, the decision was made to analyze the neoplasm signal subtracting all non-melanoma skin cancers (including squamous cell and basal cell). There were 213 (3.0%), 223 (3.2%) and 244 (3.5%) malignancies (not including non-melanoma skin cancers) in PEGASUS in the placebo, ticagrelor 60 mg and ticagrelor 90 mg treatment groups, respectively. This equates to an average rate of 1.16%/year, 1.22%/year and 1.3%/year for the 3 groups, respectively.

In PEGASUS, the types of cancers that were more common in the ticagrelor 90 mg bd arm were respiratory/mediastinal, prostate/male genitalia, and breast. In PLATO, the 3

most common cancers were respiratory/ mediastinal, prostate and colonic (see Table 44). Figure 36 shows that after ~ 2 years the curves of cumulative % of cancers (not including non-melanoma skin cancers for ticagrelor 90 mg and placebo start to separate. there was a much smaller signal for the 60 mg dose of ticagrelor shown in Figure 37. Figure 38 shows a minimal neoplasm signal for benign neoplasms.

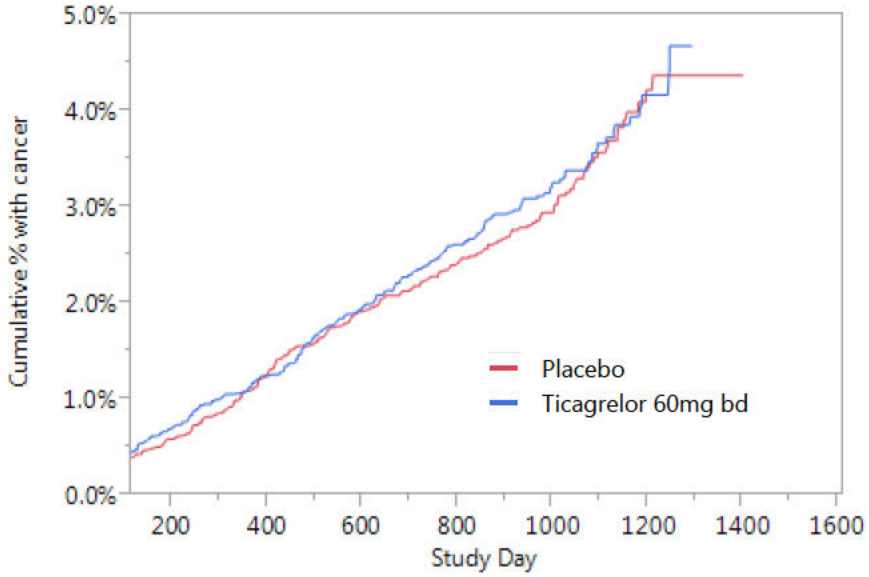
Figure 37: K-M plot of malignancies (not including non-melanoma skin cancers) during PEGASUS (Ticagrelor 90 mg vs. placebo)



Group		Number failed	Number censored	Mean		Std Error
Placebo		213	6783	1188.03	Biased	1.64245
Ticagrelor 90mg bd		244	6744	1146.58	Biased	1.63893
Combined		457	13527	1186.43	Biased	1.19265
Test	**ChiSquare**	**DF**	**Prob>ChiSq**			
Log-Rank	2.0665	1	0.1506			
Wilcoxon	2.7217	1	0.0990			

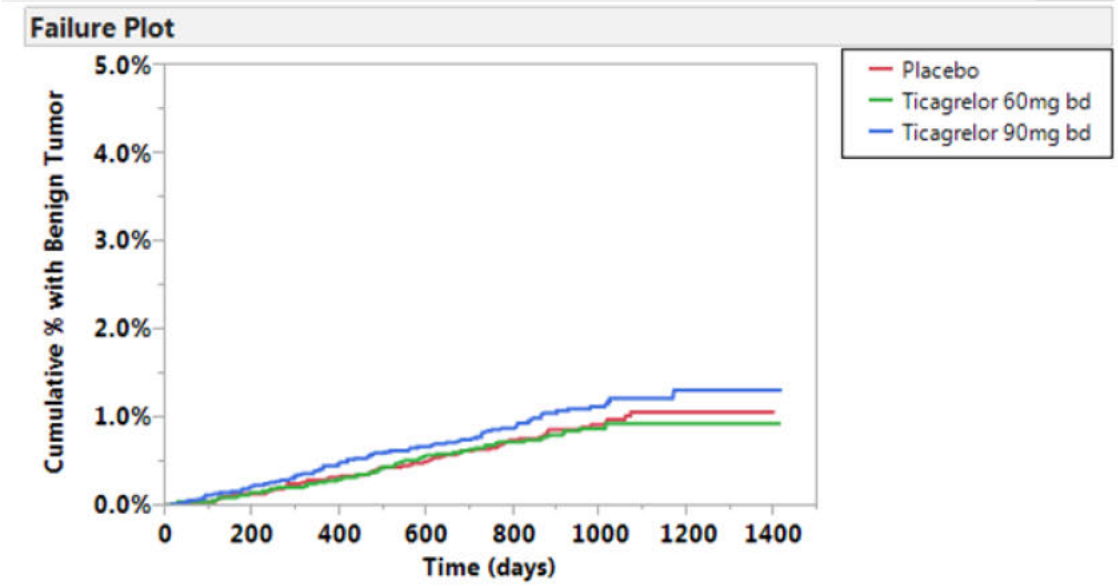
Source: Reviewer's analysis using RSAE dataset

Figure 38: K-M plot of malignancies (not including non-melanoma skin cancers) during PEGASUS (Ticagrelor 60 mg vs. placebo)



Group		Number failed	Number censored	Mean		Std Error
Placebo		213	6783	1188.03	Biased	1.64245
Ticagrelor 60mg bd		223	6735	1265.21	Biased	1.8988
Combined		436	13518	1265.83	Biased	1.32355
Test	**ChiSquare**	**DF**	**Prob>ChiSq**			
Log-Rank	0 2586	1	0.6111			
Wilcoxon	0.3545	1	0.5516			

Figure 39: Kaplan-Meier for development of a benign neoplasm (safety set)



Time to event: T benign
Censored by C benign
Censor Code 1
Grouped by Tx

Summary

Group	Number failed	Number censored	Mean		Std Error
Placebo	61	6935	1065.03	Biased	0.70478
Ticagrelor 60mg bd	57	6901	1008.62	Biased	0.64385
Ticagrelor 90mg bd	75	6913	1161.31	Biased	0.94342
Combined	193	20749	1162.49	Biased	0.4942

Quantiles

Group	Median Time	Lower 95%	Upper 95%	25% Failures	75% Failures
Placebo	.	.	.	.	.
Ticagrelor 60mg bd	.	.	.	.	.
Ticagrelor 90mg bd	.	.	.	.	.
Combined	.	.	.	.	.

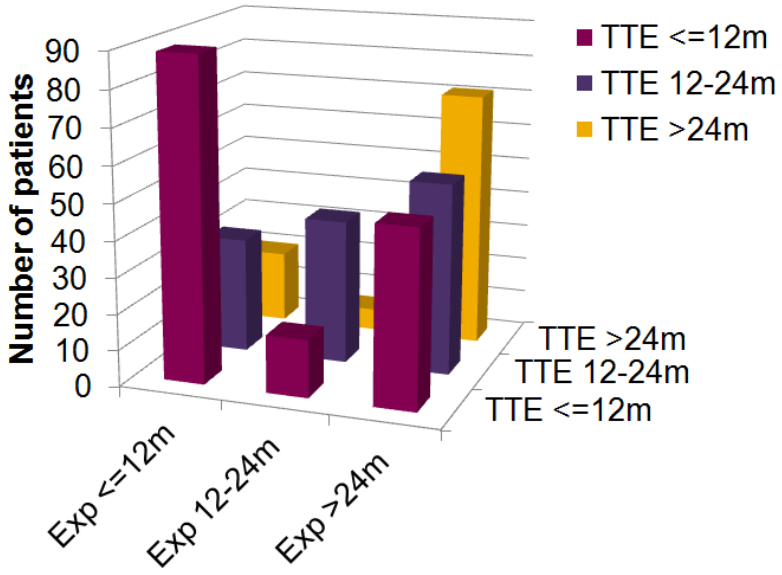
Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	2.7230	2	0.2563
Wilcoxon	2.5309	2	0.2821

The applicant was asked to address this signal.
The applicant submitted data in supplement 1226 on 6/12/2015 that demonstrated that the unfavorable imbalance in carcinoma AEs between ticagrelor 90 mg bd and placebo

occurred in subjects who had less than year of exposure. If ticagrelor were carcinogenic, one would expect that the imbalance would increase with time of exposure. See Figure 39. The applicant's position is that because the duration of exposure to study drug did not correlate with risk of carcinoma, it is less likely that ticagrelor caused the increase in neoplasm observed in the ticagrelor 90 mg bd treatment group.

Figure 40: Incidence of malignancy events by duration of exposure to study drug and time to event: ticagrelor 90 mg (Safety Analysis Set)



Exp=duration of exposure; TTE=time to malignancy event in months (m).
Source: supplement 1226

While this observation provides evidence against an exposure-response relationship, one might still question if those subjects who were exposed longer would have a cancer signal that might be delayed beyond the observation period and thus, not observed.

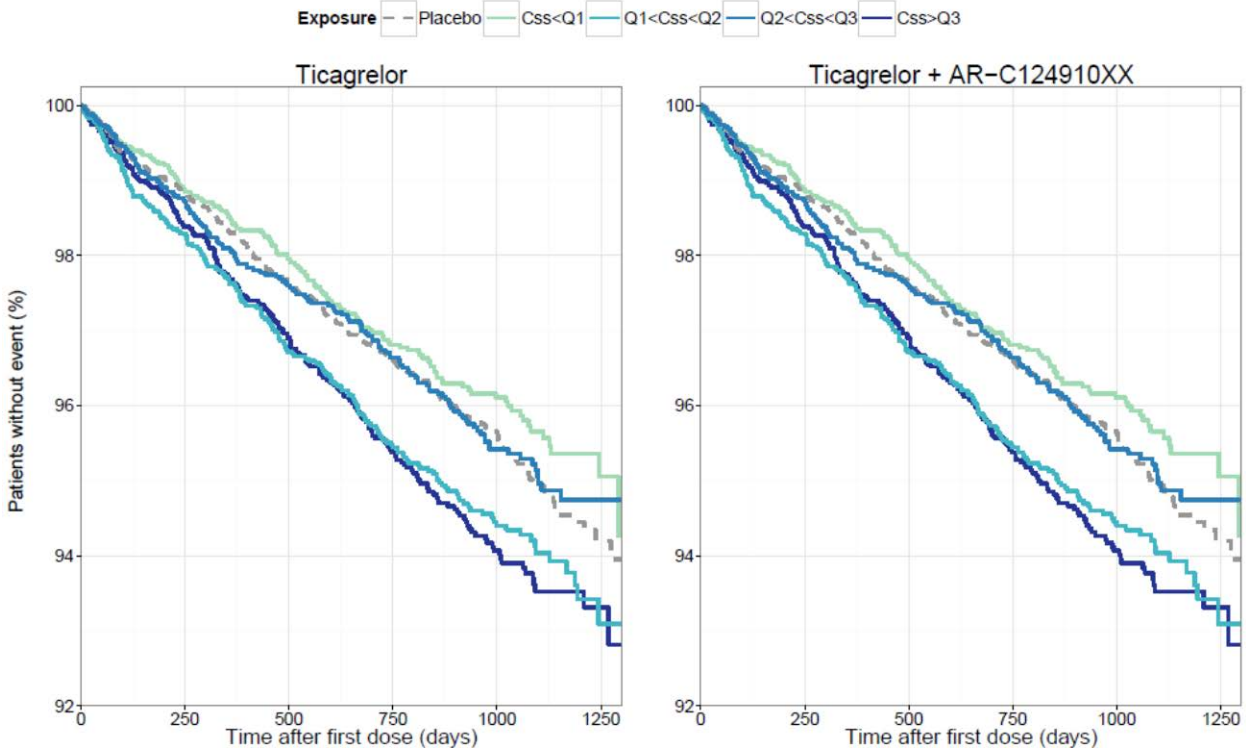
The carcinogenicity signal was further pursued by asking the applicant to provide information regarding the relationship between serum levels of ticagrelor in the PK subset and incidence of nonsquamous cell malignancies. My intention was to ask for non-squamous cell skin cancers (because these are considered to be low malignancy potential tumors), but the applicant reasonably understood my request to mean that I wanted *all* squamous cell carcinomas excluded. There were 12 cases of squamous cell carcinoma that were affecting organs other than skin that were omitted from the analyses done by applicant. Because these non-skin squamous cell carcinomas accounted for only 1.7% malignancies, the interpretability of the analysis was not affected. Another error on my part was to not specify that the applicant should remove

Reference ID: 3804604

basal cell carcinomas from the analyses. These cancers are generally benign. There were 153 basal cell carcinomas, 56 in the placebo arm, 45 in the ticagrelor 60 mg arm and 52 in the ticagrelor 90 mg arm. While they should have been excluded, they are well-balanced among the arms and therefore were not responsible for driving the signal. Furthermore, including them in the applicant's analysis would not be likely to alter the outcome of the applicant's analysis of exposure vs. cancer incidence.

The applicant's analysis of the correlation between non-squamous cell carcinomas and serum levels of ticagrelor in the PK subpopulation showed that while the 90 mg ticagrelor recipients had an average higher serum level concentration and a higher risk of cancer, the serum levels did not appear to be predictive of whether anyone in either of the ticagrelor treatment groups developed non-squamous cell carcinoma. Overall, the levels of ticagrelor in subjects who had non-squamous cell carcinoma and those who did not were similar within treatment arms (similar medians and similar 25th and 75th percentiles). There were overall higher levels in the subjects who received ticagrelor 90 mg bd than those who received ticagrelor 60 mg bd as would be expected, but there was considerable overlap of levels between the two treatment groups and one would have expected a signal in both treatment arms if it was reflective of a carcinogenic effect of ticagrelor. In the time to event of nonsquamous cell carcinoma in which the pK data from the pK population was extrapolated to the entire population, there was a steeper time to event curve for patients in the highest and the second quartile of exposure (lower % without event/ time after first dose in days) than in the 3rd quartile and placebo which overlapped. The subjects extrapolated to be in the 1st quartile of ticagrelor exposure slope were the least likely to have an event over time. See Figure 40. One needs to keep in mind that this is an extrapolated analysis based on certain characteristics of the rest of the population studied. For the pK subset alone, the 2nd, 3rd and 4th quartiles overlap and are steeper in slope than the 1st quartile and placebo which also overlap (Figure 41). When looking at the dose groups separately both by overall population extrapolation (not shown) and by the pK subpopulation (Figure 42 and Figure 43), no correlation between exposure and cancer incidence was apparent.

Figure 41: Kaplan-Meier estimate of patients without events of ALL non-squamous cell carcinoma vs. time after first dose by Css quartile[a] (overall population)

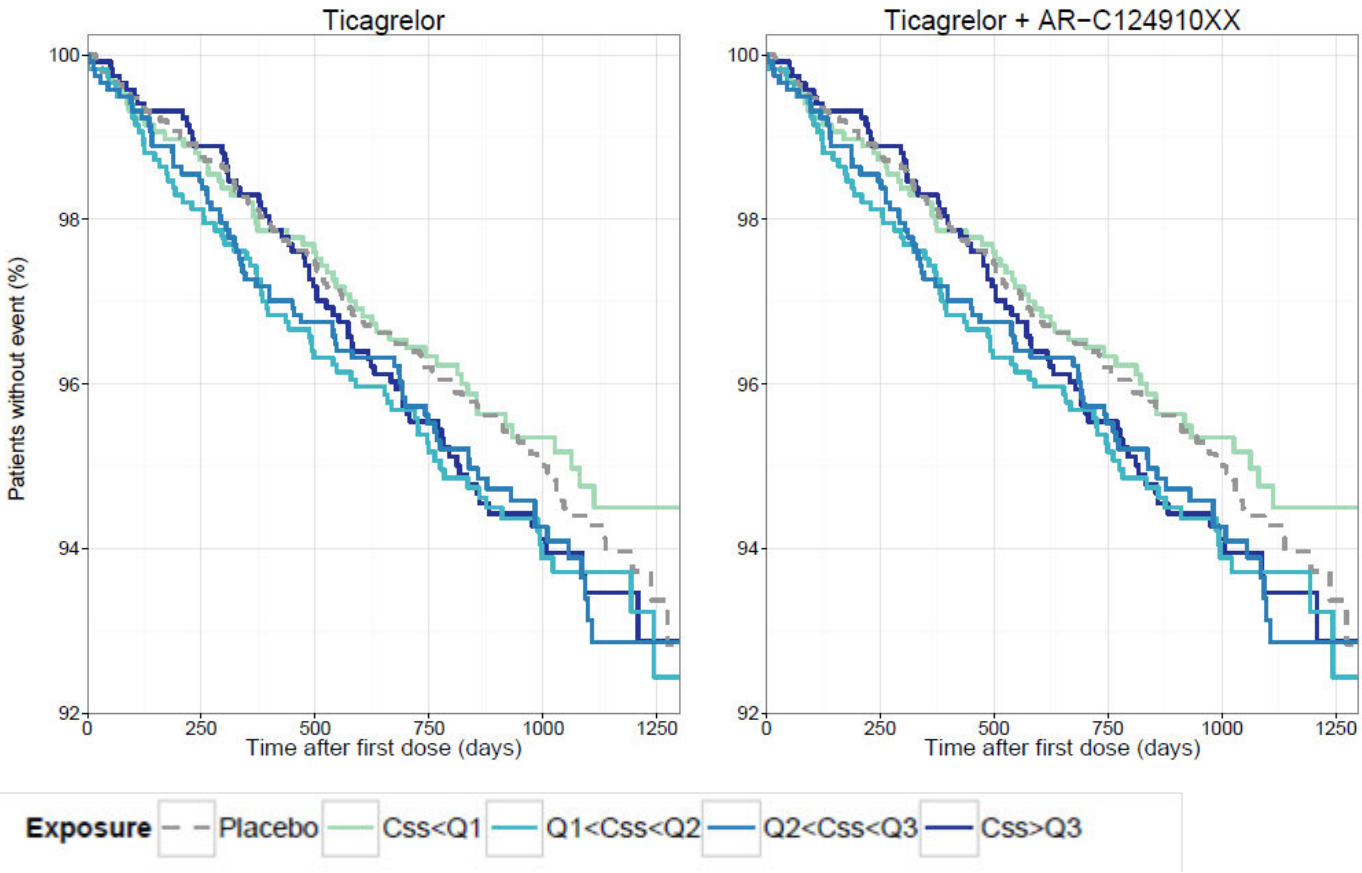


[a]: The dotted line is the Kaplan-Meier estimate for patients receiving placebo. The colored lines are Kaplan- Meier estimates for patients receiving ticagrelor based on the C_{ss} quartiles for ticagrelor/ticagrelor metabolite: Css-Q1 is patients with exposure ≤ the 25th percentile; Q1<Css<Q2 is patients with exposure >than the 25th percentile and ≤ the median; Q2<Css<Q3 is patients with exposure > than the median and ≤the 75th percentile; and Css>Q3 is patients with exposure > the 75th percentile.

C_{ss}: Steady state plasma concentration

Source supplement 1226

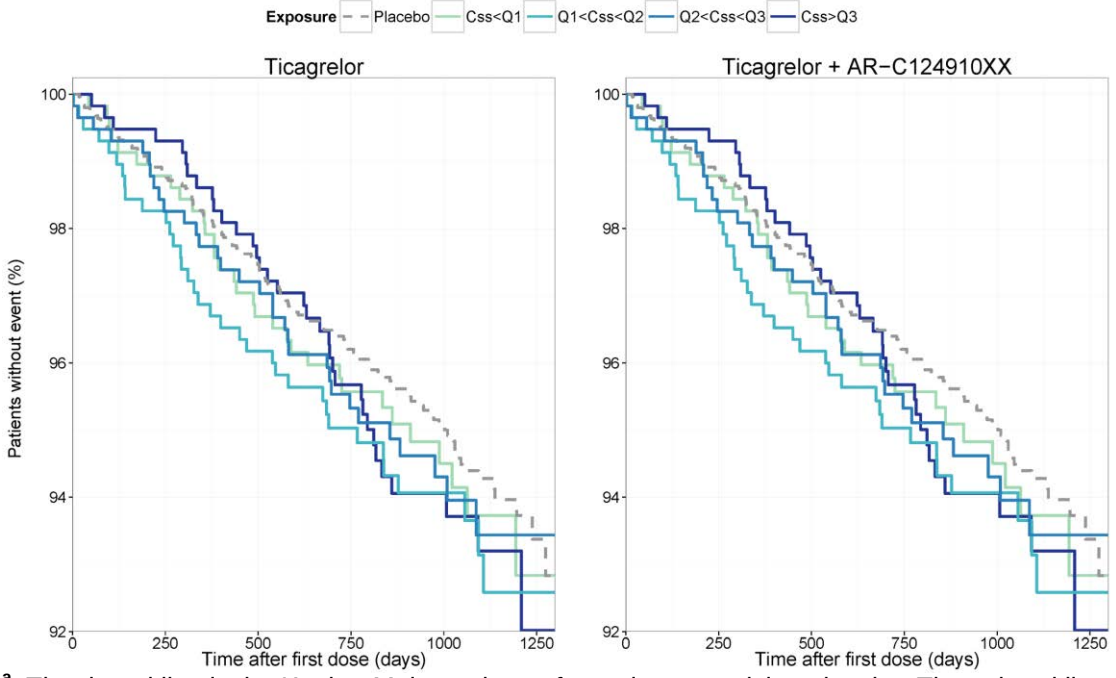
Figure 42: Kaplan-Meier estimate of patients without events of ALL non-squamous cell carcinoma vs. time after first dose by C_{ss} quartile[a] (PK subset- ticagrelor treatment groups combined vs. placebo)



[a]: The dotted line is the Kaplan-Meier estimate for patients receiving placebo. The colored lines are Kaplan- Meier estimates for patients receiving ticagrelor based on the C_{ss} quartiles for ticagrelor/ticagrelor metabolite: Css-Q1 is patients with exposure ≤ the 25th percentile; Q1<Css<Q2 is patients with exposure >than the 25th percentile and ≤ the median; Q2<Css<Q3 is patients with exposure > than the median and ≤the 75th percentile; and Css>Q3 is patients with exposure > the 75th percentile.

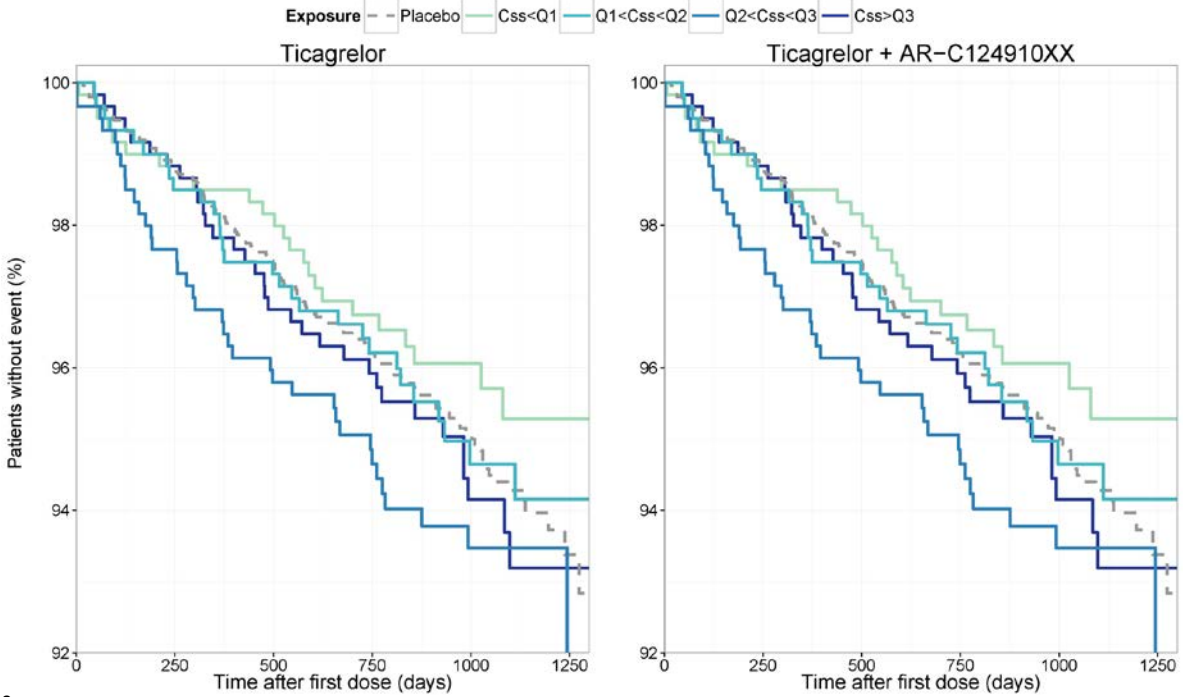
C_{ss}: Steady state plasma concentration
Source supplement 1226:

Figure 43: Kaplan-Meier estimate of patients without events of ALL non-squamous cell carcinoma vs. time after first dose by C_{ss} quartile[a] (PK subset- ticagrelor 90 mg group vs. placebo)



[a]: The dotted line is the Kaplan-Meier estimate for patients receiving placebo. The colored lines are Kaplan- Meier estimates for patients receiving ticagrelor based on the C_{ss} quartiles for ticagrelor/ticagrelor metabolite: Css-Q1 is patients with exposure ≤ the 25th percentile; Q1<Css<Q2 is patients with exposure >than the 25th percentile and ≤ the median; Q2<Css<Q3 is patients with exposure > than the median and ≤the 75th percentile; and Css>Q3 is patients with exposure > the 75th percentile.
C_{ss}: Steady state plasma concentration
Source supplement 1226:

Figure 44: Kaplan-Meier estimate of patients without events of ALL non-squamous cell carcinoma vs. time after first dose by C_{ss} quartile[a] (PK subset- ticagrelor 60 mg group vs. placebo)



[a]: The dotted line is the Kaplan-Meier estimate for patients receiving placebo. The colored lines are Kaplan- Meier estimates for patients receiving ticagrelor based on the C_{ss} quartiles for ticagrelor/ticagrelor metabolite: Css-Q1 is patients with exposure ≤ the 25th percentile; Q1<Css<Q2 is patients with exposure >than the 25th percentile and ≤ the median; Q2<Css<Q3 is patients with exposure > than the median and ≤the 75th percentile; and Css>Q3 is patients with exposure > the 75th percentile.
$C_{ss:}$ Steady state plasma concentration

If incidence of malignancy excluding squamous cell carcinoma of the skin was related to exposure one would have expected to see increased incidence in females because they were shown to have higher exposures. This was not the case. See Table 33.

Table 33: Incidence of malignancy (excluding squamous cell carcinomas of the skin) by sex and treatment

Placebo		Ticagrelor 60 mg bd		Ticagrelor 90 mg bd	
N= 6996		N=6958		N=6988	
Female N=1702	Male N=5294	Female N=1638	Male N=5320	Female N=1663	Male N=5325
n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
41 (2.4)	174 (3.3)	34 (2.1)	186 (3.5)	50 (3.0)	206 (3.9)

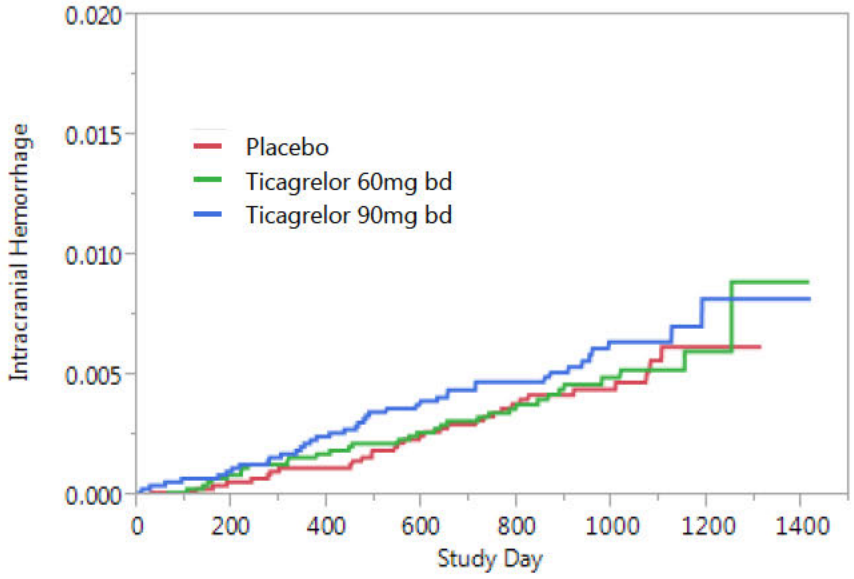
Source: Reviewer's analysis

These data overall do not provide convincing support of an exposure-mediated effect of ticagrelor on neoplastic potential/ carcinogenicity. The data also do not rule out a dose-mediated risk. So we are left with not knowing if the signal of increased neoplasm in the Ticagrelor 90 mg arm was a chance finding or reflective of a true increase in risk for neoplasm. Without a trial designed to look specifically at this carcinogenicity signal, it is wisest at this time to not make premature conclusions, nor to put the observation in the label. The unintended consequence of deterring clinicians and patients from the use of this efficacious drug for unsubstantiated fear of cancer would be unfortunate.

Intracranial hemorrhage:

According to the applicant's report, intracranial hemorrhage events were reported in 29, 28, and 23 patients on ticagrelor 90 mg, ticagrelor 60 mg, and placebo, respectively (on treatment). I looked at events that occurred during the overall treatment period (post-discontinuation as well) and got 41, 33 and 33, respectively. It is reassuring that there is little to no increased risk of intracranial hemorrhage in the ticagrelor 60 mg bd treatment group. See Figure 44.

Figure 45: K-M plot of time to Intracranial Hemorrhage (safety set)



Source: Reviewer's analysis

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The applicant's AE analysis revealed that the most common AEs including bleeding were dyspnea, epistaxis, increased tendency to bruise, nasopharyngitis, non-cardiac chest pain, dizziness, spontaneous hematoma, hypertension, bronchitis, diarrhea, and back pain. The incidence of some of these common AEs was similar among treatments making it unlikely that they were treatment related (for example, nasopharyngitis, non-cardiac chest pain, dizziness, hypertension, bronchitis and diarrhea. Only dyspnea and bleeding-related AEs occurred considerably more frequently in the ticagrelor treatment groups than in the placebo treatment groups. (~ 2 -5 X as often). The increased frequency of these AEs in the ticagrelor treatment groups made it more likely that there was a causal relationship. Making the causal relationship more plausible, dyspnea and bleeding are AEs that were identified as causally related to ticagrelor in the previous pivotal study, PLATO. Given the antiplatelet action of ticagrelor, bleeding would be expected. The reason for the dyspnea is thought to be related to P2Y12 receptor inhibition, particularly if that inhibition is reversible. There is some experimental

Reference ID: 3804604

evidence that indicates that inhibition of P2Y12 increases the conductivity of vagal C-fibers and the sensation of dyspnea.[6]

My own analysis of AEs in which I used the automated AE renaming tool (APPENDIX 6.) is presented in Table 34. Some of the AEs are endpoint events (myocardial infarction, ischemia and CAD, some bleeds). The protocol specified that clinical data for suspected endpoints (with the exception of procedural related bleeding if expected for the procedure) would be collected as AEs/ SAEs on separate forms in the eCRF. A category like "CAD, myocardial ischemia and ACS" is broader than MACE because it could include non-acute coronary disease. "Any bleed" would capture minor bleeds as well as the more serious bleeds that counted as secondary endpoint events.

