CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

022433Orig1s028

Trade Name:	Brilinta tablets
Generic or Proper Name:	ticagrelor
Sponsor:	AstraZeneca Pharmaceuticals LP
Approval Date:	May 28, 2020
Indication:	BRILINTA is indicated to reduce the risk of a first MI or stroke in patients with coronary artery disease (CAD) at high risk for such events. While use is not limited to this setting, the efficacy of BRILINTA was established in a population with type 2 diabetes mellitus (T2DM).

CENTER FOR DRUG EVALUATION AND RESEARCH

022433Orig1s028

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022433Orig1s028

APPROVAL LETTER

NDA 22433/S-028

SUPPLEMENT APPROVAL

AstraZeneca Pharmaceuticals LP
Attn: Jeffy G. John, MBA
Director, Regulatory Affairs
One MedImmune Way
Gaithersburg, MD 20878

Dear Mr. John:

Please refer to your supplemental new drug application (sNDA) dated 30 July 2019, received 30 July 2019, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Brilinta (ticagrelor) tablets.

This Prior Approval supplemental new drug application provides for the following new indication:

> *BRILINTA is indicated to reduce the risk of a first MI or stroke in patients with coronary artery disease (CAD) at high risk for such events. While use is not limited to this setting, the efficacy of BRILINTA was established in a population with type 2 diabetes mellitus (T2DM).*

Additional revisions related to this new indication have been made throughout the prescribing information.

APPROVAL & LABELING

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

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 FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information 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.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include 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 Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), 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).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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 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.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

You must submit final promotional materials and Prescribing Information, 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 FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

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[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.

[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf

[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.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 Bridget Kane, Regulatory Project Manager, at (240) 402-2170.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, MD, PhD
Director
Division of Cardiology and Nephrology
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NORMAN L STOCKBRIDGE
05/28/2020 12:46:58 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022433Orig1s028

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 daily reduce the effectiveness of BRILINTA and should be avoided. (2.3, 5.2, 14.1)**

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

Indications and Usage (1.2)	05/2020
Dosage and Administration (2 2)	05/2020
Warnings and Precautions (5.7)	10/2019

---------- INDICATIONS AND USAGE ----------
BRILINTA is a $P2Y_{12}$ platelet inhibitor indicated
- to reduce the risk of cardiovascular (CV) death, myocardial infarction (MI), and stroke in patients with acute coronary syndrome (ACS) or a history of MI. For at least the first 12 months following ACS, it is superior to clopidogrel.
  BRILINTA also reduces the risk of stent thrombosis in patients who have been stented for treatment of ACS. (1.1)
- to reduce the risk of a first MI or stroke in patients with coronary artery disease (CAD) at high risk for such events. While use is not limited to this setting, the efficacy of BRILINTA was established in a population with type 2 diabetes mellitus (T2DM). (1.2)

---------- DOSAGE AND ADMINISTRATION ----------
- ACS or History of MI
  - In the management of ACS, initiate treatment with 180 mg oral loading dose. Then administer 90 mg twice daily during the first year. After one year, administer 60 mg twice daily. (2.1)
- Patients with CAD and No Prior Stroke or MI
  - Administer 60 mg twice daily. (2.2)

Use BRILINTA with a daily maintenance dose of aspirin of 75-100 mg. (2.3, 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 from BRILINTA is self-limiting. (5.3)
- Severe Hepatic Impairment: Likely increase in exposure to ticagrelor. (5.6)
- Laboratory Test Interference: False negative platelet functional test results have been reported for Heparin Induced Thrombocytopenia (HIT). BRILINTA is not expected to impact PF4 antibody testing for HIT. (5.7)

---------- ADVERSE REACTIONS ----------
Most common adverse reactions (>5%) are bleeding and dyspnea. (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)
- Opioids: Decreased exposure to ticagrelor. Consider use of parenteral anti-platelet agent. (7.4)
- Patients receiving more than 40 mg per day of simvastatin or lovastatin may be at increased risk of statin-related adverse effects. (7.5)
- Monitor digoxin levels with initiation of or any change in BRILINTA. (7.6)