Common AEs that appeared to be drug related (dose-related and increased over placebo) were comparable to the results of the applicant's analysis.

Table 34: AEs that occurred > 3% in either ticagrelor arm (safety set), on treatment

	Placebo	Ticagrelor 60 mg bd	Ticagrelor 90 mg bd	RR T60/P	RR T90/P
	N=6996	N=6958	N=6988		
	n(%)	n(%)	n(%)		
Infection, all	1596(22.81)	1572(22.59)	1551(22.2)	0.99	0.97
Bleeding, any	507(7.25)	1215(17.46)	1347(19.28)	2.41	2.66
Dyspnea/SOB/ respiratory distress	381(5.45)	991(14.24)	1208(17.29)	2.61	3.17
URI or flu-like illness	645(9.22)	624(8.97)	632(9.04)	0.97	0.98
Chest pain (not angina or unknown etiology)	520(7.43)	489(7.03)	435(6.22)	0.95	0.84
Ecchymosis	112(1.6)	485(6.97)	585(8.37)	4.36	5.23
Angina	498(7.12)	450(6.47)	436(6.24)	0.91	0.88
Dyspepsia, gastritis, duodenitis	413(5.9)	425(6.11)	417(5.97)	1.04	1.01
Epistaxis	156(2.23)	422(6.06)	511(7.31)	2.72	3.28
Arrhythmia	404(5.77)	417(5.99)	383(5.48)	1.04	0.95
CAD, myocardial ischemia, ACS	505(7.22)	405(5.82)	382(5.47)	0.81	0.76
Arthralgia, arthritis, arthrosis	427(6.1)	403(5.79)	351(5.02)	0.95	0.82
Hypertension, BP increased	393(5.62)	390(5.61)	329(4.71)	1	0.84
Abdominal pain, distension, bloating, IBS	379(5.42)	377(5.42)	341(4.88)	1	0.9
ACS (= AMI/ unstable angina)	441(6.3)	363(5.22)	336(4.81)	0.83	0.76
Diarrhea, colitis, enteritis, gastroenteritis, C-diff	301(4.3)	357(5.13)	308(4.41)	1.19	1.03
Dizziness, light-headedness	261(3.73)	292(4.2)	307(4.39)	1.13	1.18
Asthenia, fatigue, malaise, weakness	300(4.29)	290(4.17)	272(3.89)	0.97	0.91
Diabetes, glucose intolerance, hyperglycemia, glycosuria	310(4.43)	285(4.1)	226(3.23)	0.93	0.73
Solid neoplasia, ALL (benign, malignant, unknown)	322(4.6)	282(4.05)	308(4.41)	0.88	0.96
Infection, viral	305(4.36)	264(3.79)	267(3.82)	0.87	0.88
Bronchitis, bronchiolitis, tracheitis, alveolitis	248(3.54)	242(3.48)	260(3.72)	0.98	1.05
Supra-ventricular tachycardia	228(3.26)	242(3.48)	215(3.08)	1.07	0.94
AFib or AFlutter	200(2.86)	221(3.18)	184(2.63)	1.11	0.92
Anemia	115(1.64)	219(3.15)	215(3.08)	1.92	1.88

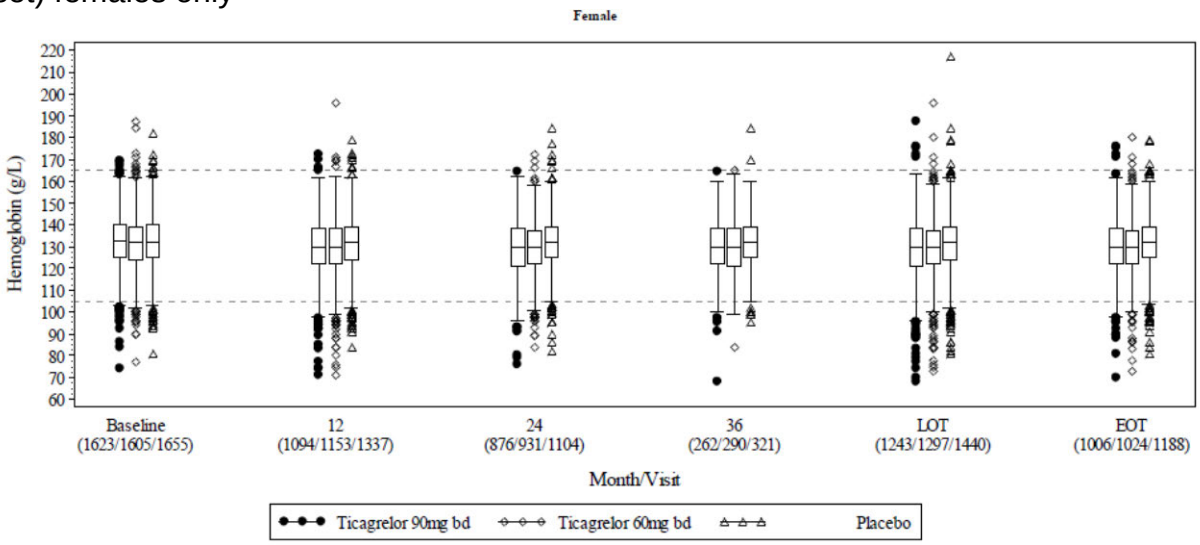
6 Cattaneo, Marco and Faioni, Elena, "Why does ticagrelor induce dyspnea?" Thrombosis and Haemostasis, 2012: 108/6 (Dec), pp. 1031-1036.

Reference ID: 3804604

7.4.2 Laboratory Findings

Hematology:
As would be expected, a minor trend for decreased mean hemoglobin values from baseline was observed during treatment with ticagrelor compared with placebo. In Figure 45, the pattern of decrease in hemoglobin for the ticagrelor treatment groups is shown. The pattern is similar to that seen in males. No other hematology parameters were clearly different by treatment over time. Also, there were no apparent treatment differences in the pattern of shifts (decreased, increased, or no change) from baseline to last visit on treatment.

Figure 46: Hematology laboratory data, box plot of Hb absolute values (safety analysis set) females only



Source: Clinical study report, p.8747

Chemistry:
Changes in creatinine and uric acid are discussed in section 7.3.4. Observed extreme changes in liver enzymes are also discussed in section 7.3.4. There were no apparent treatment differences in either mean value or mean change from baseline in ALP, AST, ALT, total bilirubin, or glucose. There were no apparent treatment differences in the pattern of shifts in clinical chemistry parameters.

Urinalysis: There were no apparent differences across treatment groups.

7.4.3 Vital Signs

There were no apparent differences across treatment groups in heart rate, blood pressure and weight.

7.4.4 Electrocardiograms (ECGs)

In the PEGASUS study, ECGs were scheduled at enrollment and end of treatment (EoT), and were only to be used as a clinical reference if indicated. ECGs were performed according to local clinical practice to document any occurrences of MI or recurrent cardiac ischemia during the study. ECG data were only collected for reference, if indicated; no analysis was performed. For AEs related to bradyarrhythmias, see Section 7.3.4.

7.4.5 Immunogenicity

There is some concern for allergic reactions/ hypersensitivity to ticagrelor. See section 7.3.4. No immunogenicity studies were conducted.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

There was a trend for increased TIMI major bleeding and dyspnea in the ticagrelor 90 mg group as compared to the ticagrelor 60 mg group. For this reason, and no increase in efficacy with the higher dose, the ticagrelor 60 mg dose was selected for marketing.

7.5.2 Time Dependency for Adverse Events

TIMI major bleeding occurred at a fairly steady rate throughout the study. Dyspnea AEs happened earlier in subjects who were on ticagrelor than in subjects on placebo. Median times to first dyspnea AE were 11, 29 and 240 days for subjects on ticagrelor 90 mg, ticagrelor 60 mg and placebo, respectively.

7.5.3 Drug-Demographic Interactions

Age may have some impact on major bleeding risk, with slight increases with increasing age quintiles. Smoking increased risk of TIMI major bleeding. Blacks and Asians and “other race” had more TIMI major bleeding in the ticagrelor 60 mg arm. However, one would expect differences in HR point estimates across subgroups given the large number of patient characteristic analyzed. It is not reasonable to make too much of these observed interactions.

7.5.4 Drug-Disease Interactions

Hepatic Disorder at Baseline:

There were 165 patients included in the study with moderate or severe increase in liver function tests at baseline. The frequency of AEs in this subgroup was similar across all treatment groups (78.7%, 69.1%, and 83.7% for placebo, ticagrelor 60 mg bd, and ticagrelor 90 mg bd groups, respectively). Also, few hepatic-related AEs were reported in patients with moderate or severe increase in liver function tests at baseline; 4 for placebo, 2 for ticagrelor 60 mg and 1 for ticagrelor 90 mg. Bleeding in this subgroup of subjects with baseline hepatic dysfunction was investigated. Five of the patients with moderate or severe elevations in liver function tests at baseline (n=165) had TIMI Major bleeding events, suggesting no increased risk in these patients: 2, 1, and 2 events in the placebo, ticagrelor 60 mg bd, ticagrelor 90 mg bd groups, respectively.

Renal Disease at Baseline
There appears to be no major interactions between renal disease and safety, although patients with end stage renal disease were not studied.

Underlying High Degree Heart Block
Patients considered to be at risk of bradycardic events (e.g. known sick sinus syndrome or second or third degree atrioventricular (AV) block]) were excluded from both PEGASUS and PLATO unless they had a permanent pacemaker. Despite this exclusion, there is some concern that patients with high degree of heart block could be adversely affected by ticagrelor because bradycardia occurred commonly in PLATO and a Holter substudy in PLATO confirmed the increased frequency of ventricular pauses and other cardiac arrhythmias. Syncope, pre-syncope and loss of consciousness were reported by 1.7% and 1.5% of ticagrelor 90 mg bd and clopidogrel subjects, respectively in PLATO. Likewise, in PEGASUS syncope and near syncope was reported by 1.7%, 1.5% and 1.2% of subjects on ticagrelor 90 mg, ticagrelor 60 mg and placebo (aspirin alone), respectively.

Reviewer's Comment: It may be wise to provide a warning regarding the possibility of worsening arrhythmia in patients with high degree of heart block.

7.5.5 Drug-Drug Interactions

There have been no further studies to elucidate drug-drug interactions. We know the following from the previous review cycle:

Coadministration of ticagrelor with CYP3A inducers results in increasing its clearance by 110%. Examples of CYP3A inducers are rifampin, dexamethasone, phenytoin, carbamazepine and phenobarbital. For this reason, ticagrelor may be less effective in patients on these medications.

Ticagrelor appears to be a weak activator of CYP3A5 which means that the bioavailability of drugs that are metabolized by CYP3A5 may be decreased when the drugs are coadministered. Examples of drugs metabolized by ticagrelor are midazolam, cyclosporine, nifedipine, testosterone, progesterone and androstenedione.

Ticagrelor is also a weak CYP3A4 inhibitor and causes decreased metabolism of simvastatin, atorvastatin, and estradiol. A study was done (D5130C00042) that evaluated the potential interaction between ticagrelor 90mg bd and Nordette®, a monophasic oral contraceptive (0.03 mg ethinyl estradiol plus 0.15 mg levonorgestrel) in 20 healthy female subjects of childbearing potential. Coadministration of ticagrelor and ethinyl estradiol/levonorgestrel resulted in increases in ethinyl estradiol exposure (30% in Cmax and 20% in AUC), but had no effect on levonorgestrel plasma levels. Low progesterone concentrations were seen throughout the luteal phase, suggesting that ovulation did not occur and that ticagrelor should not interfere with the effects of oral contraceptives.

Ticagrelor is also a weak inhibitor of P-gp, making it important to monitor digoxin levels in clinical practice.

Concomitant medications with an identified potential for interaction were simvastatin, atorvastatin, digoxin and diltiazem. Drug classes selected as they are commonly co-prescribed in ACS patients were statins, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), proton-pump inhibitors (PPI) and beta blockers.

In vitro, ticagrelor and/or AR-C124910XX were shown to moderately inhibit CYP2C9 activities. In a clinical pharmacology study, however, concomitant administration of ticagrelor with tolbutamide, a representative CYP2C9 substrate did not affect the PK parameters of tolbutamide and its primary metabolite, 4-hydroxytolbutamide (Study D5130C00051), which suggest that ticagrelor is not a CYP2C9 inhibitor *in vivo* and unlikely to alter the metabolism of drugs such as warfarin and tolbutamide whose metabolism is mediated via CYP2C9

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

The lifetime carcinogenicity study in rats with ticagrelor showed an increased incidence in uterine adenocarcinoma, a slight increase in hepatic adenomas, and one case of hepatocellular carcinoma. To provide perspective, the effected rats received 180

mg/kg/day of ticagrelor. Daily AUC exposures to ticagrelor in rats given 180 mg/kg/day are 29-fold higher than human AUC exposures following 90 mg bd and exposure to the main active metabolite AR-C124910 following exposure of 180 mg/kg/day are 24-fold higher than the clinical AUC exposures to the metabolite. No increases in tumor incidences were observed in the mouse carcinogenicity study where exposures to ticagrelor and the metabolite were comparable to those seen in rats. Toxicity studies up to a year in duration in marmosets have not shown any uterine proliferative changes. Ticagrelor and the active metabolite ARC124910 are not mutagenic in the Ames test and mouse lymphoma assay, and ticagrelor was not active in the rat micronucleus test (the metabolite was not tested in the rat micronucleus test).

In PLATO, deaths due to cancer overall were similar between treatment groups, (ticagrelor 15, 0.2%; clopidogrel 17, 0.2%) regardless of the presence or absence of a neoplasm at baseline. The frequency of patients with solid malignant tumors was 72(0.78%) for ticagrelor and 79 (0.86%) for clopidogrel. When examining frequencies of specific types of malignancies separately (hematologic, lymphoma, gastrointestinal, ovarian, prostate, testicular, hepatobiliary, respiratory system, skin, breast or CNS neoplasms), this reviewer found no concerning differences between the treatment groups.

In PEGASUS, there was a signal for malignant neoplasm. See section 7.3.5 for a comprehensive discussion.

7.6.2 Human Reproduction and Pregnancy Data

Animal studies did not indicate direct harmful effects with respect to pregnancy, embryonal/fetal development, parturition, or postnatal development. Ticagrelor did not affect male or female fertility.

The safety of ticagrelor in Humans during pregnancy or lactation has not been established. Limited clinical data on exposure to ticagrelor during pregnancy are available and none on lactation.

Despite enrollment criteria to prevent fetal exposure to ticagrelor, there was 1 documented exposure during pregnancy. A 38-year-old woman became pregnant during the study. The pregnancy continued post-study period, at which time she delivered a healthy female full-term baby.

While it is not known whether ticagrelor is excreted in human milk, studies in rats have shown that ticagrelor and its active metabolite are excreted in mammary milk.

Ticagrelor should be used during pregnancy only if the potential benefit to the mother justifies any potential risks to the fetus.

The use of ticagrelor during breastfeeding is not recommended.

7.6.3 Pediatrics and Assessment of Effects on Growth

The effect of ticagrelor in children has not been explored. A recent in vitro study concluded that ticagrelor would achieve a comparable anti-platelet effect in children of different ages as in adults at equal plasma exposure.7

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Based on its pharmacological properties, ticagrelor is not likely to have a potential for drug abuse, and no findings during the clinical studies indicate that ticagrelor induces drug abuse.

Two patients met the criteria for overdose during the study, 1 patient in each of the ticagrelor 90 mg and 60 mg groups. One patient in the ticagrelor 60 mg group took 11700 mg ticagrelor together with other drugs (4875 mg clopidogrel, 85,000 mg metformin, and 40 mg alprazolam) in an attempt to commit suicide. The patient had suffered from depression for 1 week before the event. The time period between drug intake and treatment was 3 hours. Symptoms were dizziness, nausea and somnolence. There were no signs of bleeding. The patient received no treatment other the ventricle lavage. The patient recovered.

According to limited information 1 other patient, in the ticagrelor 90 mg group, took an overdose of study medication for 57 days. The estimated mean dose taken per day was 396 mg. The patient did not have any adverse events in relation to the overdose.

There is currently no known antidote to reverse the effects of ticagrelor, and it is likely because of its high level of protein binding that it is not dialyzable. The main concern with a ticagrelor overdose would be a bleeding event. The label should alert the physician and patients of this potential concern.

As regards withdrawal and rebound, it is clear that discontinuation of any antiplatelet therapy could result in an increased risk of CV death or MI due to the patient's underlying disease. Whether withdrawal of drug causes a rebound effect is not known. See section 6.1.10 for a complete discussion of the observed increase in MACE in the ticagrelor arms compared to the placebo arm after the CSED.

[7] Soderlund, F et al, In vitro anti-platelet potency of ticagrelor in blood samples from infants and children, Thrombosis Research (2015), http://dx.doi.org/10.1016/j.thromres.2015.07.013.

7.7 Additional Submissions / Safety Issues

8 Postmarket Experience

No post-marketing experience is available from the sought indication; however, postmarketing experience in the currently approved indication ACS is being summarized in regular periodic benefit-risk evaluation reports (PBRERs) and submitted at agreed time points to regulatory authorities worldwide. The most recently finalized PBRER at the time of the NDA submission had its data lock point on December 31, 2014 and comprised post-marketing experience from approximately 797,200 patient years of treatment. It concluded that a comprehensive review of clinical studies and postmarketing experience revealed no new information during the reporting period to alter the overall positive benefit-risk profile for ticagrelor in the approved indication.

9 Appendices

APPENDIX 1: Benefit-Risk Tables

Table 35: Benefit/Risk: MACE (-hemorrhagic infarct) vs. TIMI Major Bleeding* for Ticagrelor 60 mg vs. Placebo (safety set, on treatment (until last dose or + 7 days if study drug discontinued before end of study). The percentages were calculated by dividing the number of events by the number in the subgroup. RR = %ticagrelor/% placebo. B-R = risk difference between ticagrelor and placebo for MACE(-) minus the risk difference between ticagrelor and placebo for TIMI Major Bleeding

		% of population	Tic 60	Pbo	**↓ in MACE-%**	RR	Tic 60	Pbo	**↑ in bleeding %**	RR	**B-R**
All		100%	4.7%	6.5%	**1.8%**	0.72	1.7%	0.8%	**0.9%**	2.14	**0.9%**
Age quintile	1 (<57 y/o)	17.4%	4.2%	6.5%	**2.3%**	0.64	1.2%	0.4%	**0.8%**	2.81	**1.6%**
	2 (≥57 and < 63)	20.7%	4.5%	6.0%	**1.5%**	0.75	1.1%	0.8%	**0.4%**	1.53	**1.1%**
	3 (≥63and < 67)	17.5%	5.3%	6.0%	**0.7%**	0.88	1.4%	0.6%	**0.8%**	2.24	**-0.1%**
	4(≥67 and < 73)	23.8%	4.5%	5.5%	**1.0%**	0.82	2.0%	0.8%	**1.2%**	2.59	**-0.2%**
	5(≥73)	20.5%	5.1%	8.6%	**3.5%**	0.60	2.3%	1.2%	**1.2%**	1.99	**2.3%**
Age	≥ 65	54.5%	4.9%	6.6%	**1.8%**	0.73	2.1%	0.9%	**1.2%**	2.40	**0.5%**
	≥ 75	14.5%	5.4%	9.0%	**3.6%**	0.60	2.5%	1.2%	**1.3%**	2.11	**2.2%**
Sex	Male	76.1%	4.4%	6.6%	**2.2%**	0.67	1.7%	0.8%	**0.9%**	2.11	**1.3%**
	Female	23.9%	5.7%	6.2%	**0.5%**	0.92	1.6%	0.7%	**0.9%**	2.25	**-0.4%**
Race	American Indian	0.2%	5.6%	0.0%	**-5.6%**	-	0.0%	0.0%	**0.0%**	-	**-5.6%**
	Asian	9.5%	3.9%	4.8%	**0.9%**	0.81	2.5%	0.4%	**2.1%**	5.63	**-1.2%**
	Black	1.7%	7.9%	9.6%	**1.7%**	0.82	4.8%	0.9%	**3.9%**	5.43	**-2.2%**
	Pacific Islander	1.2%	7.1%	9.1%	**2.0%**	0.78	3.5%	3.4%	**0.1%**	1.04	**1.9%**
	Other	0.7%	7.7%	2.0%	**-5.7%**	3.85	1.9%	0.0%	**1.9%**	-	**-7.6%**
	White	86.7%	4.6%	6.6%	**2.0%**	0.70	1.5%	0.8%	**0.7%**	1.89	**1.3%**
US vs. OUS	US	12.3%	4.8%	6.9%	**2.1%**	0.69	2.4%	1.0%	**1.3%**	2.26	**0.8%**
	OUS	87.7%	4.7%	6.4%	**1.7%**	0.73	1.6%	0.7%	**0.8%**	2.12	**0.9%**
Region	Asia/Pacific	11.1%	3.9%	4.9%	**1.0%**	0.79	3.1%	1.0%	**2.1%**	3.01	**-1.1%**
	Eastern EU	29.8%	5.3%	7.7%	**2.4%**	0.69	1.3%	0.7%	**0.6%**	1.93	**1.8%**
	North America	18.5%	4.2%	6.7%	**2.5%**	0.63	2.3%	0.9%	**1.3%**	2.44	**1.2%**
	South America	11.6%	5.9%	8.3%	**2.3%**	0.72	1.2%	0.9%	**0.4%**	1.44	**1.9%**
	Western EU	28.9%	4.2%	5.0%	**0.8%**	0.84	1.2%	0.6%	**0.6%**	1.93	**0.2%**
Weight quintile (All patients)	<=68 kg	20.6%	3.9%	6.8%	**2.8%**	0.58	1.9%	1.3%	**0.6%**	1.42	**2.2%**
	>68 and <= 76 kg	18.4%	5.0%	7.4%	**2.5%**	0.67	1.2%	0.6%	**0.6%**	2.02	**1.8%**
	>76 kg and <=83 kg	17.9%	5.2%	6.3%	**1.1%**	0.83	2.1%	0.7%	**1.4%**	3.00	**-0.4%**
	>83 kg and <=93 kg	20.8%	4.3%	5.8%	**1.5%**	0.74	1.8%	0.7%	**1.1%**	2.64	**0.4%**
	>93 kg	22.2%	5.1%	6.3%	**1.2%**	0.82	1.3%	0.5%	**0.7%**	2.37	**0.4%**

		% of population	Tic 60	Pbo	**↓ in MACE-%**	RR	Tic 60	Pbo	**↑ in bleeding %**	RR	**B-R**
Weight: Males by quintile	<=67 kg	15.3%	4.0%	7.3%	**3.4%**	0.54	1.8%	1.7%	**0.1%**	1.07	**3.2%**
	> 67 and <=76 kg	17.4%	4.4%	6.6%	**2.2%**	0.67	1.7%	0.6%	**1.1%**	2.65	**1.1%**
	> 76 and <=83 kg	13.8%	4.1%	5.8%	**1.7%**	0.70	1.9%	0.5%	**1.4%**	3.73	**0.3%**
	> 83 and <=93 kg	14.8%	4.6%	6.3%	**1.7%**	0.73	1.5%	0.6%	**0.9%**	2.54	**0.8%**
	> 93 kg	14.8%	4.8%	6.7%	**1.9%**	0.71	1.4%	0.5%	**0.9%**	2.87	**1.0%**
Weight: Females by quintile	<=60 kg	5.1%	4.0%	9.1%	**5.1%**	0.44	1.9%	0.9%	**1.0%**	2.20	**4.1%**
	>60 and <=68 kg	4.7%	4.0%	4.5%	**0.5%**	0.89	1.5%	0.6%	**0.9%**	2.56	**-0.4%**
	> 68 and <=76 kg	4.9%	7.7%	6.8%	**-0.9%**	1.13	1.2%	0.0%	**1.2%**	-	**-2.1%**
	> 76 and <=85 kg	4.4%	5.9%	6.3%	**0.4%**	0.94	1.3%	0.6%	**0.7%**	2.08	**-0.3%**
	> 85 kg	4.8%	7.1%	4.0%	**-3.1%**	1.76	1.9%	1.4%	**0.5%**	1.34	**-3.5%**
BMI	<=24.5	20.0%	3.7%	7.2%	**3.5%**	0.52	1.9%	1.6%	**0.3%**	1.21	**3.2%**
	>24.5 and <=27	19.9%	4.0%	5.6%	**1.6%**	0.71	1.9%	0.6%	**1.3%**	3.37	**0.3%**
	>27 and <=29	20.0%	3.9%	6.1%	**2.2%**	0.64	1.2%	0.6%	**0.6%**	1.93	**1.6%**
	> 29 and <= 32	20.0%	5.7%	6.3%	**0.7%**	0.89	1.5%	0.2%	**1.2%**	6.80	**-0.6%**
	> 32	20.0%	6.0%	7.1%	**1.1%**	0.84	1.8%	0.9%	**0.9%**	2.01	**0.2%**
Ethnicity	Hispanic or Latino	12.1%	6.0%	8.3%	**2.3%**	0.73	1.4%	1.2%	**0.3%**	1.22	**2.0%**
	Not Hispanic or Latino	84.8%	4.5%	6.3%	**1.8%**	0.71	1.7%	0.7%	**0.9%**	2.24	**0.9%**
Time from last ADP blocker	<57 days	12.2%	4.7%	7.2%	**2.5%**	0.66	2.2%	0.7%	**1.5%**	3.22	**0.9%**
	58-179 days	12.2%	4.9%	6.9%	**2.0%**	0.71	1.3%	0.7%	**0.6%**	1.84	**1.4%**
	180-352 days	12.2%	3.9%	6.2%	**2.4%**	0.62	2.2%	0.8%	**1.4%**	2.68	**1.0%**
	353 days -547 days	12.2%	4.9%	5.4%	**0.5%**	0.90	1.4%	0.7%	**0.7%**	2.02	**-0.2%**
	>547 days	12.2%	3.3%	3.9%	**0.6%**	0.85	1.4%	0.7%	**0.7%**	1.94	**-0.1%**
Time from index MI	< 1.1 yrs	20.1%	5.1%	7.3%	**2.2%**	0.70	2.3%	0.6%	**1.7%**	3.68	**0.5%**
	1.1 yrs to 1.5 yrs	19.9%	4.3%	7.1%	**2.8%**	0.60	0.8%	0.9%	**0.0%**	0.95	**2.9%**
	>1.5 yrs to 2 yrs	20.0%	4.3%	6.6%	**2.3%**	0.65	1.9%	1.1%	**0.8%**	1.72	**1.5%**
	2.0 yrs to 2.5 yrs	20.0%	4.6%	6.2%	**1.7%**	0.73	1.6%	0.8%	**0.8%**	2.05	**0.8%**
	> 2.5 yrs	19.9%	5.2%	5.2%	**-0.1%**	1.01	1.6%	0.4%	**1.2%**	4.39	**-1.3%**
MI type	STEMI	53.6%	4.0%	5.8%	**1.8%**	0.69	1.6%	0.7%	**0.9%**	2.26	**0.9%**
	NSTEMI	40.6%	5.4%	7.1%	**1.7%**	0.77	1.8%	0.8%	**1.0%**	2.33	**0.6%**
	unknown	5.8%	6.1%	9.2%	**3.1%**	0.66	1.4%	1.2%	**0.2%**	1.13	**2.9%**
	no MI	0.1%	0.0%	0.0%	**0.0%**	-	0.0%	11.1%	**-11.1%**	0.00	**11.1%**

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		% of population	Tic 60	Pbo	**↓ in MACE-%**	RR	Tic 60	Pbo	**↑ in bleeding %**	RR	**B-R**
STENT											
Type of stent	DES, any	39.2%	4.6%	6.4%	**1.8%**	0.72	1.7%	1.0%	**0.7%**	1.75	**1.1%**
	BMS, only	36.5%	3.5%	4.9%	**1.4%**	0.71	1.7%	0.6%	**1.1%**	2.62	**0.3%**
	Stent, unknown type	4.1%	3,5%	7.0%	**3.4%**	0.5	2.5%	0.0%	**2.5%**	-	**0.9%**
	no stent	19.9%	7.4%	9.3%	**1.9%**	0.65	1.3%	0.8%	**0.6%**	1.72	**1.3%**
	unknown	0.3%	0%	0%	0%	-	0%	0%	**0%**	-	**0%**
Multivessel Disease	yes	59.3%	4.8%	6.9%	**2.1%**	0.70	1.8%	0.7%	**1.1%**	2.46	**1.0%**
	no	40.7%	4.4%	5.8%	**1.3%**	0.77	1.4%	0.8%	**0.6%**	1.71	**0.8%**
Smoking history	former smoker	48.3%	4.9%	6.2%	**1.4%**	0.78	1.4%	0.6%	**0.8%**	2.46	**0.5%**
	never smoked	35.0%	4.1%	6.1%	**2.1%**	0.66	1.7%	1.0%	**0.6%**	1.61	**1.4%**
	current smoker	16.7%	5.5%	8.1%	**2.6%**	0.68	2.4%	0.8%	**1.6%**	2.95	**1.0%**
Creatinine Clearance at baseline (C-G)	<=58 mL/min	19.1%	4.3%	6.2%	**2.0%**	0.69	1.3%	0.8%	**0.5%**	1.56	**1.5%**
	> 58 and <=74 mL/min	19.9%	5.3%	5.1%	**-0.2%**	1.04	2.0%	1.2%	**0.8%**	1.69	**-1.1%**
	>74 and < =89 mL/min	19.9%	4.2%	6.5%	**2.3%**	0.65	1.3%	0.5%	**0.8%**	2.54	**1.5%**
	>89 and <=108 mL/min	19.9%	4.4%	7.0%	**2.6%**	0.63	1.7%	0.4%	**1.3%**	3.95	**1.3%**
	>108 mL/min	19.9%	5.4%	7.7%	**2.3%**	0.71	1.9%	0.9%	**0.9%**	1.95	**1.4%**
SSRI at baseline	yes	4.6%	6.5%	7.2%	**0.7%**	0.90	1.5%	0.9%	**0.6%**	1.65	**0.1%**
	no	95.4%	4.6%	6.4%	**1.8%**	0.71	1.7%	0.8%	**0.9%**	2.17	**1.0%**
H/o COPD or asthma or dyspnea	yes	10.9%	7.3%	8.0%	**0.7%**	0.91	2.2%	0.6%	**1.6%**	3.48	**-0.9%**
	no	89.1%	4.4%	6.3%	**1.9%**	0.70	1.6%	0.8%	**0.8%**	2.01	**1.1%**

*TIMI Major Bleeding = Any intracranial bleeding (excluding microhemorrhages <10 mm evident only on gradient-echo MRI) Clinically overt signs of hemorrhage associated with a drop in hemoglobin of ≥5 g/dL or a ≥15% absolute decrease in hematocrit. Fatal bleeding (bleeding that directly results in death within 7 d

Table 36: Benefit/Risk: MACE (-hemorrhagic infarct) vs. TIMI Major Bleeding for Ticagrelor 90 mg vs. Placebo