---------- USE IN SPECIFIC POPULATIONS----------
- Lactation: Breastfeeding not recommended. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 05/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

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 daily reduce the effectiveness of BRILINTA and should be avoided (2.3, 5.2, 14.1).**

1 INDICATIONS AND USAGE

1.1 Acute Coronary Syndrome or a History of Myocardial Infarction

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

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

1.2 Coronary Artery Disease but No Prior Stroke or Myocardial Infarction

BRILINTA is indicated to reduce the risk of a first MI or stroke in patients with coronary artery disease (CAD) at high risk for such events *[see Clinical Studies (14.2)]*. While use is not limited to this setting, the efficacy of BRILINTA was established in a population with type 2 diabetes mellitus (T2DM).

2 DOSAGE AND ADMINISTRATION

2.1 Acute Coronary Syndrome or a History of Myocardial Infarction

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.

2.2 Coronary Artery Disease but No Prior Stroke or Myocardial Infarction

Administer 60 mg twice daily. For all patients with ACS see *Dosage and Administration (2.1)*.

2.3 Administration

Administer BRILINTA with a daily maintenance dose of aspirin of 75-100 mg *[see Warnings and Precautions (5.2) and Clinical Studies (14)]*. A patient who misses a dose of BRILINTA should take one tablet (their next dose) at its scheduled time.

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)]*.

Do not administer BRILINTA with another oral $P2Y_{12}$ platelet inhibitor.

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), (14.2)]*.

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 (2.3) and Clinical Studies (14.1)]*.

5.3 Dyspnea

In clinical trials, about 14% (PLATO and PEGASUS) to 21% (THEMIS) 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 % (PLATO), 4.3% (PEGASUS), and 6.9% (THEMIS) of patients.

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 Bradyarrhythmias

BRILINTA can cause ventricular pauses *[see Adverse Reactions (6.1)]*. Bradyarrhythmias including AV block have been reported in the postmarketing setting. Patients with a history of sick sinus syndrome, 2nd or 3rd degree AV block or bradycardia-related syncope not protected by a pacemaker were excluded from clinical studies and may be at increased risk of developing bradyarrhythmias with ticagrelor.

5.6 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)]*.

5.7 Laboratory Test Interferences

False negative functional tests for Heparin Induced Thrombocytopenia (HIT)

BRILINTA has been reported to cause false negative results in platelet functional tests (to include, but may not be limited to, the heparin-induced platelet aggregation (HIPA) assay) for patients with Heparin Induced Thrombocytopenia (HIT). This is related to inhibition of the $P2Y_{12}$-receptor on the healthy donor platelets in the test by ticagrelor in the affected patient's serum/plasma. Information on concomitant treatment with BRILINTA is required for interpretation of HIT functional tests. Based on the mechanism of BRILINTA interference, BRILINTA is not expected to impact PF4 antibody testing for HIT.

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

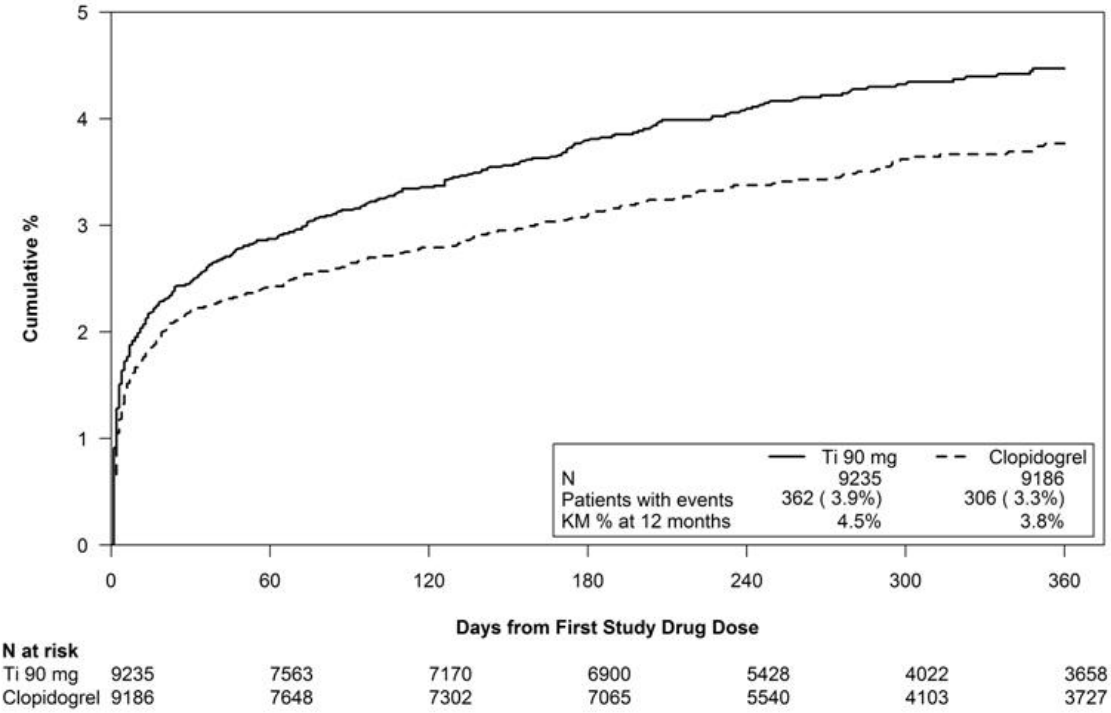
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

BRILINTA has been evaluated for safety in more than 32,000 patients.

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)

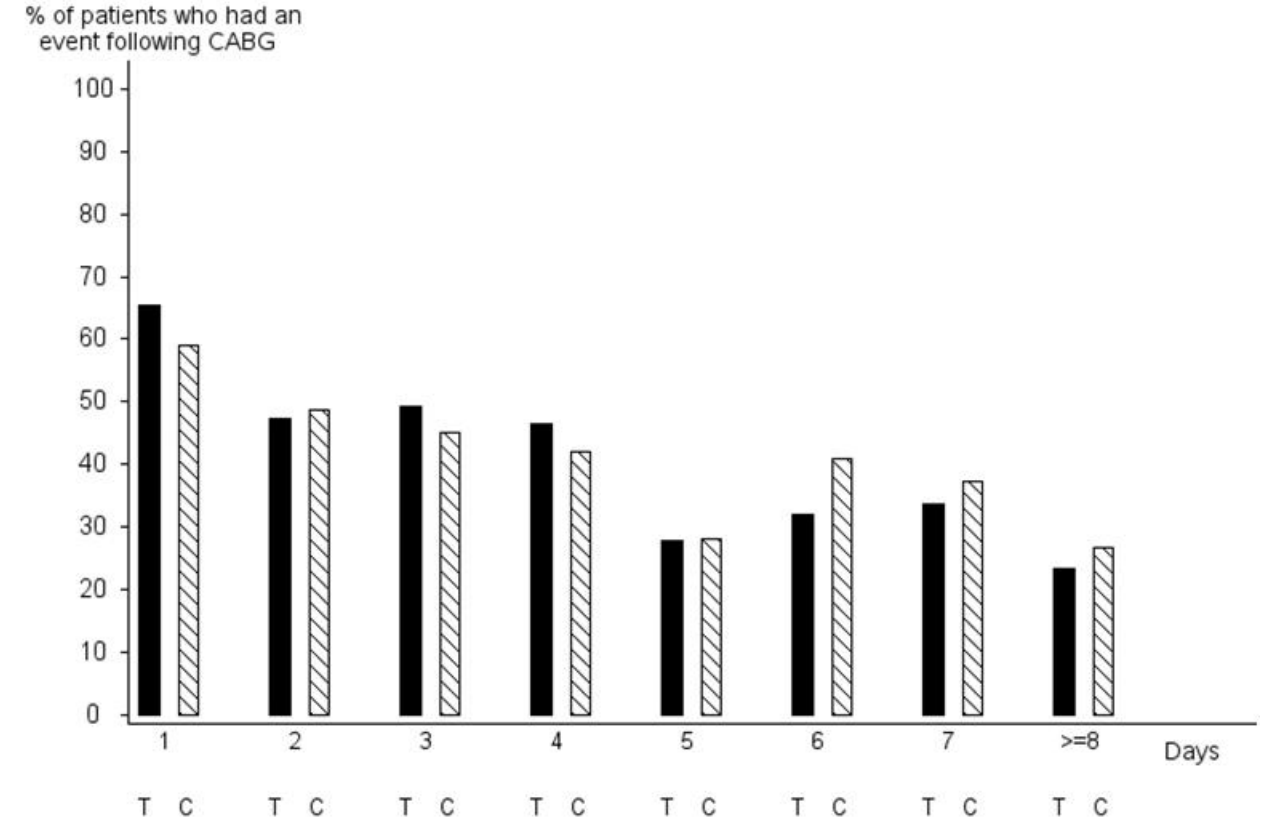
PLATO Minor bleed: requires medical intervention to stop or treat bleeding.
PLATO Major bleed: any one of the following: fatal; intracranial; intrapericardial with cardiac tamponade; hypovolemic shock or severe hypotension requiring intervention; significantly disabling (e.g., intraocular with permanent 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.