		% of population	MACE (-) Tic 90	MACE (-) Pbo	↓ in MACE-%	RR	Bleeding Tic 90	Bleeding Pbo	↑ in bleeding %	RR	B-R
ALL		100%	4.5%	6.5%	**2.0%**	0.70	1.8%	0.8%	**1.0%**	2.35	**0.9%**
Age quintile	1 (<57 y/o)	17%	3.2%	6.5%	**3.3%**	0.49	1.6%	0.4%	**1.2%**	3.79	**2.1%**
	2 (≥57 and < 63)	20.7%	4.6%	6.0%	**1.3%**	0.78	1.5%	0.8%	**0.8%**	2.01	**0.6%**
	3 (≥63and < 67)	17.5%	3.4%	6.0%	**2.5%**	0.57	1.5%	0.6%	**0.9%**	2.34	**1.7%**
	4(≥67 and < 73)	23.8%	4.6%	5.5%	**0.9%**	0.84	1.7%	0.8%	**0.9%**	2.17	**0.0%**
	5(≥73)	20.5%	6.4%	8.6%	**2.1%**	0.75	2.7%	1.2%	**1.5%**	2.30	**0.6%**
Age	≥ 65	54.5%	4.9%	6.6%	**1.7%**	0.74	2.0%	0.9%	**1.1%**	2.23	**0.6%**
	≥ 75	14.50%	6.90%	9.00%	**2.0%**	0.77	2.80%	1.2%	**1.6%**	2.39	**0.4%**
Sex	Male	76.1%	4.7%	6.6%	**1.8%**	0.72	2.0%	0.8%	**1.2%**	2.46	**0.7%**
	Female	23.9%	3.8%	6.2%	**2.3%**	0.62	1.4%	0.7%	**0.7%**	1.96	**1.6%**
	American Indian	0.2%	0.0%	0.0%	**0.0%**	-	0.0%	0.0%	0.0%	-	**0.0%**
	Asian	9.5%	2.9%	4.8%	**1.9%**	0.61	2.5%	0.4%	**2.0%**	5.46	**-0.1%**
	Black	1.7%	4.7%	9.6%	**4.9%**	0.49	0.9%	0.9%	**0.1%**	1.08	**4.9%**
	Other	0.7%	2.0%	2.0%	**0.0%**	1.02	6.1%	0.0%	**6.1%**	-	**-6.2%**
	White	86.7%	4.6%	6.6%	**2.0%**	0.70	1.8%	0.8%	**1.0%**	2.27	**1.0%**
	US	12.3%	5.0%	6.9%	**1.9%**	0.72	2.1%	1.0%	**1.1%**	2.02	**0.9%**
	OUS	87.7%	4.5%	6.4%	**2.0%**	0.69	1.8%	0.7%	**1.0%**	2.42	**0.9%**
Region	Asia/Pacific	11.1%	3.6%	4.9%	**1.3%**	0.73	2.2%	1.0%	**1.2%**	2.12	**0.1%**
	Eastern EU	29.8%	5.1%	7.7%	**2.5%**	0.67	1.5%	0.7%	**0.9%**	2.30	**1.7%**
	South America	11.6%	5.5%	8.3%	**2.8%**	0.67	2.6%	0.9%	**1.7%**	2.97	**1.1%**
	Western EU	28.9%	4.2%	5.0%	**0.8%**	0.84	1.6%	0.6%	**1.0%**	2.54	**-0.2%**
Weight: by quintile	<=68 kg	20.6%	4.8%	6.8%	**1.9%**	0.72	2.3%	1.3%	**1.0%**	1.73	**1.0%**
	>68 and <= 76 kg	18.4%	3.6%	7.4%	**3.8%**	0.48	1.9%	0.6%	**1.3%**	3.15	**2.5%**
	>76 kg and <=83 kg	17.9%	5.4%	6.3%	**0.9%**	0.86	1.4%	0.7%	**0.7%**	1.96	**0.2%**
	>83 kg and <=93 kg	20.8%	4.7%	5.8%	**1.0%**	0.82	1.5%	0.7%	**0.9%**	2.26	**0.2%**
	>93 kg	22.2%	3.9%	6.3%	**2.4%**	0.62	1.9%	0.5%	**1.4%**	3.55	**1.0%**
Weight: Males by quintile	<=67 kg	15.3%	5.2%	7.3%	**2.2%**	0.70	2.6%	1.7%	**1.0%**	1.57	**1.2%**
	>67 and <= 76 kg	17.4%	4.3%	6.6%	**2.3%**	0.65	1.9%	0.6%	**1.3%**	3.01	**1.0%**
	> 76 and <=83 kg	13.8%	5.7%	5.8%	**0.1%**	0.97	1.3%	0.5%	**0.8%**	2.47	**-0.6%**
	> 83 and <=93 kg	14.8%	4.8%	6.3%	**1.5%**	0.76	1.7%	0.6%	**1.1%**	2.92	**0.4%**
	> 93 kg	14.8%	3.9%	6.7%	**2.8%**	0.58	2.1%	0.5%	**1.6%**	4.19	**1.2%**

			MACE (-)		↓ in		Bleeding		↑ in		
		% of population	Tic 90	Pbo	MACE-%	RR	Tic 90	Pbo	bleeding %	RR	B-R
Weight: Females by quintile	<=60 kg	5.1%	3.1%	9.1%	**6.0%**	0.34	2.0%	0.9%	**1.1%**	2.31	**4.9%**
	>60 and <= 68 kg	4.7%	5.5%	4.5%	**-0.9%**	1.20	1.5%	0.6%	**0.9%**	2.51	**-1.8%**
	> 68 and <=76 kg	4.9%	3.7%	6.8%	**3.1%**	0.55	1.1%	0.0%	**1.1%**	-	**1.9%**
	> 76 and <=85 kg	4.4%	4.5%	6.3%	**1.8%**	0.71	1.4%	0.6%	**0.7%**	2.19	**1.1%**
	> 85 kg	4.8%	2.7%	4.0%	**1.4%**	0.66	0.9%	1.4%	**-0.5%**	0.62	**1.9%**
BMI quintile	<=24.5	20.0%	4.7%	7.2%	**2.5%**	0.66	2.0%	1.6%	**0.4%**	1.26	**2.1%**
	>24.5 and <=27	19.9%	4.7%	5.6%	**1.0%**	0.83	1.5%	0.6%	**0.9%**	2.67	**0.0%**
	>27 and <=29	20.0%	4.4%	6.1%	**1.8%**	0.71	2.2%	0.6%	**1.5%**	3.44	**0.2%**
	> 29 and <= 32	20.0%	4.2%	6.3%	**2.1%**	0.66	1.4%	0.2%	**1.2%**	6.69	**0.9%**
	> 32	20.0%	4.4%	7.1%	**2.8%**	0.61	2.0%	0.9%	**1.1%**	2.25	**1.7%**
Ethnicity	Hispanic or Latino	12.1%	5.5%	8.3%	**2.9%**	0.66	2.3%	1.2%	**1.1%**	1.96	**1.7%**
	Not Hispanic or Latino	84.8%	4.4%	6.3%	**1.9%**	0.70	1.6%	0.7%	**0.8%**	2.12	**1.1%**
Time from last ADP blocker	<57 days	12.2%	5.0%	7.2%	**2.1%**	0.70	1.9%	0.7%	**1.2%**	2.76	**0.9%**
	58-179 days	12.2%	4.4%	6.9%	**2.5%**	0.64	2.3%	0.7%	**1.6%**	3.19	**0.9%**
	180-352 days	12.2%	3.5%	6.2%	**2.8%**	0.56	1.0%	0.8%	**0.2%**	1.23	**2.6%**
	353 days -547 days	12.2%	2.6%	5.4%	**2.8%**	0.49	1.3%	0.7%	**0.6%**	1.79	**2.2%**
	>547 days	12.2%	3.8%	3.9%	**0.1%**	0.96	2.8%	0.7%	**2.1%**	3.97	**-2.0%**
Time from index MI	< 1.1 yrs	20.1%	4.8%	7.3%	**2.5%**	0.65	2.0%	0.6%	**1.4%**	3.22	**1.1%**
	1.1 yrs to 1.5 yrs	19.9%	4.7%	7.1%	**2.4%**	0.66	1.6%	0.9%	**0.7%**	1.76	**1.7%**
	>1.5 yrs to 2 yrs	20.0%	4.6%	6.6%	**2.0%**	0.70	1.5%	1.1%	**0.4%**	1.32	**1.6%**
	2.0 yrs to 2.5 yrs	20.0%	4.5%	6.2%	**1.7%**	0.73	1.7%	0.8%	**1.0%**	2.22	**0.7%**
	> 2.5 yrs	19.9%	3.9%	5.2%	**1.2%**	0.76	2.2%	0.4%	**1.9%**	6.27	**-0.6%**
MI type	STEMI	53.6%	3.8%	5.8%	**2.0%**	0.65	1.9%	0.7%	**1.2%**	2.76	**0.8%**
	NSTEMI	40.6%	5.5%	7.1%	**1.6%**	0.77	1.7%	0.8%	**1.0%**	2.23	**0.6%**
	unknown	5.8%	4.7%	9.2%	**4.5%**	0.52	1.6%	1.2%	**0.3%**	1.27	**4.1%**
	no MI	0.1%	16.7%	0.0%	**-16.7%**	-	0.0%	11.1%	**-11.1%**	0.00	**-5.6%**

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		% of population	**MACE (-)**		**↓ in MACE (-) %**	RR	**Bleeding**		**↑ In bleeding %**	RR	**B-R**
			Tic 90	Pbo			Tic 90	Pbo			
Type of stent	DES, any	39.2%	4.2%	6.4%	**2.2%**	0.66	2.0%	1.0%	**1.0%**	1.99	**1.2%**
	BMS, only	36.5%	4.4%	4.9%	**0.5%**	0.9	2.0%	0.6%	**1.4%**	3.17	**-0.9%**
	Stent, unknown type	4.1%	2.9%	7.0%	**1.2%**	0.41	0.4%	0.0%	**0.4%**	-	**0.8%**
	no stent	19.9%	5.7%	9.3%	**3.7%**	0.61	1.5%	0.8%	**0.7%**	1.92	**3.0%**
	unknown	0.3%	0%	0%	**0%**	-	0%	0%	**0%**	-	**0%**
Multivessel Disease	yes	59.3%	4.6%	6.9%	**2.4%**	0.66	1.8%	0.7%	**1.0%**	2.35	**1.4%**
	no	40.7%	4.5%	5.8%	**1.3%**	0.77	1.9%	0.8%	**1.1%**	2.36	**0.2%**
Smoking history	former smoker	48.3%	4.1%	6.2%	**2.1%**	0.66	1.9%	0.6%	**1.3%**	3.30	**0.8%**
	never smoked	35.0%	4.5%	6.1%	**1.6%**	0.74	1.4%	1.0%	**0.3%**	1.31	**1.3%**
	current smoker	16.7%	5.7%	8.1%	**2.3%**	0.71	2.6%	0.8%	**1.8%**	3.29	**0.5%**
Creatinine Clearance at baseline (C-G)	<=58 mL/min	19.1%	3.8%	6.2%	**2.4%**	0.61	1.8%	0.8%	**0.9%**	2.16	**1.5%**
	> 58 and <=74 mL/min	19.9%	3.8%	5.1%	**1.2%**	0.76	1.8%	1.2%	**0.6%**	1.48	**0.7%**
	>74 and < =89 mL/min	19.9%	4.7%	6.5%	**1.8%**	0.72	1.9%	0.5%	**1.3%**	3.68	**0.5%**
	>89 and <=108 mL/min	19.9%	5.4%	7.0%	**1.5%**	0.78	2.4%	0.4%	**1.9%**	5.55	**-0.4%**
	>108 mL/min	19.9%	4.3%	7.7%	**3.4%**	0.56	1.2%	0.9%	**0.2%**	1.22	**3.2%**
SSRI at baseline	yes	4.6%	6.9%	7.2%	**0.3%**	0.96	**3.8%**	0.9%	**2.8%**	4.01	**-2.5%**
	no	95.4%	4.4%	6.4%	**2.0%**	0.68	1.7%	0.8%	**1.0%**	2.26	**1.1%**
H/o COPD or asthma or dyspnea	yes	10.9%	6.4%	8.0%	**1.6%**	0.80	3.2%	0.6%	**2.5%**	4.94	**-0.9%**
	no	89.1%	4.3%	6.3%	**2.0%**	0.68	1.7%	0.8%	**0.9%**	2.10	**1.1%**

Reference ID: 3804604

APPENDIX 2: Assessment of Risk of Primary Efficacy Endpoint and TIMI Major Bleeding by Quantity and Type of PEGASUS-Qualifying Risk Factors for Heart Disease

Because very few low-risk patients, i.e., those with none of 5 named qualifying risk factors for CV disease listed in Table 38(~120) were enrolled in PEGASUS, empiric data are lacking and it is hard to make any conclusions about potential risk-benefit in that population. Yet, these patients could possibly benefit from long-term use of ticagrelor post-MI. Several analyses were done to address the question of benefit-risk difference in a lower-risk population.

The first analysis looked at the primary efficacy endpoint results by number of PEGASUS-qualifying risk factors at baseline to see if the treatment benefit (i.e., the hazard ratio vs. placebo for MACE) was associated with the number of risk factors. Table 37 shows there is no obvious trend in benefit for ticagrelor 60 mg related to the number of qualifying risk factors at baseline. This analysis suggests that the beneficial effect of ticagrelor is not lower among patients with a lower number of risk factors. In fact, the majority of subjects had just one risk factor (age ≥ 65 and multivessel CAD were the most common risk factors overall) and a favorable treatment effect in this subgroup of subjects with just one risk factor was observed.

Table 37: Primary efficacy endpoint (CV death, MI or Stroke) by number of qualifying risk factors at baseline

		Ticagrelor 60 mg N=7045		*Placebo N=7067*				
event	*Number of risk factor*	*n/N*	*ER*[a]	*n/N*	*ER*[a]	*HR*	*95CI*	*p_value*
CV Death, MI & stroke	0	3 / 47	2.31	2 / 41	1.83	1.18	(0.20, 7.09)	0.8529
	1	180 / 3676	1.90	224 / 3586	2.45	0.78	(0.64, 0.95)	0.0120
	2	174 / 2315	2.96	178 / 2406	2.93	1.01	(0.82, 1.25)	0.9138
	3	94 / 816	4.69	126 / 826	6.28	0.74	(0.57, 0.97)	0.0304
	4	30 / 171	7.49	41 / 186	9.85	0.76	(0.48, 1.22)	0.2616
	5	6 / 20	13.1	7 / 22	14.0	0.93	(0.31, 2.78)	0.9012

[a] Event Rate (per 100 patient-years)
Reviewer's Table, Data Source: ADTTE, ADSL and RSMH

We were also interested in knowing if the treatment effect was consistent among subjects who had different single PEGASUS-qualifying risk factors. In Table 38, treatment effect appeared to be fairly consistent regardless of the specific type of risk factor among subjects who only had one qualifying risk factor at baseline.

Table 38: Primary efficacy endpoint by type of risk factors among patients who had one qualifying risk factor at baseline

		Ticagrelor 60 mg N=3676		*Placebo N=3586*				
event	*Type of risk factors*	*n/N*	*ER*[a]	*n/N*	*ER*[a]	*HR*	*95CI*	*p_value*
CV Death, MI & stroke	Age≥65	69 / 1341	1.99	82 / 1353	2.33	0.85	(0.62, 1.17)	0.3215
	CRCL<60	1 / 26	1.49	1 / 29	1.29	1.09	(0.07, 17.49)	0.9493
	Diabetes requiring Tx	35 / 581	2.32	36 / 523	2.70	0.86	(0.54, 1.36)	0.5150
	>1 MI	12 / 157	3.06	19 / 170	4.40	0.69	(0.33, 1.42)	0.3088
	Multivessel CAD	63 / 1571	1.57	86 / 1511	2.26	0.70	(0.50, 0.96)	0.0286

[a] Event Rate (per 100 patient-years)
Reviewer's Table, Data Source: ADTTE, ADSL and RSMH

To further address the question of benefit-risk in a lower-risk population, a Cox Proportional Hazard (Cox PH) model was used to examine the treatment effect of ticagrelor 60 mg vs. placebo on time to first primary efficacy endpoint (CV death, MI or stroke) in a multivariable model controlling for any potential risk factor at baseline and any identified interaction between treatment and risk factors. Age, diabetes requiring treatment, history of more than one MI, multivessel CAD, chronic non-end stage renal dysfunction (CrCl <60), history of stent implant, history of angina pectoris, <30 days since ADP blocker (compared to >12 months since ADP blocker) and current smoker were identified as significant risk factors for the primary efficacy endpoint and included in the final Cox-PH model. There were no significant qualitative interaction effects found between the treatment arm and risk factors, particularly the qualifying risk factors for PEGASUS. After adjusting for the identified risk factors, the beneficial effect of ticagrelor 60 mg vs placebo on reducing the risk of primary efficacy endpoint remained significant.

Table 39 shows the parameter estimates and hazard ratios from the Cox PH model. The adjusted HR for the treatment effect is very close to the crude estimate (HR: 0.84, 95% CI: 0.74-0.95) reported in PEGASUS. This analysis suggests that the treatment effect remains consistent regardless of the type of risk factor and patients with lower risk than the study population would likely have the same treatment effect. Of note, all the PEGASUS-qualifying risk factors were identified as significant risk factors for the primary efficacy endpoint in the model. The magnitude of these risk factors was different (HR ranged from 1.25-1.97). These findings highlight the potential problem of looking at any particular subgroup analysis in PEGASUS. Because PEGASUS was a large randomized trial, the distribution of the risk factors between treatment arms would be expected to be similar overall. However, the differences in the distribution of risk factors among the treatment arms within subgroups might not have been balanced and could have conceivably confounded the HR estimates in any particular subgroup.

Table 39: Parameter Estimates and Hazard Ratios from Cox-Proportional Hazard model for the association between the treatment effect and primary efficacy endpoint

Parameter	**Estimate (SE)**	**P-value**	**HR (95% CI)**
Age[a]	0.02 (0.004)	<.0001	1.25 (1.16, 1.35)
Diabetes requiring treatment (Y vs. N)[b]	0.51 (0.06)	<.0001	1.67 (1.47, 1.90)
>1 MI (Y vs. N) [b]	0.68 (0.07)	<.0001	1.97 (1.72, 2.25)
Chronic non-end stage renal dysfunction (Y vs. N) [b]	0.53 (0.10)	0.04	1.70 (1.40, 2.08)
Multivessel CAD (Y vs. N) [b]	0.27 (0.07)	0..0001	1.30 (1.14, 1.49)
Current Smoker (Y vs. N)	0.31 (0.08)	0.0001	1.36 (1.16, 1.60)
History of Stent Implant (Y vs. N)	-0.44 (0.08)	<.0001	0.65 (0.55, 0.76)
History of Angina Pectoris (Y vs. N)	0.25 (0.06)	0.0001	1.28 (1.13, 1.45)
Time since ADP blocker (30d-12M vs. <30 days)	-0.13 (0.08)	0.08	0.88 (0.75, 1.02)
Time since ADP blocker (>12M vs. <30 days)	-0.32 (0.09)	0.0003	0.73 (0.61, 0.86)
Treatment (Ticagrelor 60 mg vs. placebo)	-0.18 (0.06)	0.0036	0.84 (0.74, 0.94)

[a] HR for age was estimated with a unit of 10. HR of 1.25 means every 10-year increase in age increases risk of CV death, MI and Stroke by 25%.
[b] These risk factors were qualifying risk factors used in PEGASUS.
Reviewer's Table, Data Source: ADTTE, ADSL and RSMH

We also looked at the primary safety endpoint results by number of PEGASUS-qualifying risk factors at baseline to see if the treatment effect (i.e., the hazard ratio vs. placebo for TIMI major bleed) was associated with the number of qualifying risk factors (Table 40). It is noted that the bleeding event rate increased as number of risk factors increased in the ticagrelor arm. This trend was less obvious in the placebo arm. Accordingly, the hazard ratio increased as the number of risk factor increased (Of note, HR in overall population is 2.32 in PEGASUS). These findings suggest that patients at higher risk for CV events may also be likely to have concurrent bleeding risk factors; thus they are more susceptible for bleeding when treated with ticagrelor. However, as mentioned earlier, the HR in this subgroup analysis could be conceivably confounded if bleeding risk factors were not distributed evenly between the two arms in each level of the subgroup.

Table 40 Primary safety endpoint (TIMI Major Bleed) by number of qualifying risk factors at baseline

		Ticagrelor 60 mg N=7045		*Placebo N=7067*				
event	*Number of risk factor*	*n/N*	*ER*[a]	*n/N*	*ER*[a]	*HR*	*95CI*	*p_value*
TIMI Major Bleeding	0	0 / 47	0.00	0 / 41	0.00	---	---	---
	1	49 / 3676	0.51	32 / 3586	0.34	1.50	(0.96, 2.34)	0.0760
	2	52 / 2315	0.87	33 / 2406	0.53	1.64	(1.06, 2.54)	0.0262
	3	27 / 816	1.30	10 / 826	0.47	2.74	(1.33, 5.67)	0.0064
	4	8 / 171	1.92	3 / 186	0.66	2.87	(0.76, 10.83)	0.1189
	5	2 / 20	4.78	0 / 22	0.00	---	---	---

[a] Event Rate (per 100 patient-years)
Reviewer's Table, Data Source: ADTTE, ADSL and RSMH

To explore further the treatment effect of ticagrelor 60 mg vs. placebo on time to first Major bleeding event (on treatment), a Cox PH model was performed. Age, chronic non-end stage renal dysfunction, smoking, non-Caucasian were identified as significant risk factors for TIMI major bleeding and included in the final Cox-PH model. Table 41 shows the parameter estimates and hazard ratios from the Cox PH model. There were no significant interaction effects found between the treatment arms and risk factors.

Table 41: Parameter Estimates and Hazard Ratios from Cox-Proportional Hazard model for the association between treatment effect and TIMI Major bleeding

Parameter	Estimate (SE)	P-value	HR (95% CI)	
Age[a]	0.04 (0.01)	<.0001	1.52	(1.25, 1.83)
Chronic non-end stage renal dysfunction (Y vs. N) [b]	0.61 (0.25)	0.01	1.85	(1.14, 3.00)
Current Smoker (Y vs. N)	0.54 (0.19)	0.005	1.71	(1.18, 2.50)
Caucasian (Y vs. N)	-0.50 (0.19)	0.009	0.61	(0.42, 0.88)
Treatment (Ticagrelor 60 mg vs. placebo)	0.85 (0.17)	<.0001	2.35	(1.70,3.25)

[a] HR for age was estimated with a unit of 10. HR of 1.52 means every 10-year increase in age increases risk of TIMI Major bleeding by 52%

[b] The qualifying risk factor used in PEGASUS.

Reviewer's Table, Data Source: ADTTE, ADSL and RSMH

Patients who are older or who have CrCl <60 are at an increased risk of having both an efficacy endpoint and a bleeding event. Because there was no significant qualitative interaction effect between these two risk factors and the treatment arms for both efficacy and safety models, there is no obvious evidence to suggest that the benefit and risk of treating with ticagrelor compared to placebo would be different between patients with lower risk for MACE and patients studied in PEGASUS.

While the Cox model demonstrates that the treatment effect (HR, both efficacy and bleeding) is likely to be consistent among MI patients with lower risk than what was enrolled in PEGASUS, the question remains as to whether the absolute benefit-risk difference is still favorable in this population.

To address the question, the Cox model was used to estimate the probability of MACE (CVD, MI, or stroke) within a year in a patient who would not have qualified for the study, i.e., a 55 y/o with no multivessel CAD, no diabetes, only 1 MI at least a year prior, and CrCl ≥ 60 mL/min or other identified risk factors*. The Cox model was also used to estimate TIMI Major bleeding probability within a year in a 55 y/o patient without any identified bleeding risk factors.* (See Table 42).

The model estimates that the absolute risk reduction in MACE (RD: -0.25%) is similar to the absolute risk increase in bleeding (RD: 0.23%) among patients with lower risk for MACE (55 y/o without any identified risk factors). This result suggests that benefit- risk difference of treating ticagrelor 60 mg will be ~0, meaning that one will likely trade 1 CVD, MI or stroke event for 1 TIMI major bleeding event in this population if treating with ticagrelor 60 mg. Considering that the majority of excess TIMI major bleeding in the ticagrelor arms is reversible in PEGASUS (i.e., it is not ICH and is not fatal), I would consider that the benefit-risk is likely to remain favorable in patients with lower risk for a MACE event, in general. However, one should note that the data regarding some bleeding risk factors such as history of prior bleeding are not available in PEGASUS. It is possible that a minority of patients at lower risk for MACE who fall within the category of higher risk for bleeding would have an unfavorable risk-benefit difference. While I think ticagrelor 60mg should be available for patients with lower risk for MACE, treatment decisions should be individualized. Prescribers should decide whether or not to treat a patient based on an individual's risk factor for CV outcomes and bleeding.

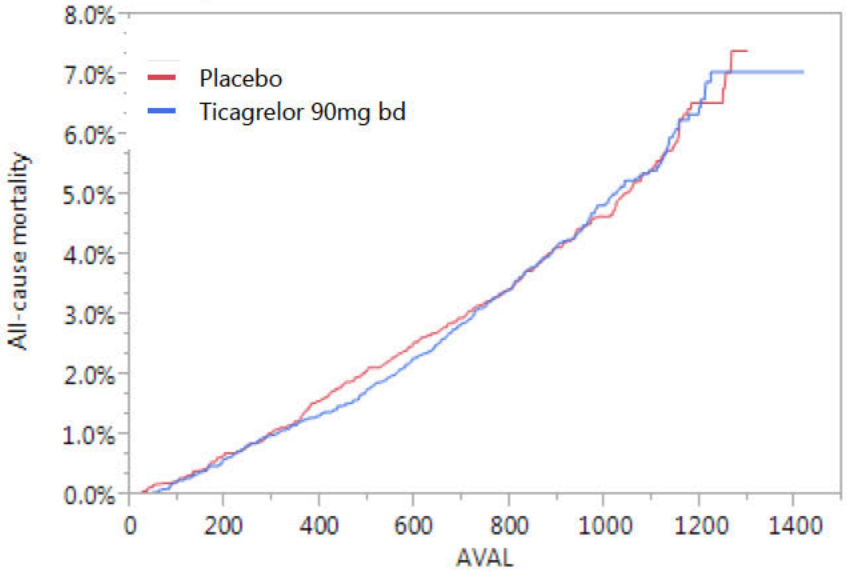
Table 42: Cox model prediction of absolute risk of MACE and TIMI major bleeding in a 55 y/o patient with no identified risk factors*

Age 55 y/o without identified risk factors*	Ticagrelor 60 mg	Placebo
	% (95% CI)	% (95% CI)
Probability of CVD, MI or stroke within a year	1.27% (0.94, 1.59)	1.52%(1.13,1.90)
Risk Difference (RD)	-0.25%	
Probability of TIMI Major bleed within a year	0.39% (0.24,0.53)	0.16% (0.09,0.24)
Risk Difference (RD)	0.23%	

* MACE risk factors: PEGASUS-qualifying risk factors + current smoker, without history of stent, history of angina, <30 days since ADP blocker
TIMI Major risk factor: CrCl <60 mL/min, current smoker, non-Caucasian
Reviewer's Table, Data Source: ADTTE, ADSL and RSMH

APPENDIX 3: K-M Plots for all-cause mortality for the 90 mg vs. placebo subjects and K-M Plots for neoplasm mortality

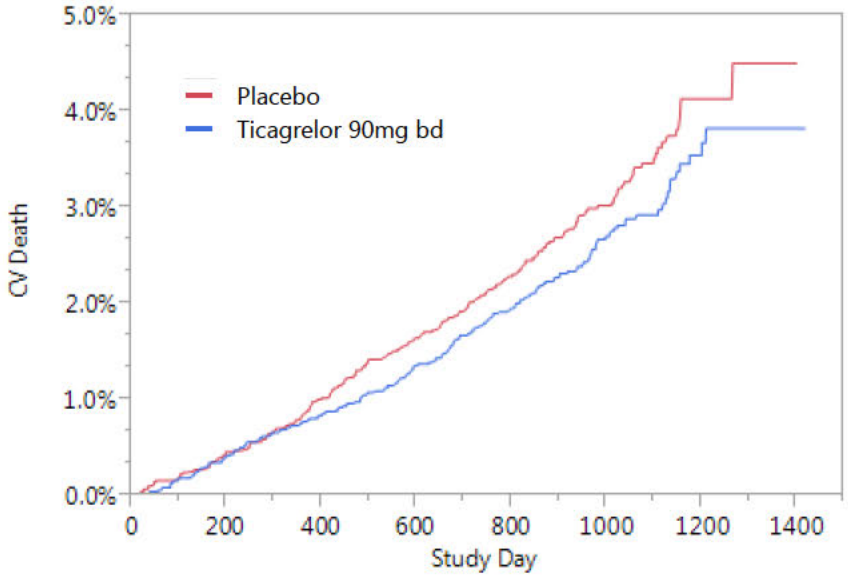
Figure 47: K-M plot of time to all-cause mortality (T90 mg bd vs. placebo) (safety set, on/off treatment)



Group	Number failed	Number censored	Mean		Std Error
Placebo	334	6662	1259.05	Biased	2.15165
Ticagrelor 90mg bd	335	6653	1188.29	Biased	1.85276
Combined	669	13315	1259.45	Biased	1.50326

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	0.0001	1	0.9903
Wilcoxon	0.0015	1	0.9691

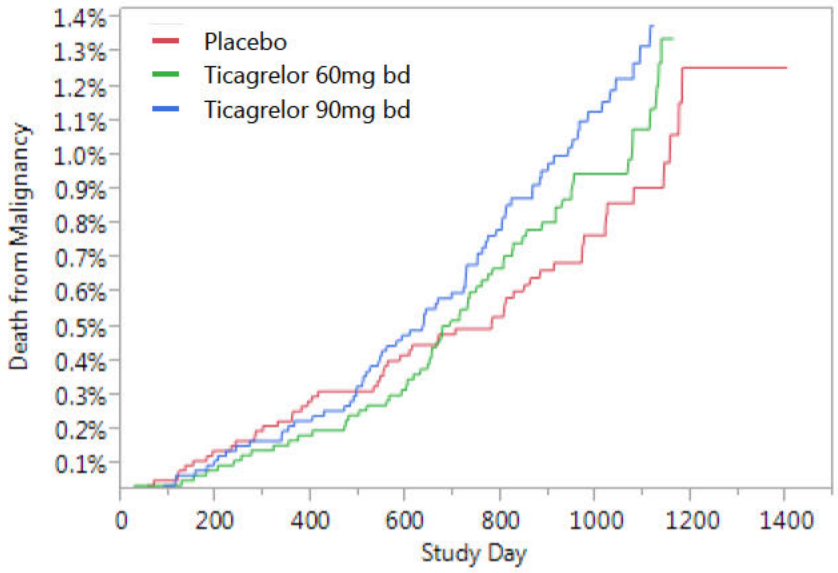
Figure 48: K-M plot of time to CV death (T90 mg bd vs. placebo) (safety set, on/off treatment)



Group	Number failed	Number censored	Mean	Std Error
Placebo	213	6783	1241.35 Biased	1.66408
Ticagrelor 90mg bd	183	6805	1190.86 Biased	1.41309
Combined	396	13588	1243.03 Biased	1.13329

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	2.3422	1	0.1259
Wilcoxon	2.4264	1	0.1193