* 90 mg BID

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)

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.

* 90 mg BID

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* N=6958	Placebo N=6996
	Events / 1000 patient years	Events / 1000 patient years
TIMI Major	8	3
Fatal	1	1
Intracranial hemorrhage	2	1
TIMI Major or Minor	11	5

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.
* 60 mg BID

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)

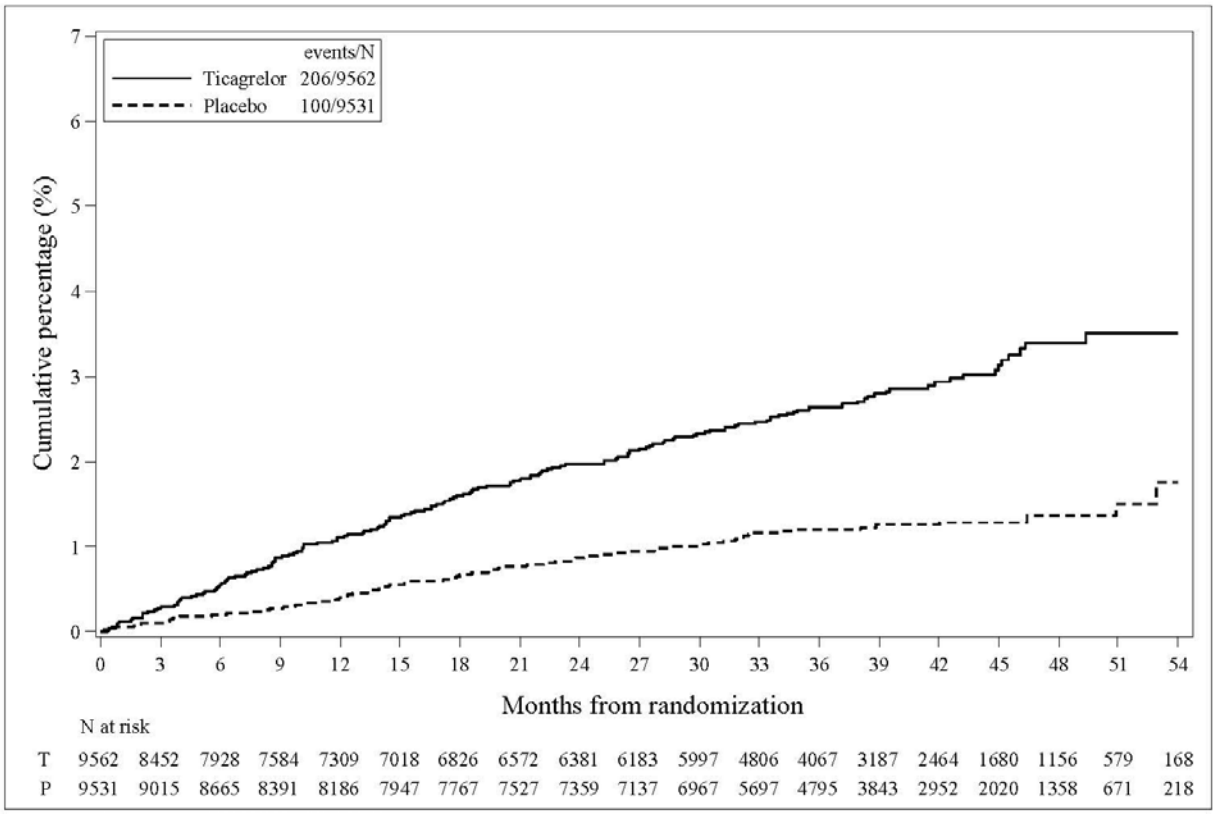
	BRILINTA* **N=6958**	**Placebo N=6996**
Dyspnea	14.2%	5.5%
Dizziness	4.5%	4.1%
Diarrhea	3.3%	2.5%

*60 mg BID

Bleeding in THEMIS (Prevention of major CV events in patients with CAD and Type 2 Diabetes Mellitus)

The Kaplan-Meier curve of time to first TIMI Major bleeding event is presented in Figure 3.

Figure 3 - Time to first TIMI Major bleeding event (THEMIS)



T = Ticagrelor; P = Placebo; N = Number of patients

The bleeding events in THEMIS are shown below in Table 6.

Table 6 – Bleeding events (THEMIS)

	BRILINTA N=9562	**Placebo N=9531**
	Events / 1000 patient years	**Events / 1000 patient years**
TIMI Major	9	4
TIMI Major or Minor	12	5
TIMI Major or Minor or Requiring medical attention	46	18
Fatal bleeding	1	0
Intracranial hemorrhage	3	2

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, PEGASUS and THEMIS 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).

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.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of BRILINTA. Because these reactions are reported voluntarily from a population of an unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and lymphatic system disorders: Thrombotic Thrombocytopenic Purpura (TTP) has been rarely reported with the use of BRILINTA. TTP is a serious condition which can occur after a brief exposure (<2 weeks) and requires prompt treatment.

Immune system disorders: Hypersensitivity reactions including angioedema *[see Contraindications (4.3)]*.

Skin and subcutaneous tissue disorders: Rash

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 Opioids

As with other oral $P2Y_{12}$ inhibitors, co-administration of opioid agonists delay and reduce the absorption of ticagrelor and its active metabolite presumably because of slowed gastric emptying *[see Clinical Pharmacology (12.3)]*. Consider the use of a parenteral anti-platelet agent in acute coronary syndrome patients requiring co-administration of morphine or other opioid agonists.

7.5 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)]*.

7.6 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

Risk Summary

Available data from case reports with BRILINTA use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Ticagrelor given to pregnant rats and pregnant rabbits during organogenesis caused structural abnormalities in the offspring at maternal doses about 5 to 7 times the

maximum recommended human dose (MRHD) based on body surface area. When ticagrelor was given to rats during late gestation and lactation, pup death and effects on pup growth were seen at approximately 10 times the MRHD (*see Data).*

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

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 (5.5 times the MRHD on a mg/m^2 basis), 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).

8.2 Lactation

Risk Summary

There are no data on the presence of ticagrelor or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. Ticagrelor and its metabolites were present in rat milk at higher concentrations than in maternal plasma. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Breastfeeding is not recommended during treatment with BRILINTA.

8.4 Pediatric Use

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

8.5 Geriatric Use

About half of the patients in PLATO, PEGASUS and THEMIS 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 Warnings and Precautions (5.5) and Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

No dosage adjustment is needed in patients with renal impairment *[see Clinical Pharmacology (12.3)]*.

Patients with End-Stage Renal Disease on dialysis

Clinical efficacy and safety studies with BRILINTA did not enroll patients with end-stage renal disease (ESRD) on dialysis. In patients with ESRD maintained on intermittent hemodialysis, no clinically significant difference in concentrations of ticagrelor and its metabolite and platelet inhibition are expected compared to those observed in patients with normal renal function *[see Clinical Pharmacology (12.3)]*. It is not known whether these concentrations will lead to similar reductions in risk of CV death, myocardial infarction or stroke or similar bleeding risk in patients with ESRD on dialysis as were seen in PLATO, PEGASUS, and THEMIS.