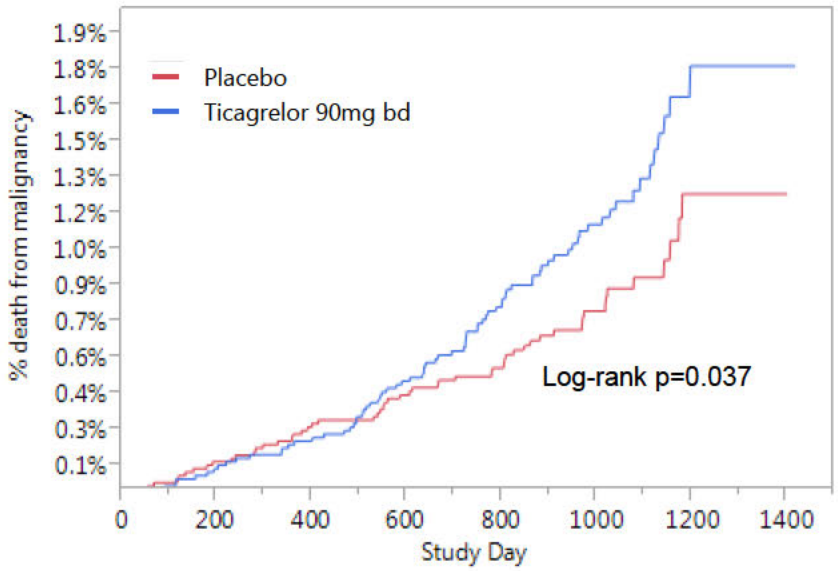
Figure 49: K-M plot of time to Neoplasm death (T90 mg bd vs.T60 mg bd vs. placebo) (safety set, on/off treatment)



Group	Number failed	Number censored	Mean		Std Error
Placebo	53	6943	1175.16	Biased	0.72922
Ticagrelor 60mg bd	63	6895	1158.96	Biased	0.69026
Ticagrelor 90mg bd	77	6911	1190.28	Biased	0.81541
Combined	193	20749	1191.24	Biased	0.44098

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	4.4285	2	0.1092
Wilcoxon	3.7384	2	0.1542

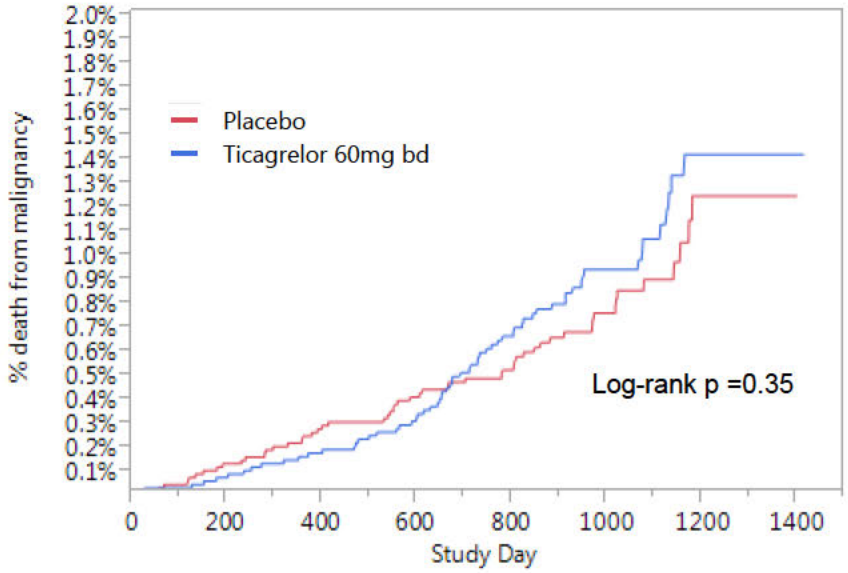
Figure 50: K-M plot of time to Neoplasm death (T90 mg bd vs. placebo) (safety set, on/off treatment)



Group	Number failed	Number censored	Mean		Std Error
Placebo	53	6943	1175.16	Biased	0.72922
Ticagrelor 90mg bd	77	6911	1190.28	Biased	0.81541
Combined	130	13854	1191.12	Biased	0.55181

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	4.3581	1	0.0368*
Wilcoxon	3.6550	1	0.0559

Figure 51: K-M plot of time to Neoplasm death (T60 mg bd vs. placebo) (safety set, overall treatment period)



Group	Number failed	Number censored	Mean	Std Error
Placebo	53	6943	1175.16 Biased	0.72922
Ticagrelor 60mg bd	63	6895	1158.96 Biased	0.69026
Combined	116	13838	1174.95 Biased	0.50733

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	0.8728	1	0.3502
Wilcoxon	0.7050	1	0.4011

APPENDIX 4: SAEs PEGASUS, Reviewer's analysis

Table 43: Complete SAE table (on treatment, safety set)

	Pbo	T60 mg bd	T90 mg bd	RR	RR
	N= 6996	N=6958	N=6988	T60 mg bd	T90 mg bd
	n(%)	n(%)	n(%)	Pbo	Pbo
Epistaxis	2(0.03)	15(0.22)	19(0.27)	7.33	9
Pneumothorax	1(0.01)	5(0.07)	2(0.03)	7	3
Glaucoma, high intraocular pressure	1(0.01)	4(0.06)	2(0.03)	6	3
Ecchymosis, hematoma, bruise	5(0.07)	27(0.39)	19(0.27)	5.57	3.86
Dizziness, light-headedness	1(0.01)	3(0.04)	9(0.13)	4	13
Fe Deficiency	3(0.04)	11(0.16)	20(0.29)	4	7.25
Hemoptysis	1(0.01)	3(0.04)	4(0.06)	4	6
Constipation	1(0.01)	3(0.04)	2(0.03)	4	3
Bacteremia	3(0.04)	11(0.16)	8(0.11)	4	2.75
Dyspnea on exertion	1(0.01)	3(0.04)	1(0.01)	4	1
Nephritis, glomerulonephritis	1(0.01)	3(0.04)	1(0.01)	4	1
Seizure	1(0.01)	2(0.03)	2(0.03)	3	3
High K+	1(0.01)	2(0.03)	1(0.01)	3	1
Ligament rupture	1(0.01)	2(0.03)	0(0)	3	0
Dyspnea, SOB, respiratory distress	9(0.13)	25(0.36)	23(0.33)	2.77	2.54
Hematuria	3(0.04)	8(0.11)	9(0.13)	2.75	3.25
Shock, non-cardiogenic	3(0.04)	7(0.1)	9(0.13)	2.5	3.25
Encephalitis, encephalopathy	2(0.03)	5(0.07)	4(0.06)	2.33	2
GI bleed	34(0.49)	78(1.12)	89(1.27)	2.29	2.59
Anemia	14(0.2)	31(0.45)	43(0.62)	2.25	3.1
Bradycardia	6(0.09)	14(0.2)	14(0.2)	2.22	2.22
Gastric, duodenal, or jejunal ulcer, erosion, perforation	16(0.23)	33(0.47)	49(0.7)	2.04	3.04
Motor vehicle accident	2(0.03)	4(0.06)	2(0.03)	2	1
Hearing loss, deafness	2(0.03)	4(0.06)	1(0.01)	2	0.33
Bleeding	90(1.29)	168(2.41)	165(2.36)	1.87	1.83
Hernia, incarcerated, obstructive, gangrenous, or ruptured	3(0.04)	5(0.07)	5(0.07)	1.75	1.75
Pulmonary edema	4(0.06)	7(0.1)	3(0.04)	1.67	0.67
Asthenia, fatigue, malaise, weakness, narcolepsy	4(0.06)	7(0.1)	2(0.03)	1.67	0.5
UTI	16(0.23)	26(0.37)	40(0.57)	1.61	2.48
Stone, renal colic	14(0.2)	22(0.32)	32(0.46)	1.6	2.3
Hypotension	5(0.07)	8(0.11)	5(0.07)	1.57	1
Hernia	24(0.34)	37(0.53)	33(0.47)	1.56	1.38
Low LVEF, low cardiac output, cardiomyopathy, LV dysfunction	3(0.04)	4(0.06)	12(0.17)	1.5	4.25
Cranial neuropathy, palsy	3(0.04)	4(0.06)	2(0.03)	1.5	0.75
Ocular hemmorhage	3(0.04)	4(0.06)	2(0.03)	1.5	0.75
Cardiac thrombus	3(0.04)	4(0.06)	1(0.01)	1.5	0.25

SAE Table
(continued)

	Pbo	T60 mg bd	T90 mg bd	RR	RR
	N= 6996	N=6958	N=6988	T60 mg bd	T90 mg bd
	n(%)	n(%)	n(%)	Pbo	Pbo
Intracranial hemorrhage (includes hemorrhagic stroke, SAH, SDH)	19(0.27)	26(0.37)	23(0.33)	1.37	1.22
Atrial fibrillation	56(0.8)	76(1.09)	61(0.87)	1.36	1.09
AFib or Aflutter	64(0.91)	86(1.24)	68(0.97)	1.36	1.07
Tendon rupture	2(0.03)	3(0.04)	4(0.06)	1.33	2
Suicidal ideation, intentional overdose, self-injury, suicide	2(0.03)	3(0.04)	3(0.04)	1.33	1.33
PVCs	2(0.03)	3(0.04)	2(0.03)	1.33	1
Cardiogenic shock	2(0.03)	3(0.04)	1(0.01)	1.33	0.33
Supra-ventricular arrhythmia	70(1)	92(1.32)	75(1.07)	1.32	1.07
Ventricular fibrillation	7(0.1)	9(0.13)	6(0.09)	1.3	0.9
Syncope	18(0.26)	23(0.33)	29(0.41)	1.27	1.58
Diverticular disease	18(0.26)	23(0.33)	28(0.4)	1.27	1.54
Pre-syncope or syncope	24(0.34)	30(0.43)	32(0.46)	1.26	1.35
Arrhythmia	110(1.57)	138(1.98)	116(1.66)	1.26	1.06
Anuria, Acute renal failure	16(0.23)	20(0.29)	17(0.24)	1.26	1.04
Sepsis	17(0.24)	21(0.3)	28(0.4)	1.25	1.67
Dehydration, volume depletion	6(0.09)	8(0.11)	4(0.06)	1.22	0.67
Cataract	12(0.17)	14(0.2)	7(0.1)	1.18	0.59
Esophagitis, hiatal hernia	4(0.06)	5(0.07)	7(0.1)	1.17	1.67
Ventricular tachycardia	12(0.17)	13(0.19)	14(0.2)	1.12	1.18
Diabetes, glucose intolerance, hyperglycemia, HbA1c, glycosuria	29(0.41)	32(0.46)	33(0.47)	1.12	1.15
Pre-syncope	6(0.09)	7(0.1)	3(0.04)	1.11	0.44
Squamous cell carcinoma	7(0.1)	8(0.11)	9(0.13)	1.1	1.3
Infection, bacteria	21(0.3)	23(0.33)	20(0.29)	1.1	0.97
Fracture	60(0.86)	65(0.93)	48(0.69)	1.08	0.8
Cholecystitis, cholelithiasis, bile duct stone	44(0.63)	46(0.66)	27(0.39)	1.05	0.62
Diarrhea, colitis, enteritis, proctitis, gastroenteritis, C-difficile	29(0.41)	29(0.42)	30(0.43)	1.02	1.05
Gout	1(0.01)	1(0.01)	3(0.04)	1	4
Gout, high uric acid	1(0.01)	1(0.01)	3(0.04)	1	4
Infestation, parasite	1(0.01)	1(0.01)	2(0.03)	1	3
Systemic embolism	1(0.01)	1(0.01)	2(0.03)	1	3
Tuberculosis	2(0.03)	2(0.03)	4(0.06)	1	2
Myalgia, myositis, rhabdomyolysis	2(0.03)	2(0.03)	3(0.04)	1	1.33
Abdominal pain, distension, bloating, spasm, IBS, megacolon	10(0.14)	10(0.14)	11(0.16)	1	1.14
Reflux, GERD	7(0.1)	7(0.1)	8(0.11)	1	1.1
Anxiety, nervousness, panic attacks	3(0.04)	3(0.04)	3(0.04)	1	1
Autoimmune disease	3(0.04)	3(0.04)	3(0.04)	1	1

SAE Table (continued)

	Pbo	T60 mg bd	T90 mg bd	RR	RR
	N= 6996	N=6958	N=6988	T60 mg bd	T90 mg bd
	n(%)	n(%)	n(%)	Pbo	Pbo
Herpes virus	1(0.01)	1(0.01)	1(0.01)	1	1
Low K+	1(0.01)	1(0.01)	1(0.01)	1	1
Ventricular arrhythmia	24(0.34)	24(0.34)	22(0.31)	1	0.91
Chest pain (not angina or unknown)	128(1.83)	127(1.83)	110(1.57)	1	0.86
Neuralgia, neuritis, neuropathy	6(0.09)	6(0.09)	5(0.07)	1	0.78
Angioedema, angioneurotic edema, laryngeal edema	3(0.04)	3(0.04)	2(0.03)	1	0.75
Elevated BUN or Cr, anuria, Acute renal failure, CRF, oliguria	34(0.49)	34(0.49)	23(0.33)	1	0.67
Allergic reaction, hypersensitivity	6(0.09)	6(0.09)	4(0.06)	1	0.67
Abscess, boil, furuncle	13(0.19)	13(0.19)	8(0.11)	1	0.58
Tardive dyskinesia, extrapyramidal symptoms	1(0.01)	1(0.01)	0(0)	1	0
Infection	262(3.74)	257(3.69)	243(3.48)	0.99	0.93
CHF or pulmonary edema	102(1.46)	100(1.44)	88(1.26)	0.99	0.86
CHF	100(1.43)	95(1.37)	85(1.22)	0.96	0.85
Cardiac arrest, sudden cardiac death, asystole, EMD	36(0.51)	34(0.49)	29(0.41)	0.96	0.8
Solid neoplasia, ALL (benign, malignant, unknown)	195(2.79)	181(2.6)	194(2.78)	0.93	1
Unstable angina	190(2.72)	177(2.54)	172(2.46)	0.93	0.9
Angina	313(4.47)	285(4.1)	271(3.88)	0.92	0.87
Cellulitis, erysipelas	18(0.26)	17(0.24)	14(0.2)	0.92	0.77
Appendicitis	8(0.11)	7(0.1)	7(0.1)	0.91	0.91
Wheeze, bronchospasm, asthma	7(0.1)	6(0.09)	6(0.09)	0.9	0.9
Cancer (non-squamous cell)	160(2.29)	140(2.01)	149(2.13)	0.88	0.93
AFlutter	11(0.16)	10(0.14)	7(0.1)	0.88	0.63
Hypoglycemia	5(0.07)	4(0.06)	6(0.09)	0.86	1.29
Benign tumor	18(0.26)	15(0.22)	22(0.31)	0.85	1.19
Tachycardia	22(0.31)	18(0.26)	11(0.16)	0.84	0.52
Conduction disturbance	17(0.24)	14(0.2)	11(0.16)	0.83	0.67
Acute coronary syndrome: AMI and unstable angina	425(6.07)	345(4.96)	322(4.61)	0.82	0.76
Pulmonary embolism	11(0.16)	9(0.13)	9(0.13)	0.81	0.81
Pancreatitis, hyperamylasemia	14(0.2)	11(0.16)	12(0.17)	0.8	0.85
Coronary artery disease, myocardial ischemia	473(6.76)	378(5.43)	359(5.14)	0.8	0.76
URI, cold, rhinitis, upper resp tract infection, flu-l ke illness	10(0.14)	8(0.11)	8(0.11)	0.79	0.79
Sick sinus syndrome	6(0.09)	5(0.07)	7(0.1)	0.78	1.11
Dyspepsia, N, V, indigestion, epigastric pain, gastritis, duodenitis	18(0.26)	14(0.2)	28(0.4)	0.77	1.54
Bronchitis, bronchiolitis, tracheitis, alveolitis, bronchiectasis	24(0.34)	18(0.26)	22(0.31)	0.76	0.91
Vertigo; vest bular dysfunction	12(0.17)	9(0.13)	10(0.14)	0.76	0.82
Thrombocytopenia	3(0.04)	2(0.03)	6(0.09)	0.75	2.25
Peritonitis	3(0.04)	2(0.03)	5(0.07)	0.75	1.75

SAE Table (continued)

	Pbo	T60 mg bd	T90 mg bd	RR	RR
	N= 6996	N=6958	N=6988	T60 mg bd	T90 mg bd
	n(%)	n(%)	n(%)	Pbo	Pbo
Pneumonia	77(1.1)	58(0.83)	63(0.9)	0.75	0.82
Palpitations	3(0.04)	2(0.03)	2(0.03)	0.75	0.75
Ischemic stroke	74(1.06)	55(0.79)	53(0.76)	0.75	0.72
Hypertension, BP increased	30(0.43)	22(0.32)	19(0.27)	0.74	0.63
AV block	16(0.23)	12(0.17)	6(0.09)	0.74	0.39
Chronic obstructive pulmonary disease, COPD exacerbation	41(0.59)	30(0.43)	42(0.6)	0.73	1.02
Benign prostatic hypertrophy	28(0.4)	20(0.29)	15(0.21)	0.73	0.53
Arthralgia, arthritis, arthrosis	71(1.01)	50(0.72)	48(0.69)	0.71	0.68
Retinopathy, retinal disorders	7(0.1)	5(0.07)	8(0.11)	0.7	1.1
Acute myocardia infarction	224(3.2)	154(2.21)	149(2.13)	0.69	0.67
Stroke (ischemic and hemorrhagic)	87(1.24)	60(0.86)	56(0.8)	0.69	0.65
Lymphoma	6(0.09)	4(0.06)	7(0.1)	0.67	1.11
Hyper/hypo thyroid, thyroiditis, goiter	4(0.06)	3(0.04)	3(0.04)	0.67	0.67
Cerebral ischemia (includes stroke, ICH, and TIA)	115(1.64)	76(1.09)	80(1.14)	0.66	0.7
Stroke, transient ischemic attack	113(1.62)	74(1.06)	77(1.1)	0.65	0.68
Arteriosclerosis, vascular disease, PVD, bowel ischemia	39(0.56)	25(0.36)	26(0.37)	0.64	0.66
Transient ischemic attach	26(0.37)	15(0.22)	21(0.3)	0.59	0.81
Depression	11(0.16)	6(0.09)	7(0.1)	0.56	0.63
Ileus, obstruction	9(0.13)	5(0.07)	9(0.13)	0.54	1
Orthostasis	4(0.06)	2(0.03)	5(0.07)	0.5	1.17
Pericarditis, effusion, tampanade	4(0.06)	2(0.03)	2(0.03)	0.5	0.5
High or third degree AV Block	10(0.14)	5(0.07)	1(0.01)	0.5	0.07
Dementia, cognitive dysfunction	6(0.09)	3(0.04)	2(0.03)	0.44	0.33
Gangrene	5(0.07)	2(0.03)	5(0.07)	0.43	1
Apnea, respiratory failure, cyanosis, hypoxemia, desaturation	10(0.14)	4(0.06)	8(0.11)	0.43	0.79
Sleep apnea	5(0.07)	2(0.03)	1(0.01)	0.43	0.14
Infection, viral	17(0.24)	7(0.1)	12(0.17)	0.42	0.71
Confusion, delirium, altered mental status, disorientation, coma	8(0.11)	3(0.04)	5(0.07)	0.36	0.64
Hemorrhagic stroke	12(0.17)	4(0.06)	1(0.01)	0.35	0.06
Dysfunctional uterine bleeding, menometrorrhagia	2(0.03)	1(0.01)	2(0.03)	0.33	1
Thrombophlebitis, thrombosis, thrombus, clot	32(0.46)	9(0.13)	13(0.19)	0.28	0.41
DVT	9(0.13)	2(0.03)	7(0.1)	0.23	0.77
Headache	4(0.06)	1(0.01)	4(0.06)	0.17	1
Leukemia	6(0.09)	1(0.01)	3(0.04)	0.11	0.44
Anaphylactic reaction	2(0.03)	0(0)	2(0.03)	0	1
Fever, rigors	2(0.03)	0(0)	2(0.03)	0	1

SAE Table (continued)

	Pbo	T60 mg bd	T90 mg bd	RR	RR
	N= 6996	N=6958	N=6988	T60 mg bd	T90 mg bd
	n(%)	n(%)	n(%)	Pbo	Pbo
Fever, rigors	2(0.03)	0(0)	2(0.03)	0	1
Low Na+	2(0.03)	0(0)	2(0.03)	0	1
Influenza	4(0.06)	0(0)	2(0.03)	0	0.5
Atrial tachycardia	2(0.03)	0(0)	0(0)	0	0
Hepatic failure, cirrhosis or progression	2(0.03)	0(0)	0(0)	0	0
Gynecomastia	0(0)	0(0)	1(0.01)	-	-
Hepatitis	0(0)	3(0.04)	0(0)	-	-
Pancytopenia, bone marrow aplasia	0(0)	2(0.03)	1(0.01)	-	-
Polycythemia	0(0)	1(0.01)	0(0)	-	-
Aplastic anemia	0(0)	1(0.01)	0(0)	-	-
Pulmonary f brosis	0(0)	2(0.03)	4(0.06)	-	-
Pulmonary hypertension, increased pulmonary vascular resistance	0(0)	1(0.01)	2(0.03)	-	-
QRS prolonged, Bundle branch block	0(0)	1(0.01)	3(0.04)	-	-
Sinus arrest, sinus pause, sinus block	0(0)	1(0.01)	2(0.03)	-	-
Stevens-Johnson syndrome, TEN	0(0)	1(0.01)	0(0)	-	-

APPENDIX 5: Neoplasm AEs PLATO

Table 44: Risk of Malignant Neoplasms in PLATO

MedDRA High Level Term Name	TICAGRELOR 90 mg BD	CLOPIDOGREL 75 MG OD	Subjects(filtered)
TOTAL MALIGNANCIES	142 (1.54%)	144 (1.57%)	18758 (100.00%)
SKIN NEOPLASMS MALIGNANT AND UNSPECIFIED (EXCL MELANOMA)	13 (0.14%)	11 (0.12%)	24 (0.13%)
PROSTATIC NEOPLASMS MALIGNANT	12 (0.13%)	11 (0.12%)	23 (0.12%)
RESPIRATORY TRACT AND PLEURAL NEOPLASMS MALIGNANCY UNSPECIFIED NEC	11 (0.12%)	14 (0.15%)	25 (0.13%)
COLONIC NEOPLASMS MALIGNANT	10 (0.11%)	3 (0.03%)	13 (0.07%)
CELL MARKER PROCEDURES	9 (0.10%)	8 (0.09%)	17 (0.09%)
RESPIRATORY TRACT AND PLEURAL NEOPLASMS MALIGNANT CELL TYPE UNSPECIFIED NEC	9 (0.10%)	13 (0.14%)	22 (0.12%)
URINARY TRACT NEOPLASMS UNSPECIFIED MALIGNANCY NEC	9 (0.10%)	6 (0.07%)	15 (0.08%)
ENDOCRINE NEOPLASMS MALIGNANT AND UNSPECIFIED NEC	7 (0.08%)	7 (0.08%)	14 (0.07%)
BLADDER NEOPLASMS MALIGNANT	5 (0.05%)	8 (0.09%)	13 (0.07%)
NEOPLASMS MALIGNANT SITE UNSPECIFIED NEC	5 (0.05%)	3 (0.03%)	8 (0.04%)
NERVOUS SYSTEM NEOPLASMS UNSPECIFIED MALIGNANCY NEC	5 (0.05%)	6 (0.07%)	11 (0.06%)
BREAST AND NIPPLE NEOPLASMS MALIGNANT	4 (0.04%)	10 (0.11%)	14 (0.07%)
ONCOLOGIC COMPLICATIONS AND EMERGENCIES	4 (0.04%)	0 (0.00%)	4 (0.02%)
RECTAL NEOPLASMS MALIGNANT	4 (0.04%)	3 (0.03%)	7 (0.04%)
GASTRIC NEOPLASMS MALIGNANT	3 (0.03%)	3 (0.03%)	6 (0.03%)
GASTROINTESTINAL NEOPLASMS MALIGNANCY UNSPECIFIED NEC	3 (0.03%)	1 (0.01%)	4 (0.02%)
LEUKEMIAS CHRONIC LYMPHOCYTIC	3 (0.03%)	1 (0.01%)	4 (0.02%)
SKIN MELANOMAS (EXCL OCULAR)	3 (0.03%)	3 (0.03%)	6 (0.03%)
HEPATIC NEOPLASMS MALIGNANT	2 (0.02%)	1 (0.01%)	3 (0.02%)
LYMPHOMAS UNSPECIFIED NEC	2 (0.02%)	1 (0.01%)	3 (0.02%)
METASTASES TO SPECIFIED SITES	2 (0.02%)	9 (0.10%)	11 (0.06%)
NEOPLASMS UNSPECIFIED MALIGNANCY AND SITE UNSPECIFIED NEC	2 (0.02%)	1 (0.01%)	3 (0.02%)
NON-SMALL CELL NEOPLASMS MALIGNANT OF THE RESPIRATORY TRACT CELL TYPE SPECIFIED	2 (0.02%)	0 (0.00%)	2 (0.01%)
OVARIAN NEOPLASMS MALIGNANT (EXCL GERM CELL)	2 (0.02%)	1 (0.01%)	3 (0.02%)
RENAL NEOPLASMS MALIGNANT	2 (0.02%)	2 (0.02%)	4 (0.02%)
CARCINOID TUMOURS	1 (0.01%)	2 (0.02%)	3 (0.02%)
COLORECTAL AND ANAL NEOPLASMS MALIGNANCY UNSPECIFIED	1 (0.01%)	5 (0.05%)	6 (0.03%)
COLORECTAL NEOPLASMS MALIGNANT	1 (0.01%)	1 (0.01%)	2 (0.01%)
ENDOMETRIAL NEOPLASMS MALIGNANT	1 (0.01%)	0 (0.00%)	1 (0.01%)
EXTRANODAL MARGINAL ZONE B-CELL LYMPHOMAS (LOW GRADE B-CELL)	1 (0.01%)	0 (0.00%)	1 (0.01%)
FEMALE REPRODUCTIVE NEOPLASMS UNSPECIFIED MALIGNANCY	1 (0.01%)	0 (0.00%)	1 (0.01%)
GASTROINTESTINAL NEOPLASMS MALIGNANT NEC	1 (0.01%)	2 (0.02%)	3 (0.02%)
GLIAL TUMOURS MALIGNANT	1 (0.01%)	0 (0.00%)	1 (0.01%)
HEPATOBILIARY NEOPLASMS MALIGNANCY UNSPECIFIED	1 (0.01%)	1 (0.01%)	2 (0.01%)
LEUKEMIAS ACUTE MYELOID	1 (0.01%)	0 (0.00%)	1 (0.01%)

LEUKEMIAS CHRONIC NEC	1 (0.01%)	1 (0.01%)	2 (0.01%)
LIP AND ORAL CAVITY NEOPLASMS MALIGNANCY UNSPECIFIED	1 (0.01%)	2 (0.02%)	3 (0.02%)
MESOTHELIOMAS MALIGNANT AND UNSPECIFIED	1 (0.01%)	1 (0.01%)	2 (0.01%)
MULTIPLE MYELOMAS	1 (0.01%)	0 (0.00%)	1 (0.01%)
MYELODYSPLASTIC SYNDROMES	1 (0.01%)	1 (0.01%)	2 (0.01%)
PANCREATIC NEOPLASMS MALIGNANT (EXCL ISLET CELL AND CARCINOID)	1 (0.01%)	1 (0.01%)	2 (0.01%)
PARANASAL SINUS AND NASAL CAVITY NEOPLASMS MALIGNANT AND UNSPECIFIED	1 (0.01%)	0 (0.00%)	1 (0.01%)
RESPIRATORY TRACT SMALL CELL CARCINOMAS	1 (0.01%)	2 (0.02%)	3 (0.02%)
SMALL INTESTINAL NEOPLASMS MALIGNANT	1 (0.01%)	0 (0.00%)	1 (0.01%)
TESTICULAR NEOPLASMS MALIGNANT	1 (0.01%)	0 (0.00%)	1 (0.01%)
THYROID NEOPLASMS MALIGNANT	1 (0.01%)	0 (0.00%)	1 (0.01%)
B-CELL LYMPHOMAS NEC	0 (0.00%)	1 (0.01%)	1 (0.01%)
BONE NEOPLASMS MALIGNANT (EXCL SARCOMAS)	0 (0.00%)	2 (0.02%)	2 (0.01%)
BONE NEOPLASMS UNSPECIFIED MALIGNANCY	0 (0.00%)	1 (0.01%)	1 (0.01%)
BREAST NEOPLASMS UNSPECIFIED MALIGNANCY	0 (0.00%)	1 (0.01%)	1 (0.01%)
CENTRAL NERVOUS SYSTEM NEOPLASMS MALIGNANT NEC	0 (0.00%)	1 (0.01%)	1 (0.01%)
LARYNGEAL NEOPLASMS MALIGNANT	0 (0.00%)	2 (0.02%)	2 (0.01%)
LIP AND ORAL CAVITY NEOPLASMS MALIGNANT	0 (0.00%)	1 (0.01%)	1 (0.01%)
MEDIASTINAL NEOPLASMS MALIGNANCY UNSPECIFIED NEC	0 (0.00%)	1 (0.01%)	1 (0.01%)
OESOPHAGEAL NEOPLASMS MALIGNANT	0 (0.00%)	2 (0.02%)	2 (0.01%)
REPRODUCTIVE NEOPLASMS MALE UNSPECIFIED MALIGNANCY	0 (0.00%)	1 (0.01%)	1 (0.01%)
URINARY TRACT NEOPLASMS MALIGNANT NEC	0 (0.00%)	1 (0.01%)	1 (0.01%)

APPENDIX 6: LIST OF AEs in REVIEWER'S AE RENAMING TOOL

	Adverse Event Category						
	PSYCHIATRIC	23	Dyskinesia	46	DRESS, Drug rash with eosinophilia and systemic symptoms	69	dermatitis
1	Dysphoria-type symptoms, not clearly depression	24	Axonal demyelinating neuropathy, demyelination, transverse myelitis	47	Systemic inflammatory response syndrome	70	Stevens-Johnson syndrome, TEN
2	Emotional mood disturbance (non-depressive)	25	Confusion, delirium, altered mental status, disorientation, coma	48	Anaphylactic reaction		**RESPIRATORY SYSTEM**
3	Depression	26	Dementia, cognitive dysfunction	49	autoimmune disease	71	Influenza
4	Suicidal ideation, intentional overdose, self-injury, suicide	27	Encephalitis, encephalopathy	50	Urticaria	72	URI, cold, rhinitis, upper resp tract infection, flu-like illne
5	Psychosis, delusions, hallucinations	28	Hepatic encephalopathy	51	Angioedema, angioneurotic edema, laryngeal edema	73	Bronchitis, bronchiolitis, tracheitis, alveolitis, bronchiectasis
6	Depersonalization, dissociation	29	Seizure		**INFECTION**	74	Pneumothorax
7	Anxiety, nervousness, panic attacks	30	Ataxia, cerebellar syndrome	52	Fever, rigors	75	Pneumonia
8	Restlessness, agitation, hyperkinesia	31	Paresthesia, hypoaesthesia	53	Infection, all	76	hypoxemia, desaturation, lung
9	Insomnia, sleep disturbance, abnormal dreams	32	Neuralgia, neuritis, neuropathy	54	Infection, bacterial	77	Dyspnea, SOB, respiratory distress
10	Irritability, agitation, stress, tension, restless, anger, homicidal ideation	33	Cranial neuropathy, palsy	55	Infection, viral	78	DOE
11	Dizziness, light-headedness	34	Tremor, shakiness, trembling	56	Herpes virus	79	COPD, COPD exacerbation
12	Bipolar disorder	35	Choreoathetosis, involuntary movements	57	Infection, fungal	80	Pulmonary embolism
13	Asthenia, fatigue, malaise, weakness, narcolepsy	36	Akinesia	58	infestation, parasite	81	Sleep apnea
	NEUROLOGICAL SYSTEM	37	Memory loss, impairment	59	TB	82	Cough
14	EPS, potential EPS, tardive dyskinesia	38	Headache	60	Peritonitis	83	Wheeze, bronchospasm, asthma

Reference ID: 3804604

15	Neuroleptic malignant syndrome	39	Vertigo; vestibular dysfunction	61	Shock, non-cardiogenic	84	Pulmonary fibrosis
16	Stroke, TIA	40	Tinnitus	62	Sepsis	85	Lung transplant
17	Stroke (includes ischemic and hemorrhagic)	41	Difficulty walking, gait disturbance	63	Bacteremia		**NEOPLASM**
18	Ichemic stroke	42	Hearing loss, deafness	64	UTI	86	Cancer (non-squamous cell)
19	Hemorrhagic stroke	43	Tinnitus		**SKIN**	87	Squamous cell Ca skin
20	TIA		**IMMUNE SYSTEM**	65	Abscess, boil, furuncle	88	Solid neoplasia, ALL (benign, malignant, unknown)
21	Cerebral ischemia (includes stroke, ICH, and TIA)	44	Allergic RXN, hypersensitivity	66	Cellulitis, erysipelas	89	Benign tumor
22	Intracranial hemorrhage (includes hemorrhagic stroke, SAH, SDH)	45	Injection site reaction (all)	67	pruritis	90	Leukemia
				68	rash, eruption, dermatitis	91	Lymphoma

	CARDIOVASCULAR SYSTEM	116	Edema, non-pulm, fluid retention, fluid overload	141	QRS prolonged, BBB	164	Back pain
92	Angina	117	Hypertension, BP increased	142	QT prolonged	165	Ligament rupture
93	CHF or pulmonary edema	118	Hypotension	143	AV block	166	Tendon rupture
94	CHF	119	Orthostasis	144	High or third deg AV Block		**LABORATORY ABNORMALITIES**
95	Pulmonary edema	120	Dehydration, volume depletion	145	Sick-sinus syndrome	167	Low K+
96	Cardiogenic shock	121	Polydipsia, thirst, dry mouth, dry tongue	146	Pre-syncope or syncope	168	High K+
97	Right Ventricular Failure	122	Cardiac arrest, SCD, asystole, EMD	147	Pre-syncope	169	Low Mg
98	CAD, myocardial ischemia,	123	Palpitations	148	Syncope	170	Low Na+
99	Acute MI	124	Arrhythmia		**ENDOCRINE SYSTEM**	171	High Na+
100	Unstable angina	125	Tachycardia	149	Diabetes, glucose intolerance, hyperglycemia, HbA1c, glycosuria,	172	Increasd osmolality
101	syndrome): AMI and unstable angina	126	Bradycardia	150	Diabetes insipidus	173	Decreasd osmolality
102	ICD SHOCK	127	Supra-ventricular arrhythmia	151	Hypoglycemia	174	Low Ca+
103	Heart transplant	128	PACs	152		175	High Ca+
104	Myocardial/papillary rupture	129	Sinus arrest, sinus pause, sinus block	153	Hyper/hypo thyroid, thyroiditis, goiter	176	Acidosis
105	Troponin or CK-MB increased	130	Atrial fibrillation	154	Parathyroid abnormalities		**RENAL / URINARY SYSTEM**
106	output, cardiomyopathy, LV dysfunction	131	Atrial flutter	155	Adrenal insufficiency	177	Elevated BUN or Cr, anuria, ARF, CRF, oliguria
107	RV dysfunction, hypertrophy, cor pulmonale	132	Atrial fibrillation or flutter	156	Hyperprolactinemia	178	Nephritis, glomerulonephritis
108	Pulmonary hypertension, increased pulmonary vascular resistance	133	Atrial tachycardia		**MUSCULOSKELETAL SYSTEM**	179	Anuria, ARF
109	Arteriosclerosis, vascular disease, PVD, bowel ischemia	134	Ventricular arrhythmia	157	CPK increased	180	Dysuria
110	Gangrene	135	Ventricular tachycardia	158	Myalgia, myositis, rhabdomyolysis	181	Nephrosis, proteinuria, nephropathy
111	Deep venous thrombosis	136	Ventricular fibrillation	159	Arthralgia, arthritis, arthrosis	182	Polyuria, increased frequency
112	Cardiac thrombus	137	TdP	160	Tendonitis, synovitis	183	Nocturia
113	Thrombophlebitis, thrombosis, thrombus, clot	138	Ventricular flutter	161	Cramps, muscle spasm	184	Kidney stone, renal colic
114	Systemic embolism	139	PVCs	162	Myopathy		**HEMATOLOGICAL SYSTEM**
115	Pericarditis, effusion, tampanade	140	conduction disturbance	163	Fracture	185	Leukopenia (neutropenia and/or lymphopenia)

186	Anemia	210	Hepatic steatosis		**GENERAL**		**BREAST**
187	Fe Deficiency	211	Ileus, obstruction	233	Weight loss, catabolic state, cachexia, Failure to thrive	254	Gynecomastia
188	PRCA, aplastic anemia	212	Elevated Bili, alk phos, jaundice	234	Weight gain	255	Breast pain, tenderness
189	Hemolysis		**GASTROINTESTINAL SYSTEM**	235	Anorexia, decreased appetite		**OTHER**
190	Polycythemia	213	Constipation	236	Fall	256	Osteonecrosis of jaw
191	Neutropenia, granulocytopenia	214	enteritis, proctitis, gastroenteritis, C-diff		**EYE/ VISION**	257	Sexual dysfunction
192	Agranulocytosis	215	Dyspepsia, N, V, indigestion, epigastric pain, gastritis, duoden	237	Cataract	258	Prostacycline-like effects
193	Lymphopenia	216	Gastric, duodenal, or	238	Retinopathy, retinal	259	Chest pain (not angina or
194	marrow aplasia	217	Reflux, GERD	239	Visual disturbance	260	Motor vehicle accident
195	Leukocytosis	218	Esophagitis, hiatal hernia	240	Corneal deposits, opa	261	Gout, high uric acid
196	Eosinophilia	219	Dry mouth, dry lips, thirst	241	Diplopia	262	Gout
197	Ecchymosis, hematoma, bruise	220	Dysphagia	242	Ocular hemmorhage		
198	Coagulopathy, prolonged PT, PTT, DIC	221	Abdominal pain, distension, bloating, spasm, IBS, megacolon	243	Uveitis		
199	Bleeding	222	Flatulence	244	Eye other		
200	Hematuria	223	GI bleed	245	Glaucoma, high intraocular pressure		
201	Thrombocytopenia	224	Esophageal varices	246	Macular degeneration, maculopathy		
202	Thrombocytosis	225	Diverticular disease		**MALE GENITAL URINARY**		
203	Epistaxis	226	Appendicitis	247	Benign prostatic hypertrophy		
204	Hemoptysis	227	Cholecystitis, cholelithiasis, bile duct stone	248	Erectile dysfunction		
	HEPATIC	228	Hernia	249	Ejaculation delay/failure		
205	Hepatorenal	229	Hernia, incarcerated, obstructive, gangrenous, or ruptured		**FEMALE GENITAL**		
206	Hepatitis	230	Gastrointestinal fistula	250	Dysfunctional uterine bleeding, menometrorrhagia		
207	Cholestatic hepatitis	231	Ascites	251	Vaginal atrophy		
208	Hepatic failure, cirhossis progression	232	Pancreatitis, hyperamylasemia	252	Miscarriage or threatened miscarriage (spont. Abortion)		
209	Elevated GOT, GPT, GGTP, LFTs			253	Amenorrhea		

Reference ID: 3804604

9.1 Labeling Recommendations

See summary sections.

9.2 Advisory Committee Meeting

There will be no advisory committee meeting.

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/s/

PRESTON M DUNNMON
08/11/2015

MELANIE J BLANK
08/11/2015

MARTIN ROSE
08/11/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-433/S015

STATISTICAL REVIEW(S)

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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA #:	22433
Drug Name:	Ticagrelor
Indication(s):	Prevention of Thrombotic Events
Applicant:	AstraZeneca
Date(s):	03/05/2015
Review Priority:	Priority
Biometrics Division:	Division of Biometrics I
Statistical Reviewer:	Steve Bai, Ph.D.
Concurring Reviewers:	James Hung, Ph.D., Director, Division of Biometrics I
Medical Division:	Division of Cardiovascular and Renal Products
Clinical Team:	Preston Dunnmon, MD Melanie Blank, MD Martin Rose, MD
Project Manager:	Alison Blaus

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1 EXECUTIVE SUMMARY

PEGASUS demonstrated the long-term treatment with ticagrelor 90 mg bd or 60 mg bd given in combination with ASA showed clear benefits over placebo for both doses of ticagrelor in patients with a history of myocardial infarction (MI) and at high risk of an atherothrombotic event.

The primary efficacy objective was met, showing a clinically relevant and statistically significant benefit on the composite primary endpoint (CV death, MI, and stroke) that was consistent for both ticagrelor doses. The clinical relevance of the results is further supported by the consistent findings over time. The benefit of ticagrelor was numerically consistent for the CV death for both doses versus placebo. For all-cause mortality, there was no difference between ticagrelor 90mg and placebo whereas the result was numerically in favor of ticagrelor 60 mg. The numerically favorable treatment effects for both ticagrelor doses in the composite primary endpoint were seen across the most of patient subgroups.

2 INTRODUCTION

2.1 Overview

Ticagrelor, an oral, reversible, antiplatelet agent, has previously established a positive benefit-risk profile for the prevention of atherothrombotic events in patients with acute coronary syndrome (ACS). It was approved in the EU in December 2010, in the US in July 2011, and subsequently in over 100 countries for the following indication:

"Ticagrelor is indicated for the prevention of thrombotic events (Cardiovascular death, MI, and stroke) in patients with ACS (unstable angina, non ST elevation Myocardial Infarction [NSTEMI] or ST elevation Myocardial Infarction [STEMI]) (b) (4)

AstraZeneca now seeks marketing approval for the use of ticagrelor in patients with a history of MI. This application is based on the recently completed Phase III study D5132C00001/ PEGASUS TIMI-54 (hereafter referred to as 'PEGASUS').

PEGASUS, a randomised, double-blind, placebo-controlled, parallel-group study, was conducted to determine whether long-term dual antiplatelet therapy with ticagrelor 90 mg or 60 mg twice daily (bd) compared to placebo, all on background low dose acetylsalicylic acid (ASA) (75 to 150 mg daily), reduces major cardiovascular events in patients with history of MI (1 to 3 years prior to randomization) and at high risk of an atherothrombotic event.

The primary efficacy objective of PEGASUS was met, showing a clinically relevant and statistically significant benefit on the composite primary endpoint (CV death, MI, and stroke) for both ticagrelor doses. Primary composite endpoint events were reported for 493, 487, and 578 patients on ticagrelor 90 mg, ticagrelor 60 mg, and placebo, respectively. The observed HR over

placebo is 0.85 (95% CI 0.75, 0.96), p=0.0080 for ticagrelor 90 mg, and the observed HR over placebo is 0.84 (95% CI 0.74, 0.95), p=0.0043 for ticagrelor 60 mg.

The proposed dosing regimen is only the Ticagrelor 60 mg twice daily.

2.2 Data Sources

The sponsor's submitted data are stored in the following directory of the CDER's electronic document room: \\cdsesub1\evsprod\NDA022433\0160\m5\datasets.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The PEGASUS was performed in compliance with GCP guidelines, including the archiving of essential documents. AstraZeneca's quality assurance and quality control procedures provide reassurance that the clinical study program was carried out in accordance with GCP guidelines. AstraZeneca undertook a GCP audit program to ensure compliance with its procedures and to assess the adequacy of its quality control measures. All investigators were trained to comply with GCP and to conduct both studies in accordance with their study protocols.

3.2 Evaluation of Efficacy

3.2.1 STUDY OBJECTIVES

The primary objective of the study was to compare the effect of long-term treatment with ticagrelor versus placebo on a background of low-dose ASA (75 to 150 mg daily) on the event rate of the composite of cardiovascular death, non-fatal MI, or non-fatal stroke in patients with history of MI (1 to 3 years prior to randomization) and high risk of developing atherothrombotic events.

The secondary objectives were to compare the effect of long-term treatment with ticagrelor versus placebo on a background of ASA on the event rates of a) CV death and b) all-cause mortality in patients with history of MI and high risk of developing atherothrombotic events.

3.2.2 STUDY DESIGN AND ENDPOINTS

PEGASUS was a randomised, double-blind, placebo-controlled, 3-arm parallel group, multinational trial to assess the prevention of cardiovascular events following dual antiplatelet therapy with ticagrelor (90 mg bd or 60 mg bd) compared to placebo on a background of ASA in patients with history of MI (1 to 3 years prior to randomization) and at high risk of an atherothrombotic event.

The study was event driven and the number of randomised patients was estimated to be required to collect 1360 primary events based on a 24-month recruitment period and 14-month follow-up

period. The study was to run until the common study end date (CSED), when all patients had been treated for a minimum of 12 months and the estimated number of primary events had been reached. The CSED was the date after which the final visits started, including end-of-treatment (EoT) visit and follow-up visit if patient was on treatment with study drug, or a final follow-up visit if the patient had prematurely discontinued treatment. The CSED was the censoring date for efficacy analyses, including events occurring on or prior to CSED. At least the target number of adjudicated primary events (ie, 1360) was to be reached on or before the predicted day for the CSED. On 12 May 2014, the CSED was set for 14 September 2014. The last follow-up patient visit took place on 3 December 2014.

The primary efficacy variable was time to first occurrence of any event after randomization from the composite of CV death, non-fatal MI, or non-fatal stroke.

The secondary efficacy endpoints of CV death and all-cause mortality were assessed in PLATO and ticagrelor was found to confer a greater relative risk reduction for these events than for the primary composite endpoint. This study again investigated these ultimate outcomes to further explore the effects of ticagrelor on mortality in patients with high cardiovascular risk. The family-wise error rate in the confirmatory analyses of primary and secondary endpoints was handled with the Dunnett's approach (see Section 3.2.3).

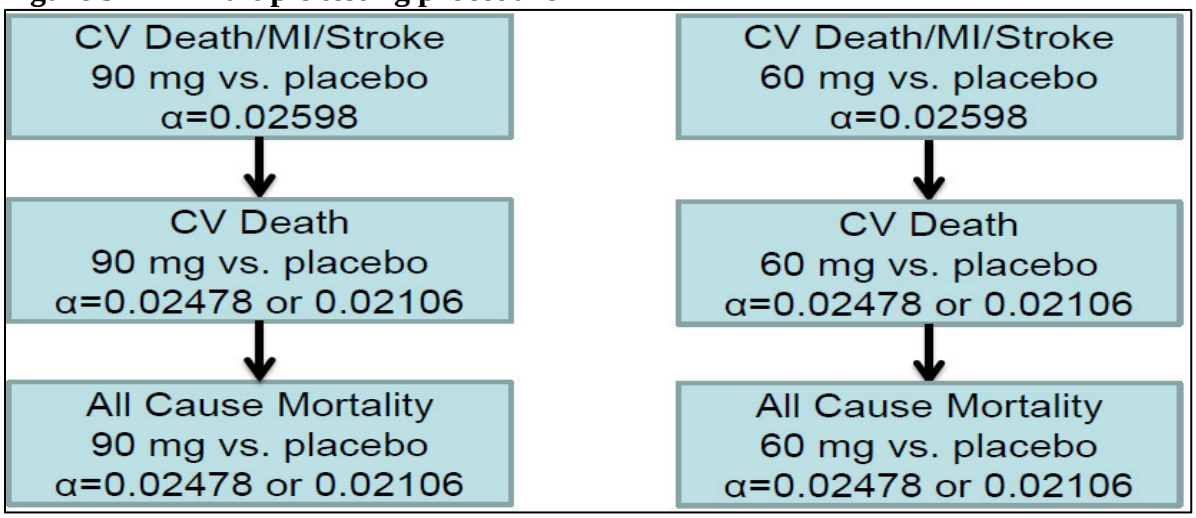
3.2.3 STATISTICAL METHODOLOGIES

The Full analysis Set (FAS) included all randomized patients. All main statistical analyses of all efficacy endpoints were based on the FAS.

Both the primary and secondary analyses are time to event analyses. The ticagrelor 60 mg and 90 mg treatment groups were analyzed separately versus the placebo group in the Cox proportional hazards model with a factor for treatment group. P-values and confidence intervals for the hazard ratio (HR) will be based on the Wald statistic. In summary tables of these analyses, in addition to HR with confidence interval and p-value for each ticagrelor dose vs. placebo, presentations will include the number of patients with event and Kaplan-Meier estimates of the event rate per treatment group calculated at a time point determined on the basis of the available follow-up.

To control the overall type I error at 5%, the alpha apportioned to each ticagrelor dose-placebo comparison is 0.0269 (2-sided), utilizing the correlation (0.5) between the test statistics. The IDMC performed one interim analysis at 46% of the final number of primary events. The Haybittle-Peto alpha-spending approach (one-sided significance level of 0.001) was applied. The resulting 2-sided significance level for each dose-placebo comparison of the primary endpoint in the final analysis was 0.02598.

Figure 3-1 Multiple testing procedure



[Source: Study Report Figure 5]

For the two secondary endpoints, if tests of both doses were significant for the endpoint at the previous level in the hierarchy, then both doses would be tested at 0.02478 significance level (Figure 3-1). If only one of the tests was significant for the previous endpoint, this dose would be tested at 0.02106 significance level, which was determined depending on proportion of events in the interim analyses.

The IDMC performed interim analyses of unblinded data. A pre-planned interim analysis of efficacy was to be conducted when approximately 50% of the total planned number of primary events had occurred, with the possibility of further interims as considered necessary by the IDMC. For each interim analysis, each of the ticagrelor 90 mg and 60 mg doses was to be compared separately versus placebo. A 1-sided significance level of 0.001 was to be applied to each ticagrelor dose-placebo comparison at each interim efficacy analysis. The Haybittle-Peto alpha spending function governed interim and final statistical testing to ensure an overall Type I error of 5%. Only one interim analysis was conducted (with 46% of the final number of events). In order to stop the trial for overwhelming benefit in a particular dose or both doses, the test(s) of all-cause mortality and the primary endpoint need to both meet the significance at 0.001 level for that dose or both doses, respectively.

3.2.4 PATIENT DISPOSITION, DEMOGRAPHIC AND BASELINE CHARACTERISTICS

In total, 21326 patients were enrolled from 1164 study sites in 31 countries. The first patient enrolled on 29 October 2010. Further, 21162 (99.2%) of the enrolled subjects were randomised and the majority of patients (72.6%) completed the study on study drug (i.e., on study drug until CSED or death). There was complete follow-up of all primary endpoint events (i.e., until death or CSED) for 98.7% of patients (n=20892).

Of the 21162 randomised patients, 7050, 7045, and 7067 patients were randomised to ticagrelor 90 mg bd, ticagrelor 60 mg bd, and placebo bd, respectively. Mean follow-up to CSED was 31.8, 31.8, and 31.7 months for the ticagrelor 90 mg, ticagrelor 60 mg, and placebo groups, respectively, and median follow-up to CSED was 33.1, 33.3, and 33.1 months, respectively.

Table 3-1 Demographic characteristics at screening, FAS

	Ticag 90mg N=7050	Ticag 60mg N=7045	Placebo N=7067	Total N=21162
Sex				
Male (%)	5368 (76.1)	5384 (76.4)	5350 (75.7)	16102 (76.1)
Age				
Mean (SD)	65.4 (8.4)	65.2 (8.4)	65.4 (8.3)	65.3 (8.3)
< 65 (%)	3190 (45.2)	3283 (46.6)	3154 (44.6)	9267 (45.5)
65-75 (%)	2977 (42.2)	2913 (41.3)	3074 (43.5)	8964 (42.4)
>=75 (%)	883 (12.5)	849 (12.1)	839 (11.9)	2571 (12.1)
Race (%)				
White	6126 (86.9)	6077 (86.3)	6124 (86.7)	18327 (86.6)
Asian	748 (10.6)	768 (10.9)	765 (10.8)	2281 (10.8)
Black	109 (1.5)	128 (1.8)	116 (1.6)	353 (1.7)
Other	67 (1.0)	72 (1.0)	62 (0.9)	201 (0.9)

[Source: Reviewer's results]

The demographic characteristics of the patients were balanced across the randomised treatment groups, see Table 3-1. The mean age of the study population was 65.3 years and 12.1% (n=2571) were aged over 75 years. The majority (76.1%) were male. The population was predominantly Caucasian (86.6%).

The geographic regions of the patients in this study are summarized in Table 3-2.

Table 3-2 Number of patients by geographic region

Region (%)	Ticag 90mg N=7050	Ticag 60mg N=7045	Placebo N=7067	Total N=21162
Asia and Australia	793 (11.2)	788 (11.2)	788 (11.2)	2369 (11.2)
Europe and S Africa	4128 (58.6)	4146 (58.9)	4154 (58.8)	12428 (58.7)
N America	1307 (18.5)	1297 (18.4)	1303 (18.4)	3907 (18.5)
S America	822 (11.7)	814 (11.6)	822 (11.6)	2458 (11.6)

[Source: Reviewer's results]

Mean weight of all patients was 82.0 kg and BMI was 28.5 kg/m^2. Overall, 16.7% of patients reported being current smokers, 48.3% were former smokers, and 35.0% reported never smoking. The treatment groups were balanced with respect to these patient characteristics (Table 3-3).

The population targeted for this study was patients with a documented history of presumed spontaneous MI, with the most recent MI occurring 1 to 3 years prior to randomization. Table 3-3 described that almost 99% of patients had the time from qualifying MI to randomization was between 1 and 3 years. Previous treatment with an ADP receptor blocker any time prior to randomization is summarized in Table 3-3. Most (89.1%) of the patients had received previous treatment with an ADP receptor blocker. For 25.8% of patients, their last dose of ADP receptor blocker was within 7 days before randomization into this study; for 23.5% of patients, their last dose of an ADP receptor blocker was more than 12 months before randomization.

Table 3-3 Patient characteristics

	Ticag 90mg N=7050	Ticag 60mg N=7045	Placebo N=7067	Total N=21162
Weight (kg)				
Mean (SD)	82.0 (16.7)	82.0 (17.0)	81.8 (16.6)	82.0 (16.8)
BMI (kg/m^2)				
Mean (SD)	28.5 (4.9)	28.5 (4.9)	28.4 (4.9)	28.5 (4.9)
Smoking History (%)				
Never	2455 (34.8)	2423 (34.4)	2528 (35.8)	7406 (35.0)
Former	3405 (48.3)	3415 (48.5)	3391 (48.0)	10211 (48.3)
Current	1187 (16.8)	1206 (17.1)	1143 (16.2)	3536 (16.7)
Time from qualifying MI (months)				
Mean (SD)	21.8 (7.6)	21.8 (7.6)	21.8 (7.6)	21.8 (7.6)
< 1year (%)	40 (0.6)	54 (0.8)	47 (0.7)	141 (0.7)
1-3 years (%)	6958 (98.9)	6944 (98.7)	6969 (98.8)	20871 (98.8)
>3 years (%)	41 (0.6)	35 (0.5)	41 (0.6)	117 (0.6)
Time from last ADP blocker				
Ongoing (%)	4 (0.1)	6 (0.1)	10 (0.1)	20 (0.1)
After first dose of study drug (%)	14 (0.2)	23 (0.3)	12 (0.2)	49 (0.2)
0-7 days (%)	1826 (25.9)	1816 (25.8)	1828 (25.9)	5470 (25.8)
8-90 days (%)	1243 (17.6)	1257 (17.8)	1243 (17.6)	3743 (17.7)
3-12 months (%)	1498 (21.2)	1520 (21.6)	1540 (21.8)	4558 (21.5)
>12 months (%)	1676 (23.8)	1661 (23.6)	1645 (23.3)	4982 (23.5)
Unknown (%)	10 (0.1)	6 (0.1)	7 (0.1)	23 (0.1)

[Source: Reviewer's results]

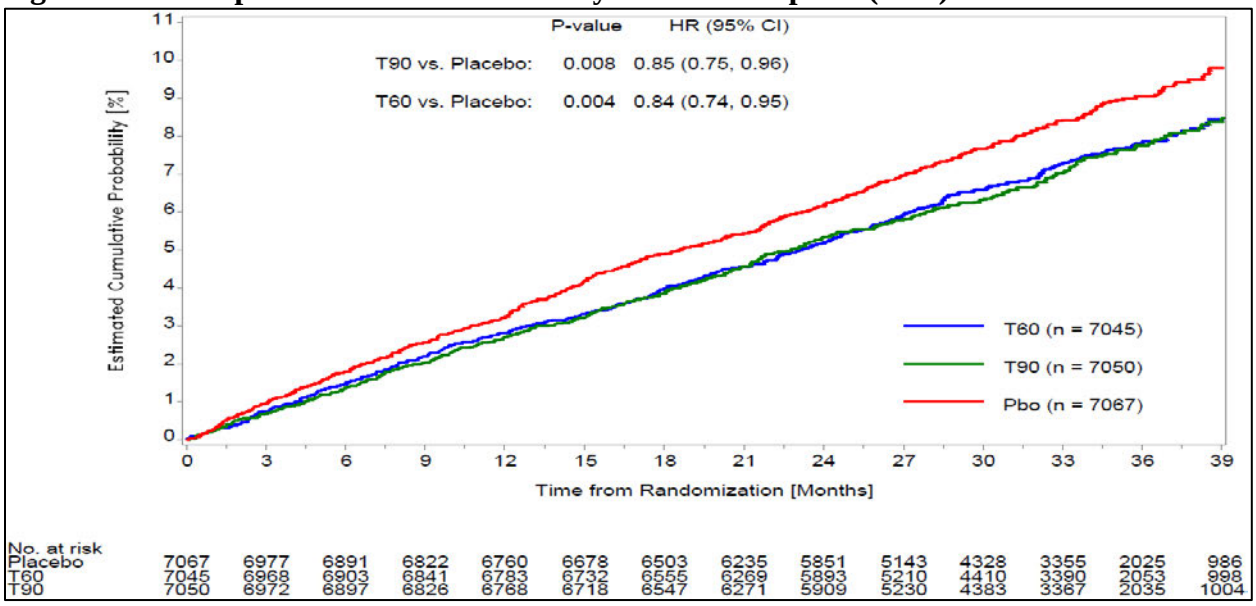
3.2.5 RESULTS AND EXPLORATORY ANALYSES

Primary and Secondary Efficacy Results

Primary composite endpoint events on or prior to CSED were reported for 493, 487 and 578 patients on ticagrelor 90 mg, ticagrelor 60 mg, and placebo, respectively. The Hazard Ratio of 0.85 and a 95% CI of (0.75, 0.96) was observed for ticagrelor 90 mg versus placebo. The Hazard Ratio 0.84 and a 95% CI of (0.74, 0.95) was observed for ticagrelor 60 mg versus placebo. The superior treatment effect of ticagrelor compared with placebo was consistent throughout the study as evident from the Kaplan-Meier plot (Figure 3-2).

However, statistical significance was not demonstrated for the first secondary endpoint of CV death in neither dose (Table 3-4). Therefore, hierarchical testing was stopped and the next secondary endpoint of all-cause mortality was not tested for statistical significance.

Figure 3-2 Kaplan-Meier Plot of Primary Clinical Endpoint (FAS)



[Source: Reviewer's Results]

There was a numerical decrease in CV death for both ticagrelor 90 mg (HR 0.87 [95% CI 0.71, 1.06], p=0.155) and ticagrelor 60 mg (HR 0.83 [95% CI 0.68, 1.01], p=0.068) compared with placebo. The rate of all-cause mortality was same for ticagrelor 90 mg and placebo with HR of 1.00, whereas ticagrelor 60 mg showed a numerical reduction in the rate of all-cause mortality with HR of 0.89.

Table 3-4 Summary and Results of primary and secondary endpoints (FAS)

Endpoints	Placebo (N=7067)	Ticagrelor 90mg (N=7050)			Ticagrelor 60mg (N=7045)		
	# Events (%)	# Events (%)	HR (95% CI)	p-value	# Events (%)	HR (95% CI)	p-value
Composite of CVD/MI/Stroke	578 (8.2%)	493 (7.0%)	0.85 (0.75, 0.96)	0.008	487 (6.9%)	0.84 (0.74, 0.95)	0.004
CV Death	210 (3.0%)	182 (2.6%)	0.87 (0.71, 1.06)	0.155	174 (2.5%)	0.83 (0.68, 1.01)	0.068
All-Cause Mortality	326 (4.6%)	326 (4.6%)	1.00 (0.86, 1.16)	0.985	289 (4.1%)	0.89 (0.76, 1.04)	0.135

[Source: Reviewer's Results]

Analyses on Components of Primary Composite Endpoint

The numerical superior treatment effects of both ticagrelor doses compared with placebo were similarly favorable for each of the components of the primary composite endpoint (Table 3-5). All 3 components competed with each other since the occurrence of one prevented the observation of the others. Many CV deaths were not first occurring component of the primary composite endpoint, which almost nullified all the treatment effects on CV deaths in both ticagrelor doses (Table 3-5).

Table 3-5 Analyses on the components of PCE (FAS)

Endpoints	Placebo (N=7067)	Ticagrelor 90mg (N=7050)		Ticagrelor 60mg (N=7045)	
	# Events	# Events	HR (95% CI)	# Events	HR (95% CI)
Composites of PCE	578 (8.2%)	493 (7.0%)	0.85 (0.75, 0.96)	487 (6.9%)	0.84 (0.74, 0.95)
Decomposition of the first composite endpoint event					
CVD	128 (1.8%)	127 (1.8%)		116 (1.6%)	
MI	336 (4.8%)	272 (3.9%)		283 (4.0%)	
Stroke	114 (1.6%)	94 (1.3%)		88 (1.2%)	
Time to First occurrence of each component event					
CVD	210 (3.0%)	182 (2.6%)	0.87 (0.71, 1.06)	174 (2.5%)	0.83 (0.68, 1.01)
MI	338 (4.8%)	275 (3.9%)	0.81 (0.69, 0.95)	285 (4.0%)	0.84 (0.72, 0.98)
Stroke	122 (1.7%)	100 (1.4%)	0.82 (0.63, 1.07)	91 (1.3%)	0.75 (0.57, 0.98)

[Source: Reviewer's Results]

Interim Analysis

As per the IDMC Charter, the first formal interim analysis for potential early termination for overwhelming efficacy is planned after 50% of the targeted number of primary endpoint events (680 of 1360) have occurred, with additional analyses at the discretion of the IDMC. The following is the results of the first formal interim efficacy analysis based on adjudicated events only. It includes data on 332 adjudicated all-cause mortality events and 721 adjudicated primary events based on data transferred to Statistical Data Analysis Center on July 1, 2013 with a data cut-off date of June 27, 2013. The results in Table 3-6 did not meet the suggested criteria to recommend stopping the trial for overwhelming efficacy.