10 OVERDOSAGE

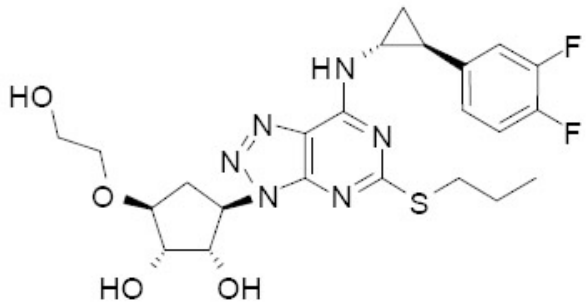
There is currently no known treatment to reverse the effects of BRILINTA, and ticagrelor is not dialyzable. Treatment of overdose should follow local standard medical practice. Bleeding is the expected pharmacologic effect of overdosing. If bleeding occurs, appropriate supportive measures should be taken.

Platelet transfusion did not reverse the antiplatelet effect of BRILINTA in healthy volunteers and is unlikely to be of clinical benefit in patients with bleeding.

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 4, 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 5, mean maximum IPA following the last dose of ticagrelor was 88% and 62% for clopidogrel. The insert in Figure 5 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 4 – Mean inhibition of platelet aggregation (±SE) following single oral doses of placebo, 180 mg ticagrelor or 600 mg clopidogrel

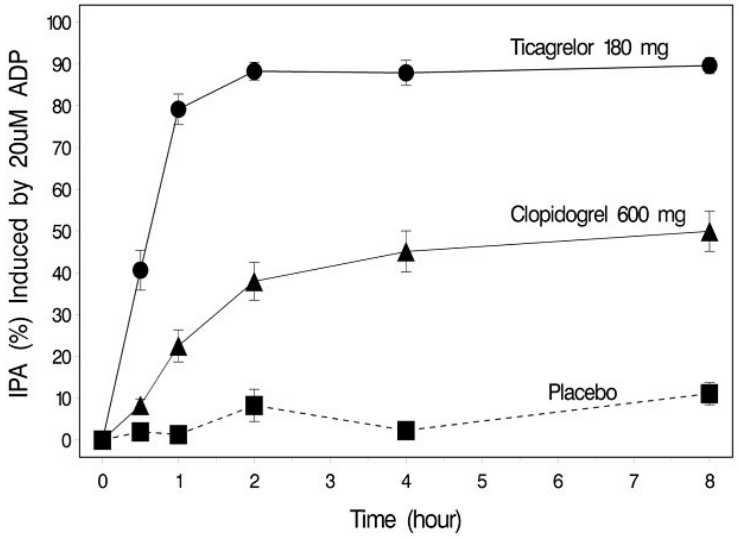
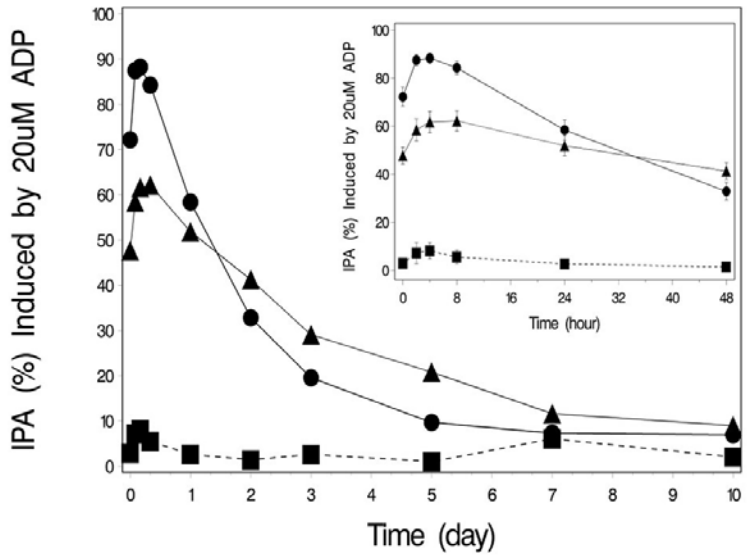


Figure 5 – Mean inhibition of platelet aggregation (IPA) following 6 weeks on placebo, ticagrelor 90 mg twice daily, or clopidogrel 75 mg daily



● **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.