Table 3-6 First Formal Interim Analysis Results on ACM and PCE

	Events			P-value		Hazard Ratio		
All-Cause Mortality Comparison	Total	A	B/C	Observed	Critical for Efficac	Observed	Critical for Futility	Result
A vs. B	229/14113	126/7068	103/7045	0.063	≤ 0.001	0.816	≥ 0.920	P-value not signif cant
A vs. C	229/14117	126/7068	103/7049	0.060	≤ 0.001	0.814	≥ 0.920	P-value not signif cant

	Events			P-value		Hazard Ratio		
Primary Endpoint Comparison	Total	A	B/C	Observed	Critical for Efficac	Observed	Critical for Futility	Result
A vs. B	505/14113	276/7068	229/7045	0.016	≤ 0.001	0.826	≥ 0.920	P-value not signif cant
A vs. C	492/14117	276/7068	216/7049	0.003	≤ 0.001	0.778	≥ 0.920	P-value not signif cant

[Source: Sponsor's Response to FDA Information Request on 4/25/2015]

Exploratory analysis with both ticagrelor doses combined versus placebo

Results of the exploratory analysis of the primary and secondary endpoints with both ticagrelor doses combined, versus placebo, are summarized in Table 3-7.

Table 3-7 Analysis of primary and secondary endpoints with ticagrelor doses combined

Endpoints	Placebo (N=7067)	Ticagrelor (N=14095)		
	# Events	# Events	HR	95% CI
Composites of PCE	578 (8.2%)	980 (7.0%)	0.84	(0.76, 0.94)
All-cause Mortality	326 (4.6%)	615 (4.4%)	0.94	(0.82, 1.08)
Decomposition of the first composite endpoint event				
CVD	128 (1.8%)	243 (1.7%)		
MI	336 (4.8%)	555 (3.9%)		
Stroke	114 (1.6%)	182 (1.3%)		
Time to First occurrence of each component event				
CVD	210 (3.0%)	356 (2.5%)	0.85	(0.71, 1.00)
MI	338 (4.8%)	560 (4.0%)	0.83	(0.72, 0.95)
Stroke	122 (1.7%)	191 (1.4%)	0.78	(0.62, 0.98)

[Source: Reviewer's Results]

3.3 Evaluation of Safety

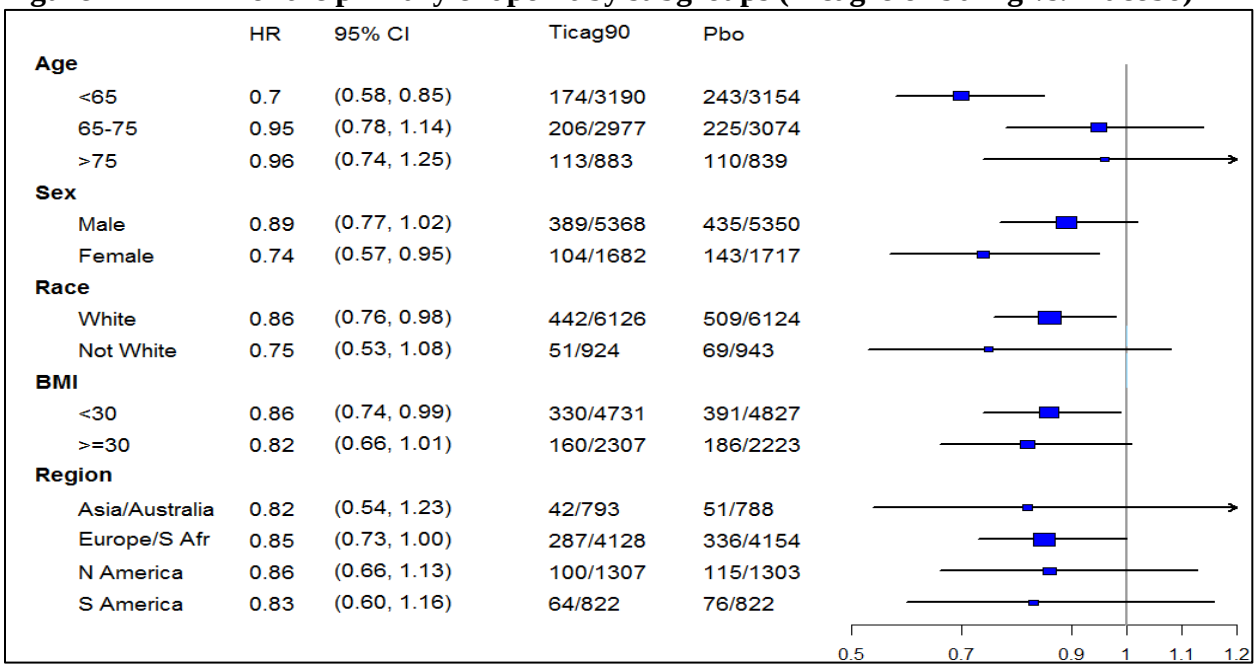
Safety is not evaluated in this review. Please see the clinical review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Age, Gender, and Race group

A wide range of pre-specified subgroup analyses (see Figure 4-1 and Figure 4-2) were conducted to examine the influence of patient characteristics on the primary endpoint. These characteristics are age groups, gender, race (Whites versus Non Whites), BMI, and geographical regions.

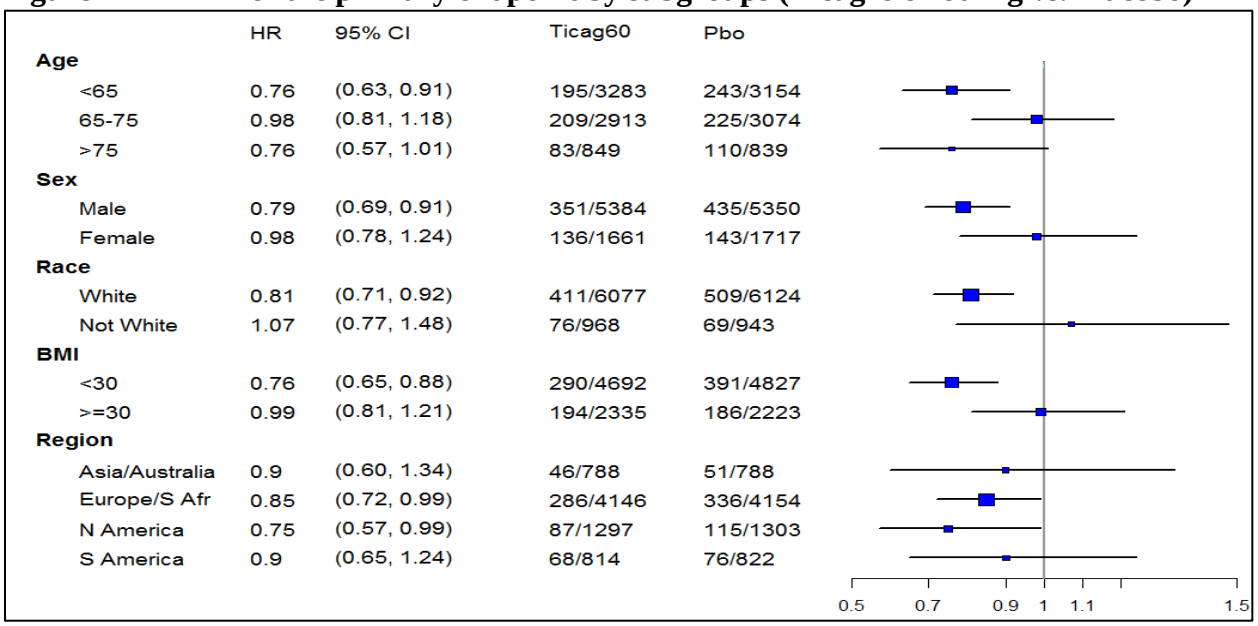
Figure 4-1 HR of the primary endpoint by subgroups (Ticagrelor 90 mg vs. Placebo)



[Source: reviewer's Results]

The treatment effect seems consistent across most pre-defined patient subgroups when comparing Ticagrelor 90 mg with placebo.

Figure 4-2 HR of the primary endpoint by subgroups (Ticagrelor 60 mg vs. Placebo)



[Source: reviewer's Results]

On the other hand, the treatment effects of ticagrelor 60 mg over placebo were not seen in some patient subgroups, such as patients who are in between 65 and 75 years of age, Female subjects, and patients' baseline BMI over 30 kg/m^2.

4.2 Other Subgroup Populations

This section explored subgroup analyses by patients' background concomitant antithrombotic medication and qualifying risk factors.

Figure 4-3 Subgroup by Time since last ADP blocker (90mg)

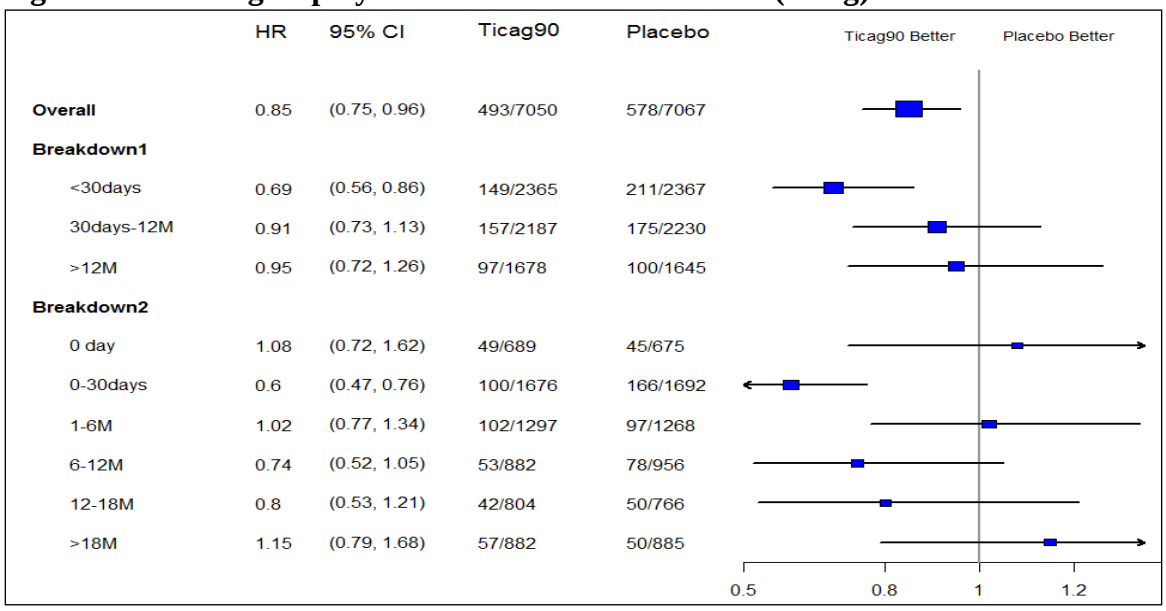
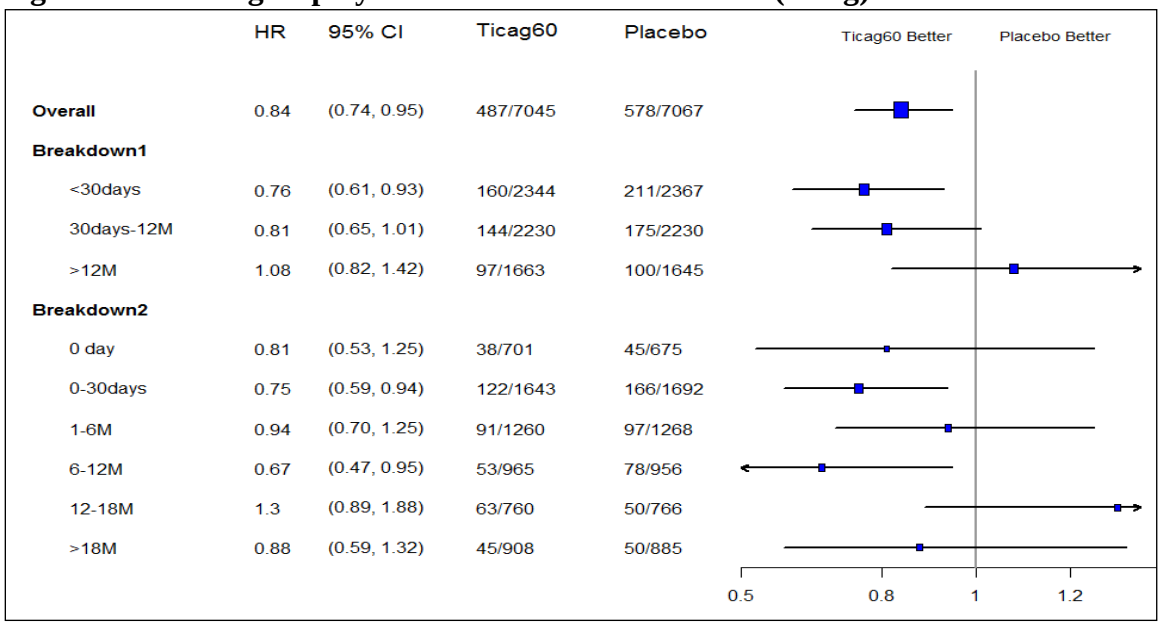


Figure 4-4 Subgroup by Time since last ADP blocker (60mg)



[Source: Reviewer's Results]

Most of the patients had received previous treatment with an ADP receptor blocker. There were about one third of patients in each of following subgroups:

- whom had previous ADP receptor blocker less than 30 days to randomization

- whom had previous ADP receptor blocker between 1 and 12 months to randomization
- whom had previous ADP receptor blocker more than 12 months to randomization

The observed effect of ticagrelor did appear less pronounced in patients with longer (>12 months) time from last dose of ADP receptor blocker to randomization. However, if we break this time variable into much finer subgroups, then it described fairly random treatment effects of ticagrelor (see Figure 4-3 and Figure 4-4).

Figure 4-5 Subgroup by Time from qualifyng MI to randomization (90mg)

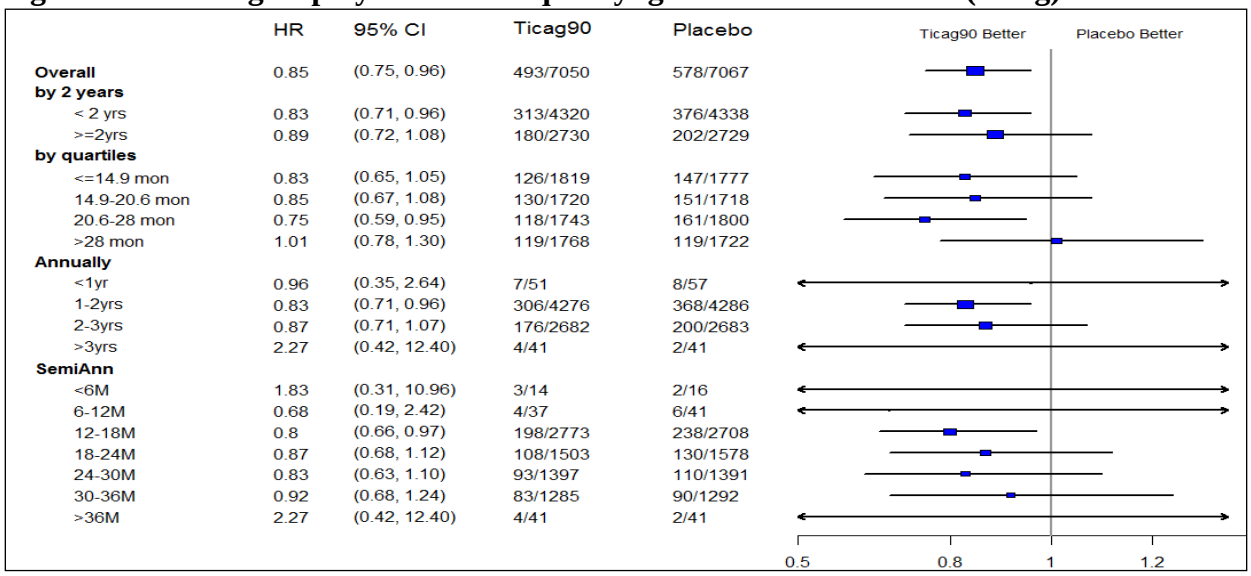
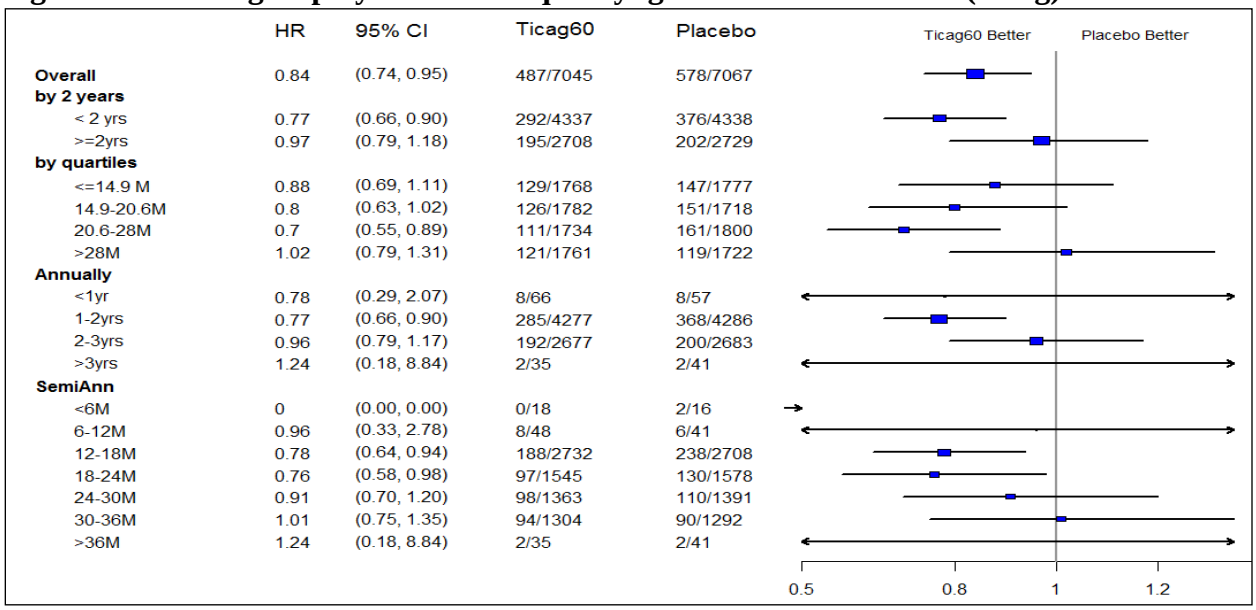


Figure 4-6 Subgroup by Time from qualifyng MI to randomization (60mg)



[Source: Reviewer's Results]

The Sponsor dichotomized patients' time from qualifying MI to randomization into less than or greater than 2 years. It appeared that the ticagrelor 60 mg was less effective in patients with more than 2 years since their last qualifying MI. Both patient subgroups seemed fairly consistent with the overall result when comparing ticagrelor 90 mg with placebo group (see Figure 4-5 and Figure 4-6). These figures also sectioned the time from qualifying MI to randomization into by quartiles, annually and every six months. Both doses appeared to have little effect in patients who had their qualifying MI more than 28 months before the randomization.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

There are no statistical issues when reviewing the design, conduct, and results of PEGASUS.

Primary composite endpoint events prior to the CSED were reported for 493, 487, and 578 patients on ticagrelor 90 mg, 60 mg, and placebo, respectively. The Hazard Ratio of 0.85 and a 95% CI of (0.75, 0.96) was observed for ticagrelor 90 mg versus placebo. The Hazard Ratio 0.84 and a 95% CI of (0.74, 0.95) was observed for ticagrelor 60 mg versus placebo. Each component contributed to the reduction in the primary composite endpoint. The treatment effect in the primary endpoint was consistent across pre-defined patient subgroups, based on demographic and important baseline characteristics.

The benefit of ticagrelor was consistent for the secondary endpoint of CV death, with a numerical decrease for both 90 mg and 60 mg versus placebo observed although this did not reach statistical significance for either dose. The observed Hazard Ratios are 0.87 and 0.83, respectively. Since no difference versus placebo for CV death could be claimed for either of the doses in the hierarchical testing procedure, the testing procedure stopped. For all-cause mortality, there was no difference versus placebo for ticagrelor 90 mg (HR=1.00); however, for 60 mg, the result was numerically in favor of ticagrelor (HR=0.89).

5.2 Conclusions and Recommendations

PEGASUS demonstrated the long-term treatment with ticagrelor 90 mg bd or 60 mg bd given in combination with ASA showed clear benefits over placebo for both doses of ticagrelor in patients with a history of myocardial infarction (MI) and at high risk of an atherothrombotic event.

The primary efficacy objective was met, showing a clinically relevant and statistically significant benefit on the composite primary endpoint (CV death, MI, and stroke) that was consistent for both ticagrelor doses. The clinical relevance of the results is further supported by the consistent findings over time. The benefit of ticagrelor was numerically consistent for the CV death for both doses versus placebo. For all-cause mortality, there was no difference between ticagrelor 90mg and placebo whereas the result was numerically in favor of ticagrelor 60 mg. The numerically favorable treatment effects for both ticagrelor doses in the composite primary endpoint were seen across the most of patient subgroups.

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/s/

STEVE G BAI
07/02/2015

HSIEN MING J HUNG
07/02/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-433/S015

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA Number:	22433 – S015
Submission Type:	Efficacy Supplement
Submission Date:	3/06/2015
Review Classification:	Priority
PDUFA goal date:	9/06/2015
Drug Name:	ticagrelor
Trade Name:	BRILINTA®
Drug Class:	Platelet $P2Y_{12}$ receptor antagonist
Proposed Indication:	[redacted] (b) (4)
Proposed dose:	60 mg twice daily
Applicant:	AstraZeneca Pharmaceuticals
OCP Division:	DCP1
OND Division:	Division of Cardiovascular and Renal Products (DCRP)
Reviewer:	Sreedharan Sabarinath, PhD
Team Leaders:	Jeffry Florian, PhD
	Rajanikanth Madabushi, PhD

Table of Contents

Reference ID: 3795573

1. EXECUTIVE SUMMARY

Ticagrelor is an oral P2Y12 antiplatelet drug, approved for reducing the rate of thrombotic cardiovascular (CV) events in patients with acute coronary syndrome (ACS). The approval was based on the PLATO study that compared 90 mg twice daily ticagrelor with 75 mg once daily clopidogrel for up to 12 months, in ACS patients taking aspirin.

The current application seeks to extend this indication to patients with a history of myocardial infarction (b) (4) The proposed indication is supported by a single pivotal Phase 3 study, PEGASUS, which evaluated whether long term dual antiplatelet therapy with ticagrelor 90 mg or 60 mg twice daily in combination with low dose aspirin once daily was superior compared with low dose aspirin (75-150 mg). The primary endpoint of the study was a reduction in the event rate of the composite CV death, nonfatal myocardial infarction, or non-fatal stroke in patients with history of myocardial infarction and high risk of developing thrombotic events. The PEGASUS study randomized 21,162 patients at 1164 sites in 31 countries. Relative risk reduction for the primary composite endpoint (cardiovascular death, MI and stroke) was about 15-16 % for both 60 and 90 mg dose groups of ticagrelor ($p<0.01$). The TIMI major bleeding events were 127, 115 and 54 on ticagrelor 90 mg, 60 mg and placebo, respectively. The applicant is seeking approval for only the 60 mg dose based on the similar efficacy and lower TIMI major bleeding results compared to the 90 mg dose.

The current submission relies on the clinical pharmacology information that supported the approval of ticagrelor for the ACS indication. The proposed draft label incorporates information from the PEGASUS study and there are no changes to Section 7 Drug Interactions or Section 12 Clinical Pharmacology.

1.1 Recommendations

The efficacy supplement for ticagrelor (NDA 22433-S015) is acceptable and can be approved from a clinical pharmacology perspective.

1.2 Phase 4 Commitments

None.

1.3 Summary of OCP Findings

- No clinical pharmacology issues affecting approval[1]
- PK observations from PEGASUS Phase 3 study (~30 % higher exposure in females relative to males) cannot explain the subgroup findings in females administered 60 mg twice daily. For males in both active treatment arms and for women on the 90 mg treatment arm, there was a finding of improved efficacy relative to the control arm. However, a finding of comparable efficacy in females (HR: 0.98 [95 % CI 0.78-1.24]) was observed between the 60 mg treatment arm relative to control. Further evaluation suggests that this finding is not exposure related as consistent trends in efficacy and safety were not identified between doses and male/female subgroups.
- No changes to Section 7 and 12 of the approved label

2. ABBREVIATED QUESTION BASED REVIEW

Ticagrelor is an oral, reversible, platelet P2Y12 receptor antagonist, approved in the US in 2011 for the prevention of atherosclerotic events in patients with acute coronary syndrome (ACS). The approved dose of ticagrelor in ACS is 90 mg twice daily (BID) with a 180 mg loading dose.

The applicant is currently seeking approval for 60 mg BID dose of ticagrelor, with no loading dose, for the prevention of thrombotic events in patients with a history of myocardial infraction (MI) (b) (4) The submission relies on a single pivotal efficacy study called PEGASUS.

Detailed information on the clinical pharmacology of ticagrelor is available in the original submission reviews for NDA 22433[2]. This is an abbreviated QBR addressing review questions relevant to this efficacy supplement.

2.1 What are the characteristics of the PEGASUS Phase 3 study?

PEGASUS was a randomized, double-blind, placebo-controlled, 3-arm parallel group, multi-national, event-driven trial to assess the prevention of cardiovascular events following dual antiplatelet therapy with ticagrelor (90 mg or 60 mg BID) compared to placebo on a background

[1] The current submission did not provide any new clinical pharmacology information. Please refer to approved label for BRILINTA®, approval package for NDA22433 or clinical pharmacology reviews in DARRTS (6/27/2010 & 8/29/2010) for detailed information.

[2] NDA 22433 Clinical Pharmacology Reviews, DARRTS dated 6/27/2010 and 8/29/2010

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of low dose aspirin (75-150 mg daily) in patients with a history of MI (1 to 3 years prior to randomization) and at high risk of an atherosclerotic event. A schematic of the study design features are shown in Figure 1.

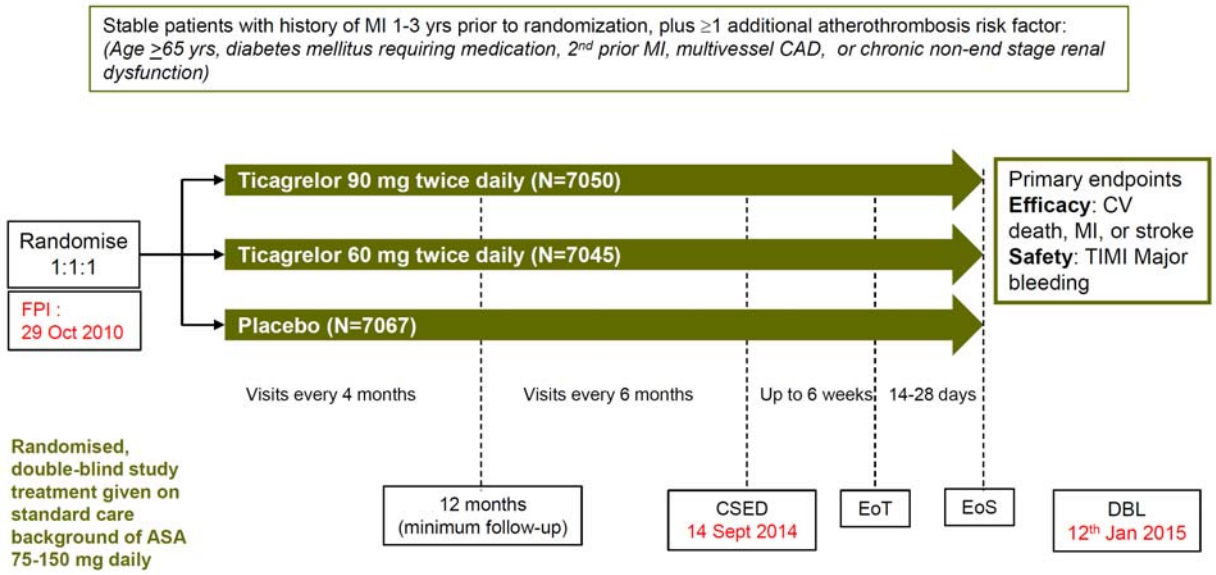

Figure 1. PEGASUS Phase 3 study design. PK samples were collected from ~ 4690 patients at months 4, 8 and 12. CSED: common study end date, EoT: End of treatment visit, EoS: End of study visit. Source: Adapted from Clinical Study Report D5132C00001, Page 25, Figure 1.

The primary efficacy endpoint was a composite of CV death, myocardial infarction (MI) and stroke. Safety analyses included assessment of bleeding by TIMI, GUSTO, ISTH and PLATO bleeding definitions. A total of 21162 patients were randomized and 99.3 % completed the study.

2.2 How was ticagrelor dose/dosing regimen selected for PEGASUS study?

PEGASUS study included two dose levels of ticagrelor, 90 mg and 60 mg given BID. The approved dose for ticagrelor for reducing the rate of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) is 90 mg BID[3]. In PLATO study in ACS patients ticagrelor 90 mg BID reduced major CV events by about 16 % compared to clopidogrel while the major bleeding events were similar to clopidogrel. Since the risk-benefit balance for ticagrelor 90 mg BID was favorable in ACS patients, the same dose was considered appropriate to be

[3] BRILINTA® USPI: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/022433s013lbl.pdf

tested in stable patients with coronary artery disease (CAD), 1 to 3 years following their most recent MI.

The risk for recurrent thrombotic events following an MI persists over time but is considered higher in the first year post MI. The necessary extent of platelet inhibition that is needed in this population is not known, and during the development, the Agency recommended studying another dose[4]. The applicant chose a lower intensity of platelet inhibition than that utilized in the ACS setting to be studied in the PEGASUS study as a second dose level (60 mg BID). The 60 mg dose of ticagrelor showed lesser degree of inhibition in platelet aggregation (IPA) relative to the 90 mg dose, but IPA with 60 mg ticagrelor was higher than that with clopidogrel 75 mg. It should be noted that considerable overlap in systemic exposures from these doses are expected because the two doses are separated by only 50 %.

The study was placebo controlled because current medical guidelines do not recommend continuing dual antiplatelet therapy beyond 12 months after an MI event. Note that all patients received low dose aspirin as standard of care and the study did not include patients who are eligible for currently approved clinical indication for dual antiplatelet therapy at the time of enrollment. Those patients who developed an indication for use of ADP receptor blocker according to medical guidelines (e.g. ACS or PCI) were switched to either clopidogrel in place of placebo or ticagrelor 90 mg in place of ticagrelor 60 mg.

2.3 Is there a dose-response relationship for efficacy or safety?

Dose-response was not evident for the primary efficacy endpoint in PEGASUS between 60 mg and 90 mg dose groups. Ticagrelor showed superiority to placebo in reducing the event rate of the primary composite endpoint: 15 % relative risk reduction (RRR), HR 0.85 (95% CI 0.75, 0.96), p=0.008 for ticagrelor 90 mg, and 16 % RRR, HR 0.84 (95 % CI 0.74, 0.95), p=0.004 for ticagrelor 60 mg (Figure 2). The lack of separation between the two ticagrelor treatment arms could be because of the considerable overlap in systemic exposures from the two dose levels tested.