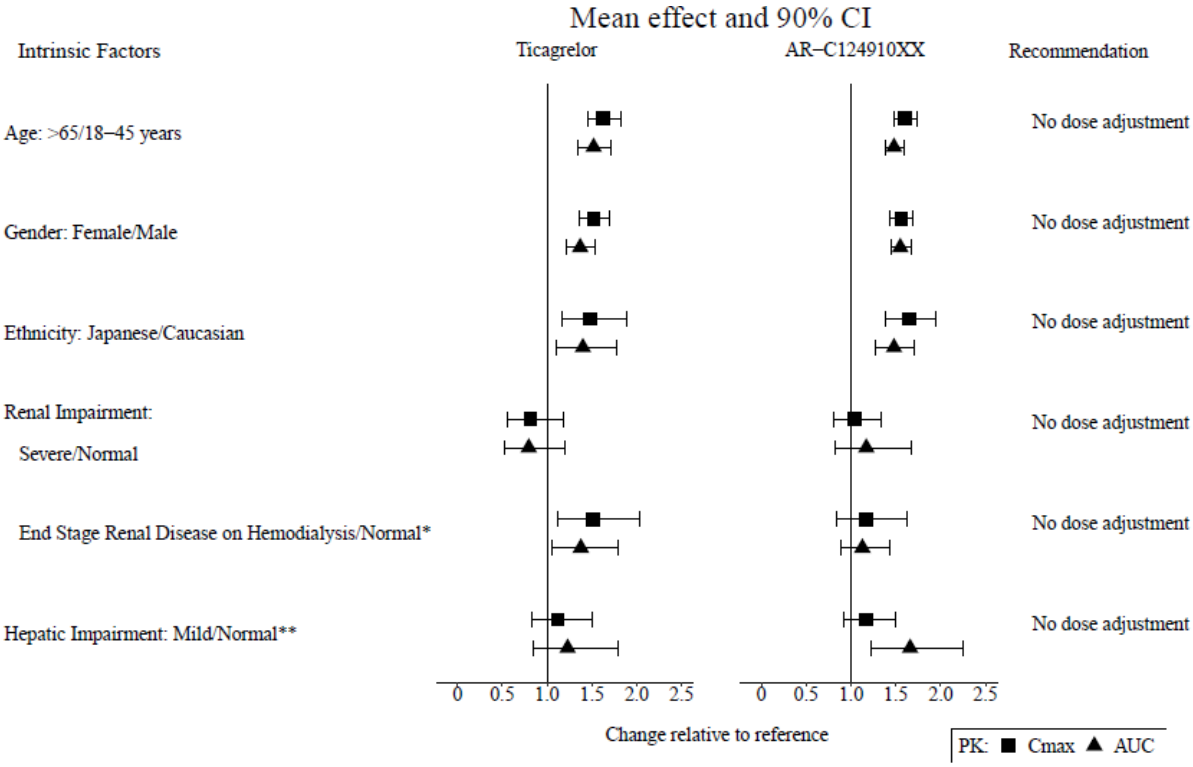
Specific Populations

The effects of age, gender, ethnicity, renal impairment and mild hepatic impairment on the pharmacokinetics of ticagrelor are presented in Figure 6. Effects are modest and do not require dose adjustment.

Patients with End-Stage Renal Disease on Hemodialysis

In patients with end stage renal disease on hemodialysis AUC and C_{max} of BRILINTA 90 mg administered on a day without dialysis were 38% and 51% higher respectively, compared to subjects with normal renal function. A similar increase in exposure was observed when BRILINTA was administered immediately prior to dialysis showing that BRILINTA is not dialyzable. Exposure of the active metabolite increased to a lesser extent. The IPA effect of BRILINTA was independent of dialysis in patients with end stage renal disease and similar to healthy adults with normal renal function.