[4] IND 65808 ticagrelor, Meeting Minutes, DARRTS dated 7/19/2010

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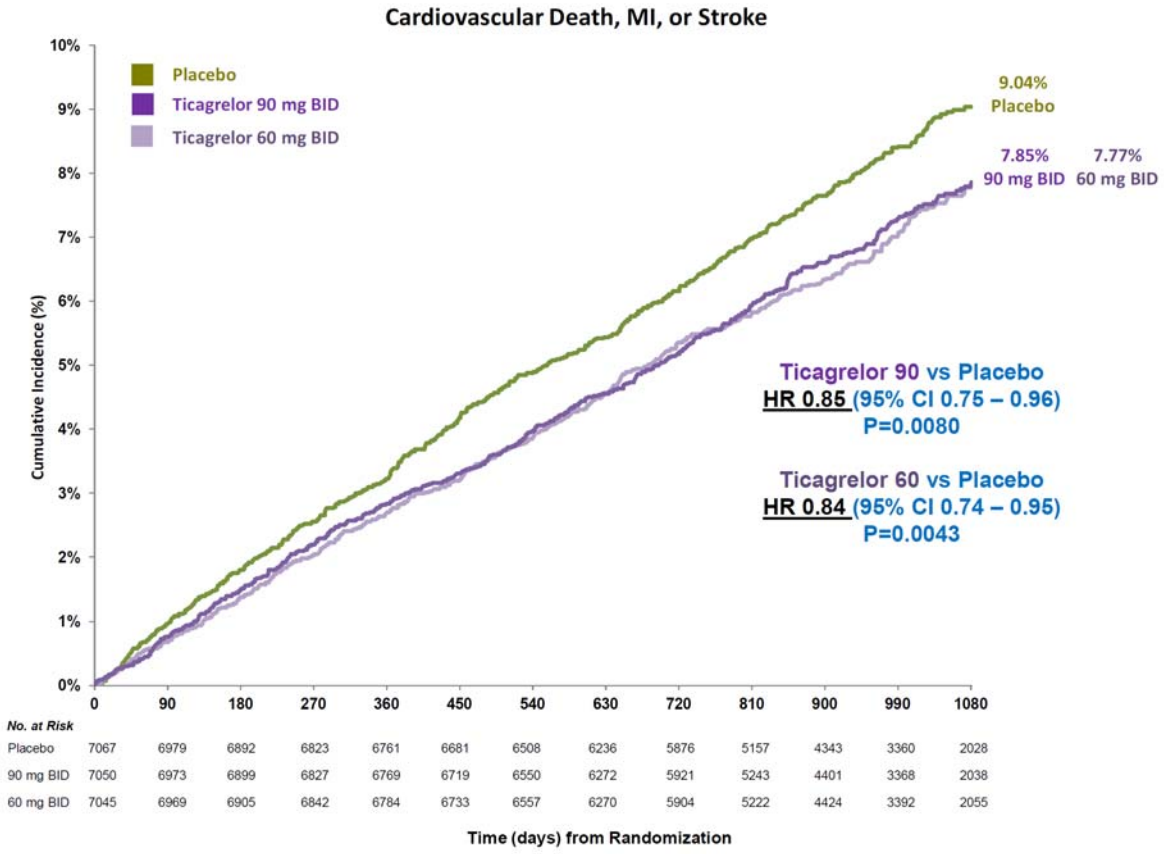

Figure 2. Kaplan-Meier plot of primary efficacy endpoint (full analysis set). Both 90 mg and 60 mg BID dose levels showed a relative risk reduction of 15-16 %. Source: Adapted from PEGASUS Clinical Study Report D5132C00001.

The hazard ratio for TIMI major bleeding[5] for ticagrelor 90 mg and ticagrelor 60 mg was 2.69 and 2.32 respectively (Figure 3). This suggests that risk for bleeding increases with dose for ticagrelor.

The lack of a dose dependent relationship to the primary efficacy endpoint and a dose dependent increase in TIMI major bleeding risk begs the question of whether a lower dose of ticagrelor could achieve similar efficacy while further lowering the bleeding risk in this patient population.

[5]TIMI major bleeding is defined as any of the following: Fatal bleeding - a bleeding event that led to death within 7 days, Intracranial hemorrhage, Clinically overt signs of hemorrhage associated with a drop in hemoglobin ≥5 g/dL or a fall in hemocrit ≥ 15 % when hemoglobin data is not available.

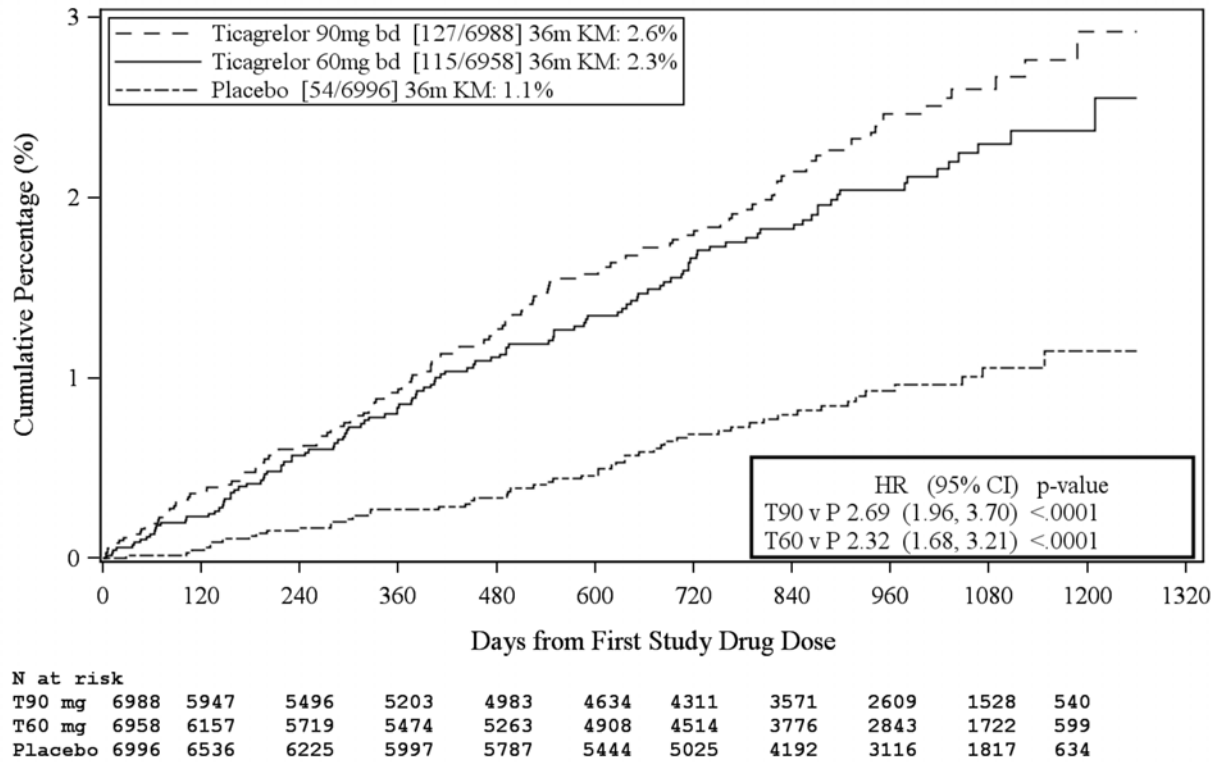

Figure 3. Kaplan-Meier plot of cumulative percentage of patients with TIMI major bleeding (safety set). The 90 mg BID dose group showed a numerically higher TIMI major bleeding rates than the 60 mg dose group. Source: Figure 16, PEGASUS Clinical Study Report D5132C00001.

PK samples were collected from ~ 4690 patients on months 4, 8 and 12 in PEGASUS study. An exploratory analysis[6] conducted by the applicant was in agreement with the efficacy and safety results between the two dose groups described above and no further analysis was conducted by the clinical pharmacology review team.

2.4 Can exposure difference explain subgroup findings for efficacy in females?

The applicant conducted several pre-specified subgroup analyses for the primary efficacy endpoint and bleeding events. The results were consistent with the overall study results in most cases. A snap-shot of subgroup findings for efficacy and safety for male and female patients are shown below (Figure 4).

[6] Population PK analysis report PEGASUS – TIMI-54 study

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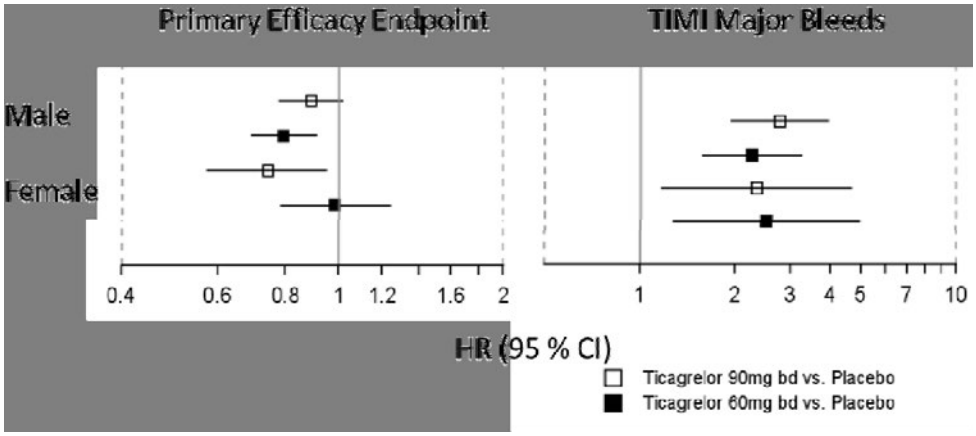

Figure 4. Hazard ratios and 95 % CI of the primary efficacy endpoint (full analysis set) and TIMI Major bleeding (safety set) for male and female patients by dose group. Source: Adapted from PEGASUS Clinical Study Report D5132C00001.

The 60 mg dose of ticagrelor showed a hazard ratio of 0.98 (95 % CI 0.78-1.24) while other subgroups showed clinical benefit consistent with overall study results. Since the applicant is seeking approval only for the 60 mg dose, which was similar to placebo in female subjects in this subgroup analysis, the review team evaluated the potential reasons for this finding.

A comparison of the demographic characteristics, including some CV risk factors for these subgroups, showed that these subsets did not have any noticeable difference in their composition (Table 1).

Table 1. Patient characteristics in PEGASUS study

Characteristics/Dose Group	**Females 60 mg BID (N=1639)**	**Females 90 mg BID (N=1664)**	**Males 60 mg BID (N=5321)**	**Males 90 mg BID (N=5326)**
Age in years (SD)	67.9 (8.4)	68.0 (8.2)	64.3 (8.2)	64.5 (8.3)
BW in Kg (SD)	73.1 (16.4)	73.4 (16.5)	84.7 (16.6)	84.5 (17.1)
BMI in Kg/m^2 (SD)	28.9 (5.8)	28.8 (7.9)	28.2 (7.0)	28.1 (6.7)
Asians (%)	8.6	8.3	11.6	11.2
Current Smokers (%)	13.2	12.8	18.3	18.2
Former Smokers (%)	27.2	29.2	55.0	54.3
Never Smoked (%)	59.5	57.9	26.7	27.5

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Hypertension (%)	84.2	85.8	75.4	74.9
History of MI* (%)	15.3	14.6	16.9	16.7
Diabetes (%)	37.0	37.3	31.5	30.0
PAD (%)	5.6	4.7	5.1	5.4
Unstable angina (%)	36.6	35.3	30.2	29.2
STEMI (%)	48.4	47.4	54.9	55.3

*Previous MI before the qualifying event, F-Females, M-Males, Source: E-R dataset, Prepared by FDA.

A comparison of the observed average steady state exposures between the subsets are shown in Figure 5.

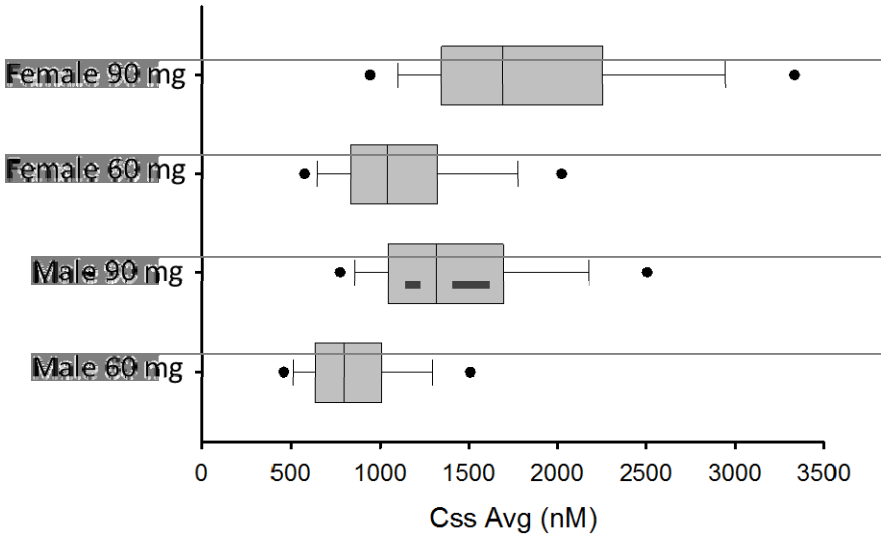

Figure 5. Boxplot of the observed average steady-state concentrations of ticagrelor and its active metabolite (sum) from the PK subset in PEGASUS. Source: Prepared by FDA.

The average age and body weight of the subsets were also similar, just as in the case of overall population, and are presented in Table 2.

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Table 2. Average age, body weight and observed steady state concentrations in male and female patients from PEGASUS PK subset

Characteristics/Dose Group	Males		Females	
	60 mg	90 mg	60 mg	90 mg
Median C_{ss} (nM)	796	1314	1040	1688
Mean Body Weight (kg)	87	86	76	75
Mean Age (years)	64	64	67	67

Source: Prepared by FDA, PEGASUS study PK subset

It is evident from Figure 5 that female subjects had relatively higher average plasma concentrations of ticagrelor and its active metabolite in both 60 mg and 90 mg dose groups compared to male subjects receiving corresponding doses. This is in agreement with the impact of gender described in BRILINTA® USPI[7]. If exposure is a contributing factor to the observed response in females on 60 mg BID, the expectation will be a decrease in efficacy in males receiving 60 mg BID. However, efficacy findings in males suggest greater efficacy for 60 mg BID compared to 90 mg BID. Furthermore, there is no complimentary finding of decreased bleeding risk in women administered 60 mg BID to suggest such patients were receiving insufficient ticagrelor exposures. Therefore, based on contradictory findings between ticagrelor doses and male/female subgroups, we conclude that the observed differences in efficacy in the pre-specified subgroup analysis cannot be explained based on patient characteristics or systemic exposure to ticagrelor and its active metabolite. The subgroup analysis results are most likely a chance finding, especially given the relatively smaller number of female subjects enrolled in the study.

2.5 Pharmacodynamic study in self-identified Hispanic patients

Since majority of the clinical pharmacology studies in the ticagrelor ACS program were conducted in Caucasian population, with very few Hispanic patients enrolled, the applicant conducted a pharmacodynamic (PD) study (D5130L00012) in self-identified Hispanic patients with stable CAD (N=40). This was a randomized, open label, cross-over study and all patients received low dose aspirin. The two treatments were ticagrelor (180 mg loading dose + 90 mg BID for 7-9 days) and clopidogrel (60 mg loading dose + 75 mg QD for 7-9 days) with 10-14 days washout period between the two treatments. The primary objective was to assess the on-treatment platelet reactivity of ticagrelor relative to clopidogrel in Hispanics, using VerifyNow® P2Y12 assay. The mean platelet reactivity units (PRU) at 2 hours after loading dose was lower

[7] BRILINTA® USPI: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/022433s013lbl.pdf

Reference ID: 3795573

for ticagrelor (34.1) compared to clopidogrel (201.3). Similarly, patients who received ticagrelor showed larger reduction from baseline in PRU activity than with clopidogrel (86 % vs 29 %). On treatment PRU values with ticagrelor was consistently lower than that with clopidogrel at all other time points. These observations are in agreement with the established PD characteristics of both ticagrelor and clopidogrel.

2.6 How was the clinical trial formulation bridged to the to-be-marketed formulation?

The PEGASUS study evaluated ticagrelor 90 mg (the currently marketed formulation) and 60 mg (a clinical trial formulation) tablets. The applicant is seeking approval only for the 60 mg tablet strength for the proposed indication. The applicant states that to-be-marketed 60 mg tablet has identical tablet core as in the clinical trial formulation but there are minor changes to debossing and non-functional coating composition. ONDQA-Biopharmaceutics is reviewing the in vitro dissolution data related to the 60 mg to-be-marked tablet formulation.

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/s/

SREEDHARAN N SABARINATH
07/21/2015

JEFFRY FLORIAN
07/21/2015

RAJANIKANTH MADABUSHI
07/22/2015

CLINICAL PHARMACOLOGY FILING FORM

Application Information

NDA Number	22433	**Supplement**	15
Applicant	AstraZeneca Pharmaceuticals	**Submission Date**	3/06/2015
Generic Name	Ticagrelor	**Brand Name**	BRILINTA®
Drug Class	Platelet $P2Y_{12}$ antagonist		
Indication	(b) (4)		
Dosage Regimen	60 mg twice daily		
Dosage Form	Tablet	**Route of Administration**	Oral
OCP Division	DCP1	**OND Division**	DCRP

OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**
Division	Sreedharan Sabarinath	Rajanikanth Madabushi
Pharmacometrics	-	Jeffry Florian
Genomics	-	-

Review Classification	☐ Standard ☑ Priority ☐ Expedited		
Filing Date	5/5/2015	**74-Day Letter Date**	5/19/2015
Review Due Date	7/6/2015	**PDUFA Goal Date**	9/6/2015

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes

☐ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☐ Yes

☑ No

If yes list comment(s)

Is there a need for clinical trial(s) inspection?

☐ Yes

☑ No

If yes explain

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No
Bioanalytical and Analytical Methods	☑ Yes ☐ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies

Study Type	**Count**	**Comment(s)**
In Vitro Studies		
☐ Metabolism Characterization		
☐ Transporter Characterization		
☐ Distribution		
☐ Drug-Drug Interaction		

In Vivo Studies			
Biopharmaceutics			
☐ Absolute Bioavailability			
☐ Relative Bioavailability			
☐ Bioequivalence			
☐ Food Effect			
☐ Other			
Human Pharmacokinetics			
Healthy Subjects	☐ Single Dose		
	☐ Multiple Dose		
Patients	☐ Single Dose		
	☐ Multiple Dose		
☐ Mass Balance Study			
☐ Other (e.g. dose proportionality)			
Intrinsic Factors			
☐ Race			
☐ Sex			
☐ Geriatrics			
☐ Pediatrics			
☐ Hepatic Impairment			
☐ Renal Impairment			
☐ Genetics			
Extrinsic Factors			
☐ Effects on Primary Drug			
☐ Effects of Primary Drug			
Pharmacodynamics			
☐ Healthy Subjects			
☑ Patients	1	Study D513L00012. Patients with coronary artery disease. Platelet inhibition in Hispanic subjects, ticagrelor 180/90 mg vs clopidogrel 600/75 mg for 7-9 days.	
Pharmacokinetics/Pharmacodynamics			
☐ Healthy Subjects			
☐ Patients			
☐ QT			
Pharmacometrics			
☑ Population Pharmacokinetics	1	Pop-PK analysis report for P3 study	
☑ Exposure-Efficacy	1	Report with E-R analyses for efficacy and safety from P3 study	
☑ Exposure-Safety	1		

Total Number of Studies	**In Vitro**	0	**In Vivo**	2
Total Number of Studies to be Reviewed		0		2

Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☐Yes ☐No ☑N/A	(b) (4) [redacted]
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☐Yes ☐No ☑N/A	This is an efficacy supplement and relies on clinical pharmacology information from approved submission for ACS indication.
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☐Yes ☐No ☑N/A	See comment to Q2.
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☐Yes ☐No ☑N/A	
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☑Yes ☐No ☐N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☑Yes ☐No ☐N/A	P3 study tested two doses for ticagrelor: 90 mg BID (approved dose in ACS) and 60 mg BID (as a lower dose level).
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☐Yes ☐No ☑N/A	See comments to Q2.
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☐N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have	☑Yes ☐No ☐N/A	

appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?		
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	☑Yes ☐No ☐N/A	
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☑Yes ☐No ☐N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐Yes ☐No ☑N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☐Yes ☐No ☑N/A	This is an efficacy supplement and relies on clinical pharmacology information from approved submission for ACS indication.
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☑Yes ☐No ☐N/A	The P3 study included 2 dose levels for ticagrelor.
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☑Yes ☐No ☐N/A	The applicant submitted E-R analyses for efficacy and safety.
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	☐Yes ☐No ☑N/A	See comments to Q3.
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐Yes ☐No ☑N/A	Efficacy supplement. There is an agreed upon iPSP for BRILINTA® FDA granted a waiver from pediatric studies for the use of ticagrelor in ACS.
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☐Yes ☐No ☑N/A	See comments to Q3.
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐Yes ☑No ☐N/A	Not needed.

Filing Memo

Ticagrelor is an oral P2Y12 antiplatelet drug, approved for reducing the rate of thrombotic cardiovascular (CV) events in patients with acute coronary syndrome (ACS). The approval was based on the PLATO study that compared 90 mg twice daily ticagrelor with 75 mg once daily clopidogrel for up to 12 months, in ACS patients taking aspirin.

The current application is based on a single pivotal Phase 3 study PEGASUS, which evaluated whether long term dual antiplatelet therapy with ticagrelor 90 mg or 60 mg twice daily in combination with low dose aspirin once daily compared with low dose aspirin (75-150 mg), reduces the event rate of the composite CV death, non-fatal myocardial infarction, or non-fatal stroke in patients with history of myocardial infarction and high risk of developing thrombotic events. Relative risk reduction for the primary composite endpoint was about 15-16 % for both 60 and 90 mg dose groups of ticagrelor ($p<0.01$). The TIMI major bleeding events were 127, 115 and 54 on ticagrelor 90 mg, 60 mg and placebo, respectively. The applicant is seeking approval for only the 60 mg dose.

The current submission relies on the clinical pharmacology information that supported the approval of ticagrelor for the ACS indication, but includes a population PK analysis from PEGASUS study and a Pharmacodynamic study (platelet inhibition) in Hispanic patients. The proposed draft label incorporates information from the PEGASUS study and there are no changes to Section 7 Drug Interactions or Section 12 Clinical Pharmacology.

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/s/

SREEDHARAN N SABARINATH
04/16/2015

RAJANIKANTH MADABUSHI
04/16/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-433/S015

OTHER REVIEW(S)

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

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: August 24, 2015

To: Alison Blaus
Regulatory Project Manager
Division of Cardiovascular and Renal Products

From: Zarna Patel, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **Brilinta (ticagrelor) Tablets**
NDA: 022433-S015
Comments on draft product labeling

OPDP has reviewed the proposed Package Insert (PI) and Medication Guide submitted for consult on March 25, 2015, for Brilinta (ticagrelor) tablets. OPDP's comments on the proposed PI are provided directly on the attached copy of the proposed labeling emailed to us on August 18, 2015. Please note that our comments on the proposed Medication Guide are provided on DMPP's version of the Medication Guide sent to DCRP on August 20, 2015.

Thank you for the opportunity to comment on the proposed labeling.

If you have any questions, please contact Zarna Patel at 301.796.3822 or zarna.patel@fda.hhs.gov.

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

Reference ID: 3810488

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/s/

ZARNA PATEL
08/24/2015

LABEL AND LABELING REVIEW

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

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

Date of This Review:	June 16, 2015
Requesting Office or Division:	Division of Cardiovascular and Renal Products (DCRP)
Application Type and Number:	NDA 22433/S-015
Product Name and Strength:	Brilinta (ticagrelor) Tablets, 60 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	AstraZeneca Pharmaceuticals LP
Submission Date:	March 6, 2015, May 8, 2015, and June 9, 2015
OSE RCM #:	2015-663
DMEPA Primary Reviewer:	Tingting Gao, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

Reference ID: 3779902

1 REASON FOR REVIEW

AstraZeneca submitted NDA 22433/S-015 to propose a new indication for Brilinta (b) (4) [redacted]. Additionally, AstraZeneca is proposing a new strength of 60 mg for this new indication.

The Division of Cardiovascular and Renal Products (DCRP) requested that we review the submitted container labels, carton labeling, and prescribing information for areas of vulnerability that could lead to medication errors.

2 MATERIALS REVIEWED

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

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information (PI)	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine post-market safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We identified medication error cases in FAERS describing wrong loading dose, loading dose omission, and wrong aspirin dose. We evaluated the PI and determined that the PI adequately stated the correct loading dose and aspirin dose for Brilinta therapy. However, we recommended defining "low dose aspirin" with the actual dose of aspirin in the Highlights of Prescribing Information to be consistent with the dosing instructions in Section 2.2 Dosage Administration in the Full Prescribing Information, which will also minimize the risk of wrong aspirin dose errors.

The container labels and carton labeling appear adequate and we have no recommendations for the container labels and carton labeling based on these medication errors cases.

Reference ID: 3779902

4 CONCLUSION & RECOMMENDATIONS

The proposed container label and carton labeling are acceptable from medication error perspective. However, we conclude that the proposed PI for Brilinta may be improved to promote the safe use of the product as described in Section 4.1.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Dosage and Administration, Highlights of Prescribing Information

a. We recommend defining "low dose aspirin" with the actual dose of aspirin to be consistent with the dosing instructions in Section 2.2 Dosage Administration in the Full Prescribing Information.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Brilinta that AstraZeneca submitted on May 8, 2015.

Table 2. Relevant Product Information for Brilinta	
Initial Approval Date	July 20, 2011
Active Ingredient	ticagrelor
Indication	**Current:** to reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) (unstable angina, non-ST elevation myocardial infarction, or ST elevation myocardial infarction). **Proposed addition:** (b) (4) (b) (4)
Route of Administration	Oral
Dosage Form	Tablets
Strength	**Current:** 90 mg **Proposed addition:** 60 mg
Dose and Frequency	**For Acute Coronary Syndrome:** Initiate treatment with 180 mg (two 90 mg tablets) oral loading dose. Continue treatment with 90 mg twice daily. **Proposed addition:** Take 60 mg twice daily in combination with daily low dose aspirin.
How Supplied	**Current 90 mg:** Bottles of 14, Bottles of 60, Bottles of 180, 100 count Hospital Unit Dose **Proposed 60 mg:** Bottles of 14, Bottles of 60, 100 count Hospital Unit Dose
Storage	Store at 25°C (77°F); excursions permitted to 15°-30°C (59°- 86°F)
Container Closure	Bottle

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On April 23, 2015, we searched the L:drive and AIMS using the terms, Brilinta, to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified 5 previous reviews[1,2,3,4,5], and we confirmed that our previous recommendations were implemented or considered.

[1] Stewart, J. Label and Labeling Review Memo for Brilinta (NDA 022433/S-011). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 JAN 30. RCM No.: 2013-2291.

[2] Stewart, J. Label and Labeling Review for Brilinta (NDA 022433/S-011). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 JAN 17. RCM No.: 2013-2291.

[3] Siahpoushan, M. Label and Labeling Review for Brilinta (NDA 022433). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2011 JULY 13. RCM No.: 2011-195-1.

[4] Toombs, L. Label and Labeling Review for Brilinta (NDA 022433). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2011 MAY 10. RCM No.: 2011-195.

[5] Toombs, L. Label and Labeling Review for Brilinta (NDA 022433). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2010 JULY 30. RCM No.: 2009-2288.

Reference ID: 3779902

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On April 23, 2015, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newletter(s)	Acute Care, Community
Search Strategy and Terms	Match Exact Word or Phrase: Brilinta

D.2 Results

There were two Acute Care newsletter articles[6,7] describing confusion between Brilinta and Brintellix. The wrong drug confusion was attributed to the look-alike nature of these drug names because they "share the same first three letters and other letters as well". The articles did not indicate confusion due to label and labeling of Brilinta and Brintellix. Therefore, we determined that these articles to be not relevant for this label and labeling review.

[6] Institute for Safe Medication Practices. Safety briefs: Similar drug names confused. ISMP Med Saf Alert Acute Care. 2014;19(12):1-5.

[7] Institute for Safe Medication Practices. Safety briefs: A reminder about Brilinta and Brintellix. ISMP Med Saf Alert Acute Care. 2015;20(2):1-8.

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

E.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on April 24, 2015 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.[8]

Table 3: FAERS Search Strategy	
Date Range	**November 1, 2013* to April 1, 2015** *Date of last search in OSE RCM 2013-2291[9]
Product	**BRILINTA** [product name]
Event (MedDRA Terms)	**DMEPA Official FBIS Search Terms Event List:** Medication Errors [HLGT] Product Packaging Issues [HLT] Product Label Issues [HLT] Product Adhesion Issue [PT] Product Compounding Quality Issue [PT] Product Difficult to Remove [PT] Product Formulation Issue [PT] Product Substitution Issue [PT] Inadequate Aseptic Technique in Use of Product [PT]
Country	**USA**

[8] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website http://www.nccmerp.org/pdf/taxo2001-07-31.pdf.

[9] Stewart, J. Label and Labeling Review for Brilinta (NDA 022433/S-011). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 JAN 17. RCM No.: 2013-2291.

Reference ID: 3779902

E.2 Results

Our search identified 57 cases, of which 3 described errors that may be relevant for this review.

Error type	#	Reported Outcome	Reported Root Cause(s)/ Contributing Factors
Wrong loading dose (Patient missed 90 mg on day 1, and took 180 mg loading dose on day 2)	1	Patient experienced vision problems on unknown date and was then airlifted to hospital and was diagnosed with intracranial bleeding/hemorrhage	Unknown if patient missed dose or HCP did not administer
No loading dose	1	Shortness of breath	Not provided
Wrong aspirin dose (Patient took 325 mg aspirin instead of 81 mg.)	1	bruising	Not provided.

We excluded 54 cases because they described accidental overdose (n=1), adverse event reactions not related to medication error (n=6), concomitant medication (n=2), insufficient information to determine medication error (n=1), off label use (n=1), patient noncompliance (n=1), dose omission not related to label and labeling (n=39), wrong drug error not related to label and labeling (n=3)

E.3 List of FAERS Case Numbers

Below is a list of the FAERS case number and manufacturer control numbers for the cases relevant for this review.

FAERS Case #	Manufacturer control #
10242986	US-ASTRAZENECA-2014SE40427
10558610	US-ASTRAZENECA-2014SE81018
9995683	US-ASTRAZENECA-2014SE15506

E.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[10] along with postmarket medication error data, we reviewed the following Brilinta labels and labeling submitted by AstraZeneca Pharmaceuticals LP on March 6, 2015, May 8, 2015 and June 9, 2015.

- Container label submitted March 6, 2015
- Carton labeling submitted March 6, 2015
- Professional Sample - Blister card submitted March 6, 2015
- Professional Sample Carton Labeling for blister card submitted June 9, 2015
- Prescribing Information submitted May 8, 2015

G.2 Label and Labeling Images

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

[10] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

TINGTING N GAO
06/16/2015

CHI-MING TU
06/16/2015

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

Application: sNDA 22433-S015

Application Type: Efficacy Supplement

Name of Drug/Dosage Form: BRILINTA (ticagrelor) 60 and 90 mg Tablets

Applicant: AstraZeneca

Receipt Date: 6 March 2015

Goal Date: 6 September 2015

1. Regulatory History and Applicant's Main Proposals

See RPM Filling Review

2. Review of the Prescribing Information

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

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

In addition, the following labeling issues were identified:

Please make the following changes to any forest plot:

1. For the graphic representation of the hazard ratio, the dots representing the point estimate should be proportional in size to the subgroup size.
2. Please ensure the scale is log and not linear. A log scale is one where 0.5 and 2 are the same distance from the line of unity (e.g., Eliquis' forest plots in the approved label) to show the magnitude of the effect.
3. The geographic subgroup should be broken down by "US" and "OUS" only.
4. Please include percent of patients in the label of all subgroups. They should appear as follows, for example:
    - Diabetes
      Yes (51%)
      No (49%)
5. The following standard cautionary paragraph should be included at the bottom of the plot noting that not all subgroups were prespecified, that there are multiplicity concerns, etc.:
   "The { table | figure } above presents effects in various subgroups { all | most } of which are baseline characteristics and { all | most } of which were pre-specified { , if not the groupings }. The 95% confidence limits that are shown do not take into account how many comparisons were made, nor do they reflect the effect of a particular factor after adjustment for all other

factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted."

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format 2 weeks after the date of the 74-day letter. The resubmitted PI will be used for further labeling review.

Appendix

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

Highlights

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

HIGHLIGHTS GENERAL FORMAT

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

NO 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment: *Without the box, the HL section exceeds one-half page. Please bring the HL down to one half page. Please keep in mind, the verbiage in the HL does not have to be verbatim to the FPI as all wording cross-references the appropriate section in the FPI.*

YES 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

YES 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

Reference ID: 3735119

YES 7. Section headings must be presented in the following order in HL:

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

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

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

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

Comment:

Highlights Limitation Statement

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

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

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

Comment:

Reference ID: 3735119

Selected Requirements of Prescribing Information

Boxed Warning (BW) in Highlights

YES 12. All text in the BW must be **bolded**.

Comment:

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

Comment:

YES 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

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

Comment:

Recent Major Changes (RMC) in Highlights

YES 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

YES 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013".

Comment:

YES 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

YES 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment:

Reference ID: 3735119

Selected Requirements of Prescribing Information

Dosage Forms and Strengths in Highlights

YES 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

YES 21. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

YES 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement in Highlights

YES 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling"**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide"**

Comment:

Revision Date in Highlights

YES 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 9/2013**").

Comment:

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

YES 25. The TOC should be in a two-column format.

Comment:

YES 26. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS"**. This heading should be in all UPPER CASE letters and **bolded**.

Comment:

YES 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment:

YES 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "FULL PRESCRIBING INFORMATION: CONTENTS" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]"* or *"*[*see Warnings and Precautions (5.2)*]".

Comment:

Reference ID: 3735119

NO 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment: *The sections in the FPI that are noted in the "Recent Major Changes" do not have a vertical line on the left edge bringing the readers attention to that change. Please add the vertical lines.*

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 35. The following heading must be **bolded** and appear at the beginning of the FPI: "**FULL PRESCRIBING INFORMATION".** This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

YES 36. In the BW, all text should be **bolded**.

Comment:

YES 37. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**").

Comment:

CONTRAINDICATIONS Section in the FPI

N/A 38. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 39. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

N/A 40. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

YES 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

YES 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Reference ID: 3735119

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]
See full prescribing information for complete boxed warning.

- [text]
- [text]

----------RECENT MAJOR CHANGES----------
[section (X.X)] [m/year]
[section (X.X)] [m/year]

----------INDICATIONS AND USAGE----------
[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

----------DOSAGE AND ADMINISTRATION----------
- [text]
- [text]

----------DOSAGE FORMS AND STRENGTHS----------
[text]

----------CONTRAINDICATIONS----------
- [text]
- [text]

----------WARNINGS AND PRECAUTIONS----------
- [text]
- [text]

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
- [text]
- [text]

----------USE IN SPECIFIC POPULATIONS----------
- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

Reference ID: 3735119

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
04/20/2015

RPM FILING REVIEW

(Including Memo of Filing Meeting)

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

Application Information		
NDA # 22433 BLA# n/a	NDA Supplement #: S- 015 BLA Supplement #: S- n/a	Efficacy Supplement Category: ☒ New Indication (SE1) ☒ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Animal Rule Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Pediatric
Proprietary Name: BRILINTA Established/Proper Name: ticagrelor Dosage Form: Tablets Strengths: 60 and 90 mg		
Applicant: AstraZeneca Agent for Applicant (if applicable): n/a		
Date of Application: 6 March 2015 Date of Receipt: 6 March 2015 Date clock started after UN: n/a		
PDUFA/BsUFA Goal Date: 6 September 2015	Action Goal Date (if different): n/a	
Filing Date: 5 May 2015	Date of Filing Meeting: 9 April 2015	
Chemical Classification (original NDAs only) : ☐ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☐ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch		
Proposed indication: (b) (4)		

Reference ID: 3731858

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***	☐ 505(b)(1) ☐ 505(b)(2) ☒ 505(b)(1) ☐ 505(b)(2)
Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☐ Standard ☒ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)
☐ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*): n/a	
List referenced IND Number(s): 65808	

Reference ID: 3731858

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	☒	☐		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				n/a
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:	☐	☐		n/a
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		User fee ID: 3009833

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov):* ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter	Payment of other user fees: ☒ Not in arrears ☐ In arrears

and contact the user fee staff.	
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☒ Yes ☐ No

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form, cover letter, and annotated labeling).* **If yes**, answer the bulleted questions below:	☐	☐		
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☐		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**	☐	☐		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.***	☐	☐		
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☐		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

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Exclusivity	YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***	☐	☒		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: THREE ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☒	☐	☐	
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☐	☒	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☒	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM*** ***Note****: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☒	

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Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?	n/a			
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.	☐	☐		Hyperlinks are working but in at least one instance, it pointed to the wrong part of the submission.
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☒	
Forms and Certifications				
***Electronic** forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, **paper** forms and certifications with hand-written signatures must be included. **Forms** include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); **Certifications** include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

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Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	☒	☐		
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."*	☒	☐	☐	

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Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	Electronic submission
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	☒	☐		
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☒	☐	☐	Previously discussed at 14Jan15 PeRC; Scheduling request for sNDA sent to Perc on 2Apr15
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	
<u>BPCA</u>: Is this submission a complete response to a pediatric Written	☐	☒		

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829.htm

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Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]				
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☐	☐	☒	Efficacy supplement
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☒ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		
Is the PI submitted in PLR format?[4]	☒	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
For applications submitted on or after June 30, 2015: Is the PI submitted in PLLR format?[5]	☐	☐	☒	

[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837 htm

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

[5] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

If PI not submitted in PLLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.***	☐	☐	☒	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☒	☐	☐	Consulted 25Mar15
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☒	☐	☐	Patient Labeling Consulted 25Mar15
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	☒	☐	☐	DMEPA Consulted 25Mar15
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☐	☒	☐	

Reference ID: 3731858

Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? **Date(s):** n/a ***If yes, distribute minutes before filing meeting***	☐	☒		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** 8Apr14 (WRO) and 11Feb15 ***If yes, distribute minutes before filing meeting***	☒	☐		PreNDA WRO dated 8Apr14; Topline minutes dated 19Mar15
Any Special Protocol Assessments (SPAs)? **Date(s):** 1Oct09 and 29Dec09 ***If yes, distribute letter and/or relevant minutes before filing meeting***	☒	☐		No Agreement Letters Dated 13Nov09 and 18Feb10 – There was a follow-up meeting to discuss the "No Agreement Letters" on 1Jul10 (minutes dated 19Jul15).

Reference ID: 3731858

ATTACHMENT

MEMO OF FILING MEETING

DATE: 9 April 2015

BACKGROUND:

BRILINTA (ticagrelor) is an oral, reversible blocker of the platelet $P2Y_{12}$ receptor, an action which blocks ADP-mediated platelet activation and aggregation. Ticagrelor was approved for marketing in the USA in 2011 for reduction of the rate of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) (unstable angina, non-ST elevation myocardial infarction, or ST elevation myocardial infarction) based on the results from the trial PLATO.

AstraZeneca (AZ) conducted a second trial is entitled, "*A Randomized, Double-Blind, Placebo Controlled, Parallel Group, Multinational Trial, to Assess the Prevention of Thrombotic Events with Ticagrelor Compared to Placebo on a Background of Acetyl Salicylic Acid (ASA) Therapy in Patients with History of Myocardial Infarction* ("**PEGASUS**")" aimed to support the indication listed above.

PEGASUS was an event-driven trial in which about 21,000 subjects with previous MI (1 to 3 years prior to enrollment) and at least one additional risk factor (age ≥65 years, diabetes, a second prior MI, evidence of multi-vessel coronary artery disease, or chronic non-end-stage renal dysfunction) were randomized 1:1:1 to ticagrelor 90 mg or 60 mg BID or placebo. The primary endpoint was a composite of cardiovascular (CV) death, myocardial infarction (MI), and stroke.

Pre-sNDA Meeting: 8Apr14 (WRO) (clarifications dated 10Sep14)
Top Line Meeting: 11Feb15 (minutes dated 19Mar15)

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Alison Blaus	Y
	CPMS/TL:	Edward Fromm	Y
Cross-Discipline Team Leader (CDTL)	Martin Rose		Y
Division Director and Deputy	Norman Stockbridge and Stephen Grant		Y Y
Office Director/Deputy	n/a		n/a
Clinical	Reviewer:	Preston Dunnmon (Efficacy) Melanie Blank (Safety)	Y Y

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	TL:	Martin Rose	Y
Social Scientist Review (*for OTC products*)	Reviewer:	n/a	n/a
	TL:	n/a	n/a
OTC Labeling Review (*for OTC products*)	Reviewer:	n/a	n/a
	TL:	n/a	n/a
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	n/a	n/a
	TL:	n/a	n/a
Clinical Pharmacology	Reviewer:	Sreedharan Sabarinath	Y
	TL:	Raj Madabushi	N
Biostatistics	Reviewer:	Steve Bai	Y
	TL:	Jim Hung	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	n/a	n/a
	TL:	n/a	n/a
Statistics (carcinogenicity)	Reviewer:	n/a	n/a
	TL:	n/a	n/a
Immunogenicity (assay/assay validation) *(for protein/peptide products only)*	Reviewer:	n/a	n/a
	TL:	n/a	n/a
Product Quality (CMC)	Reviewer:	Kris Raman	Y
	TL:	Zedong Dong	N
Biopharmaceutics	Reviewer	Banu Zolnik	N
	TL:	Elsbeth Chikhale	N
Quality Microbiology	Reviewer:	n/a	n/a
	TL:	n/a	n/a
CMC Labeling Review	Reviewer:	n/a	n/a
	TL:	n/a	n/a

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Facility Review/Inspection	Reviewer:	n/a	n/a
	TL:	n/a	n/a
OSE/DMEPA (proprietary name, carton/container labels))	Reviewer:	TingTing Gao	Y
	TL:	Chi-Ming (Alice) Tu	Y
OSE/DRISK (REMS)	Reviewer:	n/a	n/a
	TL:	Kim Lehrfield	Y
OC/OSI/DSC/PMSB (REMS)	Reviewer:	n/a	n/a
	TL:	n/a	n/a
Bioresearch Monitoring (OSI)	Reviewer:	Sharon Gershon	N
	TL:	Susan Thompson	N
Controlled Substance Staff (CSS)	Reviewer:	n/a	n/a
	TL:	n/a	n/a
Other reviewers/disciplines	Reviewer:	n/a	n/a
	TL:	n/a	n/a
Other attendees	Darrell Lyons (OSE-PM)		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., BA/BE studies):	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation?	☒ YES ☐ NO

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If no, explain: n/a	
• Electronic Submission comments **List comments**: n/a	☐ Not Applicable ☒ No comments
CLINICAL **Comments**: No issues for the 74-day Letter	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain: The need for clinical site inspections is being debated as the patients were evenly distributed between sites and no particular site drove the results. Sites based on financial disclosure (or lack thereof) might be chosen for inspection. If we decide to inspect, a consult will be placed in DARRTS. If not, the rationale for no inspections will be in the clinical review.	☐ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason: n/a
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**: n/a	☒ Not Applicable ☐ YES ☐ NO

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CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**: n/a	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**: n/a	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**: No issues for the 74-day Letter	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**: n/a	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
IMMUNOGENICITY (protein/peptide products only) **Comments**: n/a	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**: No issues for the 74-day Letter - Filing issues already discussed with the sponsor via TC on 7Apr15	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

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New Molecular Entity (NDAs only) • Is the product an NME?	 ☐ YES ☒ NO
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	 ☐ YES ☒ NO ☒ YES ☐ NO ☐ YES ☐ NO
Quality Microbiology • Was the Microbiology Team consulted for validation of sterilization? **Comments**: n/a	☒ Not Applicable ☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**: Dr. Raman noted that they have contacted Yvonne Knight to schedule the facility inspection, but it has not been scheduled as of the 9Apr15 filing meeting.	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☒ NO
Facility/Microbiology Review (BLAs only) **Comments**: n/a	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments**:	 ☐ Review issues for 74-day letter

Reference ID: 3731858

APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)	☒ N/A
• Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application?	☐ YES ☐ NO
• If so, were the late submission components all submitted within 30 days?	☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	n/a
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Norman Stockbridge, M.D., Ph.D. **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): 11 June 2015 **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): **Comments**: n/a	

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REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. Review Classification: ☐ Standard Review ☒ Priority Review
ACTIONS ITEMS	
☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	351(k) BLA/supplement: If filed, send filing notification letter on day 60
☒	If priority review: • notify sponsor in writing by day 60 (see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: September 2014

Reference ID: 3731858

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
04/14/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-433/S015

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 22433 SUPPL # 015 HFD # 110

Trade Name: BRILINTA

Generic Name: ticagrelor

Applicant Name: AstraZeneca

Approval Date, If Known: TBD

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

SE1

b) 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.

n/a

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:

n/a

c) Did the applicant request exclusivity?

YES ☒ NO ☐

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

Three

d) 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?

n/a

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 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:

n/a

(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:

n/a

(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:

n/a

(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:

PEGASUS Phase 3 Trial (A Randomized, Double-Blind, Placebo Controlled, Parallel Group, Multinational Trial, to Assess the Prevention of Thrombotic Events with Ticagrelor Compared to Placebo on a Background of Acetyl Salicylic Acid (ASA) Therapy in Patients with History of Myocardial Infarction - "**PEGASUS**")

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.")

PEGASUS 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:

n/a

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?

PEGASUS YES ☐ NO ☒

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

n/a

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

PEGASUS Phase 3 Trial (A Randomized, Double-Blind, Placebo Controlled, Parallel Group, Multinational Trial, to Assess the Prevention of Thrombotic Events with Ticagrelor Compared to Placebo on a Background of Acetyl Salicylic Acid (ASA) Therapy in Patients with History of Myocardial Infarction - "**PEGASUS**")

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

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

PEGASUS

IND # 65808 YES ☒ NO ☐
Explain:

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

n/a

(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: Alison Blaus, RAC
Title: Senior Regulatory Health Project Manager
Date: 26 August 2015

Name of Division Director signing form: Norman Stockbridge, MD, PhD
Title: Division Director

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

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
08/26/2015

NORMAN L STOCKBRIDGE
08/26/2015

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 22433 BLA # n/a	NDA Supplement # 015 BLA Supplement # n/a	If NDA, Efficacy Supplement Type: SE1 *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: BRILINTA Established/Proper Name: ticagrelor Dosage Form: Tablets		Applicant: AstraZeneca Agent for Applicant (if applicable): n/a
RPM: Alison Blaus, RAC		Division: Cardiovascular & Renal Products

NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☒ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☐ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is 6 September 2015	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None NME Approval 20Jul11
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain	☐ Received

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

❖ Application Characteristics [3]

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other require actions: CST SharePoint)

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action and date: Approval 3Sep15
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	n/a – efficacy supplement n.a
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☒ None DMEPA: ☐ None 16Jun15 DMPP/PLT (DRISK): ☐ None 20Aug15 OPDP: ☐ None 24Aug15 SEALD: ☒ None CSS: ☒ None Product Quality ☒ None Other: ☐ None

Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	14Apr15 (Filing Review) and 3Sep15 (RPM Primary Review) ☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☐ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 3Jun15 If PeRC review not necessary, explain:	
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) *(do not include previous action letters, as these are located elsewhere in package)*	Included
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	Included
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 8Apr14 (WRO) (clarifications dated 10 September 2014) – Topline Meeting 11 February 2015 (minutes dated 19 March 2015)
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Mid-cycle Communication *(indicate date of mtg)*	☒ N/A

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

• Late-cycle Meeting *(indicate date of mtg)*	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None 14Aug15
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 11Aug15
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Clinical review(s) *(indicate date for each review)*	10Apr15 and 11Aug15
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	See clinical review dated 11Aug15
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	n/a n/a ☒ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☒ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Review(s) *(indicate date for each review)*	☐ None 2Jul15

Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 22Jul15
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Nonclinical ☒ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ No separate review
• Supervisory Review(s) *(indicate date for each review)*	☐ No separate review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☐ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☐ No carc
❖ ECAC/CAC report/memo of meeting	☐ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☐ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• Tertiary review (*indicate date for each review*)	☒ None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	☒ None
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	☐ None 30Apr15, 7Aug15, and 10Aug15 (two)
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	See CMC review dated 10Aug15
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ Facilities inspections (*action must be taken prior to the re-evaluation date*) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☒ Acceptable Re-evaluation date: 30Sep15 ☐ Withhold recommendation ☐ Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☐ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done *(Send email to CDER OND IO)*
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☒ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	☐ Done

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/s/

ALISON L BLAUS
09/03/2015

PeRC Meeting Minutes
June 3, 2015

PeRC Members Attending:
Lynne Yao
Linda Lewis (Did not review Daklinza, Zomig)
Gettie Audain
Gregory Reaman
Hari Cheryl Sachs
Wiley Chambers
Lily Mulugeta
Kevin Krudys
Thomas Smith
Peter Stark
Gilbert Burckart
Robert 'Skip' Nelson
Dianne Murphy
Andrew Mulbert
Olivia Ziolkowski

Reference ID: 3780974

Agenda

(b) (4)

NDA	*22433/015*	*Brilinta (ticagrelor) Full Waiver*	*Secondary prevention of myocardial infarction*

(b) (4)

5 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Reference ID: 3780974

(b) (4)

Brilinta (ticagrelor) Full Waiver

- NDA 22433/015 seeks marketing approval for Brilinta (ticagrelor) for secondary prevention of myocardial infarction.
- The application triggers PREA as directed to a new indication and dosage form.
- The PDUFA goal date is September 6, 2015.
- *PeRC Recommendations:*
    - The PeRC agreed with a full waiver because studies would be impossible or highly impracticable.
    - The PeRC recommends that the sponsor provide any plans for study of this product under a WR in the iPSP.

(b) (4)

Reference ID: 3780974

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/s/

GEORGE E GREELEY
06/18/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22433-S015

FILING COMMUNICATION -
NO FILING REVIEW ISSUES IDENTIFIED

AstraZeneca LP
ATTENTION: Robert Griffin
Director, Regulatory Affairs
One MedImmune Way
Gaithersburg, MD, 20878

Dear Mr. Griffin:

Please refer to your supplemental New Drug Application (sNDA) dated 6 March 2015, received 6 March 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for BRILINTA (ticagrelor) 60 & 90 mg Tablets.

We also refer to your amendments dated March 23 and 30, and April 7, 10 and 17, 2015.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is **6 September 2015**.

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.

We request that you submit the following information:

1. The SAP had pre-specified one planned interim analysis of efficacy to be conducted when 50% of total planned number of primary events had occurred. The CSR section 7.6.4 just stated that the interim analysis had no impact on study conduct. Please submit the full detailed results and SAS code for the interim analysis.

2. For all "analysis of composite of …" tables in the PEGASUS final study report (e.g. tables 22, 24, 26, 27, 28 and any unique tables of this format in section 11.2.6), please generate a version of these tables in which the first-occurring component of the composite is included in the component analyses below the composite endpoint for each patient with a composite endpoint event. The sum of the component events in each column of these tables should equal the total number of composite events in each column (i.e., each patient is represented in only one component row).

3. It is our understanding that patients who suffered an MI or stroke who arrived to hospital alive but died shortly thereafter (potentially on the same day), are not counted as CV deaths for the purpose of the primary composite analysis. Is this correct?

PRESCRIBING INFORMATION

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

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances, and
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

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

1. Without the box, the Highlights (HL) section exceeds one-half page. Please bring the HL down to one half page. Please keep in mind, the verbiage in the HL does not have to be verbatim to the Full Product Labeling (FPI) as all wording cross-references the appropriate section in the FPI.
2. The sections in the FPI that are noted in the "Recent Major Changes" section of the HL do not have a vertical line on the left edge bringing the readers attention to that change. Please add the vertical lines.
3. You should revise Table 8 in Section 14 to be consistent with the analysis requested for the primary endpoint component results requested above under information request 2. The component names should be indented in this table and the results should be presented without hazard ratios, confidence intervals or p values. You may propose to include a table of the results of the primary endpoint components considered sepratetly. An indivudual should be counted no more than once in each row, but could possibley be represented in more than one row. This table may include hazard ratios and confidence intervals, but not p-values unless the calculation of a p-value is allowed pursuant to a pre-specified hierarchical analysis plan.
4. Please make the following changes to the efficacy forest plots in Section 14 (PLATO and PEGASUS):
    a. For the graphic representation of the hazard ratio, the dots representing the point estimate should be proportional in size to the subgroup size.
    b. Please ensure the scale is log and not linear. A log scale is one where 0.5 and 2 are the same distance from the line of unity (e.g., Eliquis' forest plots in the approved label) to show the magnitude of the effect.
    c. The geographic subgroup should be broken down by "US" and "OUS" only.
    d. Please include percent of patients in the label of all subgroups. They should appear as follows, for example:
        - Diabetes
          Yes (51%)
          No (49%)
    e. The following standard cautionary paragraph should be included at the bottom of each plot noting that not all subgroups were prespecified, that there are multiplicity concerns, etc.:

> "The { table | figure } above presents effects in various subgroups { all | most } of which are baseline characteristics and { all | most } of which were pre-specified { , if not the groupings }. The 95% confidence limits that are shown do not take into account how many comparisons were made, nor do they reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted."

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by **8 May 2015**. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

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

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

REQUIRED PEDIATRIC ASSESSMENTS

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

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:

Alison Blaus, RAC
Senior Regulatory Project Manager
(301) 796-1138

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular & Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

NORMAN L STOCKBRIDGE
04/24/2015

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 22433-s015 **Applicant: AstraZeneca** **Stamp Date: 6 March 2015**

Drug Name: BRILINTA (ticagrelor) **NDA/BLA Type: Supplement**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?			X	PEGASUS not integrated with PLATO with agreement of Division
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			X	PEGASUS not integrated with PLATO with agreement of Division
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).	X			
505(b)(2) Applications					
13.	If appropriate, what is the reference drug?			X	
14.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the referenced product(s)/published literature?			X	
15.	Describe the scientific bridge (e.g., BA/BE studies)			X	
DOSE					
16.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms:	X			

Reference ID: 3729311

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Location in submission:				
EFFICACY					
17.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1: PEGASUS: PrEvention with TicaGrelor of SecondAry Thrombotic Events in High-RiSk Patients with Prior AcUte Coronary Syndrome - Thrombolysis In Myocardial Infarction Study Group] Indication: "In patients with prior MI and a high risk of developing an atherothrombotic event, BRILINTA™ is indicated for the reduction of cardiovascular death, nonfatal MI or non-fatal stroke." Pivotal Study #2 Indication:	X			
18.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
19.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
20.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		X		Information requested
SAFETY					
21.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			In the Clinical – overview there is an "Overview of Safety". Additionally, there is a more detailed summary of Clinical Safety. As this is just one study, this is sufficient.
22.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	The QT studies were reviewed during the first NDA review cycle. There are no QT concerns.
23.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
24.	For chronically administered drugs, have an adequate	X			The proposed dose is

Reference ID: 3729311

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?				lower than the approved dose. In this trial, almost 14,000 patients were exposed to the proposed dose or higher for a mean duration of exposure of ~2 years.
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
26.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?		X		The coding dictionary was not submitted but MeDRA 17 was used. Therefore, there is no need to provide the dictionary.
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			There is an agreed-upon iPSP for Brilinta (ticagrelor). FDA granted a waiver from pediatric studies for the use of ticagrelor in ACS on the grounds that the necessary studies are impossible or highly impracticable because there are too few children with this

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

Reference ID: 3729311

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					disease. The applicant is seeking the same waiver for the prevention indication now being sought because the underlying condition of history of ACS makes pediatric studies impossible or highly impracticable for the same reasons provided above.
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		X		Information requested
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
37.	Are all datasets to support the critical safety analyses available and complete?	X			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? _Yes_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Reference ID: 3729311

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Preston Dunnmon / Melanie Blank

Reviewing Medical Officer Date

Martin Rose

Clinical Team Leader Date

Reference ID: 3729311

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/s/

PRESTON M DUNNMON
04/09/2015

MELANIE J BLANK
04/10/2015

MARTIN ROSE
04/10/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 22433/S-015

ACKNOWLEDGEMENT --
PRIOR APPROVAL SUPPLEMENT

AstraZeneca LP
c/o AstraZeneca Pharmaceuticals LP
Attention: Mr. Ian Hunt, US Agent
Executive Director, Regulatory Affairs
One Medimmune Way
Gaithersburg, MD 20878

Dear Mr. Hunt:

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

NDA Number: 22433

Supplement Number: 015

Product Name: Brilinta (ticagrelor) Tablets, 60 and 90 mg

Date of Submission: March 6, 2015

Date of Receipt: March 6, 2015

This supplemental application proposes to (b) (4)

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 May 5, 2015, in accordance with 21 CFR 314.101(a).

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

FDAAA TITLE VIII RESPONSIBILITIES

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

SUBMISSION REQUIREMENTS

Please cite the application number listed above 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, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have questions, please contact:

Alison Blaus, RAC
Regulatory Health Project Manager
(301) 796-1138

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

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/s/

EDWARD J FROMM
03/26/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**REQUEST FOR PATIENT LABELING REVIEW CONSULTATION**

TO:	FROM: (Name/Title, Office/Division/Phone number of requestor)
CDER-DMPP-PatientLabelingTeam	Alison Blaus, ODE 1/DCaRP, (301)796-1138

REQUEST DATE:	NDA/BLA NO.:	TYPE OF DOCUMENTS:
25 March 2015	22433-S015	(PLEASE CHECK OFF BELOW)

NAME OF DRUG:	PRIORITY CONSIDERATION:	CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE:
Brilinta (ticagrelor) Tablets	Priority sNDA		2 Weeks after receiving substantially complete labeling

SPONSOR:	
AstraZeneca	PDUFA Date: 6 September 2015

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
☐ PATIENT PACKAGE INSERT (PPI)
☒ MEDICATION GUIDE
☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
☐ ORIGINAL NDA/BLA
☒ EFFICACY SUPPLEMENT
☐ SAFETY SUPPLEMENT
☐ LABELING SUPPLEMENT
☐ MANUFACTURING (CMC) SUPPLEMENT
☐ PLR CONVERSION

REASON FOR LABELING CONSULT
☐ INITIAL PROPOSED LABELING
☒ LABELING REVISION

EDR link to submission:

EDR Location: \\CDSESUB1\evsprod\NDA022433\0160

Please Note: DMPP uses substantially complete labeling, which has already been marked up by the CDER Review Team, when reviewing MedGuides, IFUs, and PPIs. Once the substantially complete labeling is received, DMPP will complete its review within 14 calendar days. Please provide a copy of the sponsor's proposed patient labeling in Word format.

COMMENTS/SPECIAL INSTRUCTIONS: Please let me know the reviewer assigned and I will invite them to the below.

Filing/Planning Meeting: 9 April 2015

Mid-Cycle Meeting: 2 June 2015

Labeling Meetings: TBD

Wrap-Up Meeting: TBD

SIGNATURE OF REQUESTER: Alison Blaus, RAC

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one)
	☐ eMAIL (BLAs Only) ☒ DARRTS

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/s/

ALISON L BLAUS
03/25/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:			FROM:	
Mail: OSE			Alison Blaus, ODE 1/DCaRP, (301)796-1138	
DATE 25 March 2015	IND NO. 65808	NDA NO. 22433-S015	TYPE OF DOCUMENT sNDA Submission	DATE OF DOCUMENT 6 March 2015
NAME OF DRUG ticagrelor	PRIORITY CONSIDERATION Priority sNDA Review		CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE 6 July 2015

NAME OF FIRM: AstraZeneca

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: Carton/Container Labels

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Please review these carton/container labels for this sNDA, ticagrelor (90mg carton/container labels are already approved).
Link to the Application
EDR Location: \\CDSESUB1\evsprod\NDA022433\0160

PDUFA DATE: 6 September 2015

ATTACHMENTS: Draft Package Insert, Container and Carton Labels (please see these documents at the above EDR location.

CC: Archival IND 65808/NDA 22433-S015
HFD-110/Division File
HFD-110/RPM
HFD-110/Reviewers and Team Leaders

NAME AND PHONE NUMBER OF REQUESTER	METHOD OF DELIVERY (Check one)		
Alison Blaus	☒ DFS ONLY	☐ MAIL	☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER		

Reference ID: 3721659

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/s/

ALISON L BLAUS
03/25/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

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

TO:	FROM: (Name/Title, Office/Division/Phone number of requestor)
CDER-DDMAC-RPM	Alison Blaus, ODE 1/DCaRP, (301)796-1138

REQUEST DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS
25 March 2015	65808	22433-S015	(PLEASE CHECK OFF BELOW)

NAME OF DRUG:	PRIORITY CONSIDERATION:	CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting):
ticagrelor	Priority sNDA		**2 weeks after receipt of SCPI**

NAME OF FIRM:	PDUFA Date: 6 September 2015
AstraZeneca	

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
X PACKAGE INSERT (PI)
☐ PATIENT PACKAGE INSERT (PPI)
☐ CARTON/CONTAINER LABELING
X MEDICATION GUIDE
☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
☐ ORIGINAL NDA/BLA
☐ IND
X EFFICACY SUPPLEMENT
☐ SAFETY SUPPLEMENT
☐ LABELING SUPPLEMENT
☐ PLR CONVERSION

REASON FOR LABELING CONSULT
☐ INITIAL PROPOSED LABELING
X LABELING REVISION

EDR link to submission:
EDR Location: \\CDSESUB1\evsprod\NDA022433\0160

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. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to DDMAC. Once the substantially complete labeling is received, DDMAC will complete its review within 14 calendar days.

COMMENTS/SPECIAL INSTRUCTIONS:

Mid-Cycle Meeting: 2 June 2015 (OPDP invited)

Labeling Meetings: Labeling Planning Meeting not yet scheduled but OPDP will be included.

Wrap-Up Meeting: n/a

SIGNATURE OF REQUESTER: Alison Blaus

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) X eMAIL ☐ HAND

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/s/

ALISON L BLAUS
03/25/2015