Figure 6 – Impact of intrinsic factors on the pharmacokinetics of ticagrelor



* Single dose of BRILINTA administered on a day without dialysis.
** BRILINTA has not been studied in patients with moderate or severe hepatic impairment.

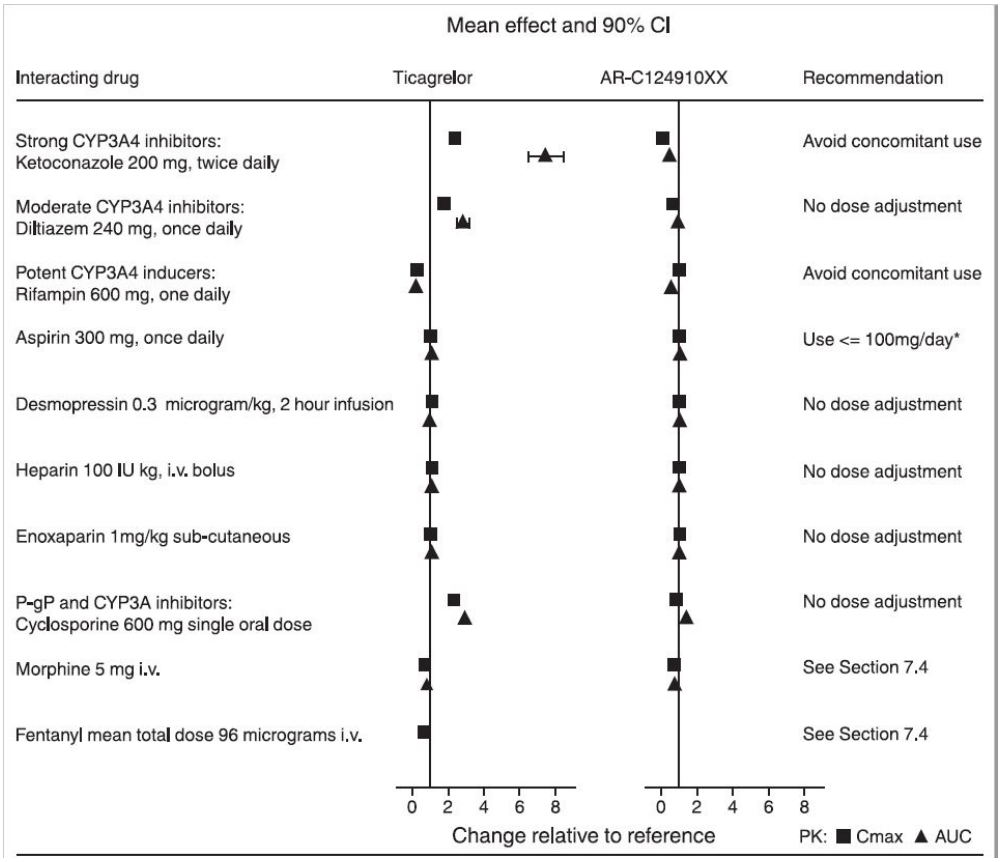
Effects of Other Drugs on BRILINTA

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 7 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.

Co-administration of 5 mg intravenous morphine with 180 mg loading dose of ticagrelor decreased observed mean ticagrelor exposure by up to 25% in healthy adults and up to 36% in ACS patients undergoing PCI. T_{max} was delayed by 1-2 hours. Exposure of the active metabolite decreased to a similar extent. Morphine co-administration did not delay or decrease platelet inhibition in healthy adults. Mean platelet aggregation was higher up to 3 hours post loading dose in ACS patients co-administered with morphine.

Co-administration of intravenous fentanyl with 180 mg loading dose of ticagrelor in ACS patients undergoing PCI resulted in similar effects on ticagrelor exposure and platelet inhibition.

Figure 7 – Effect of co-administered drugs on the pharmacokinetics of ticagrelor



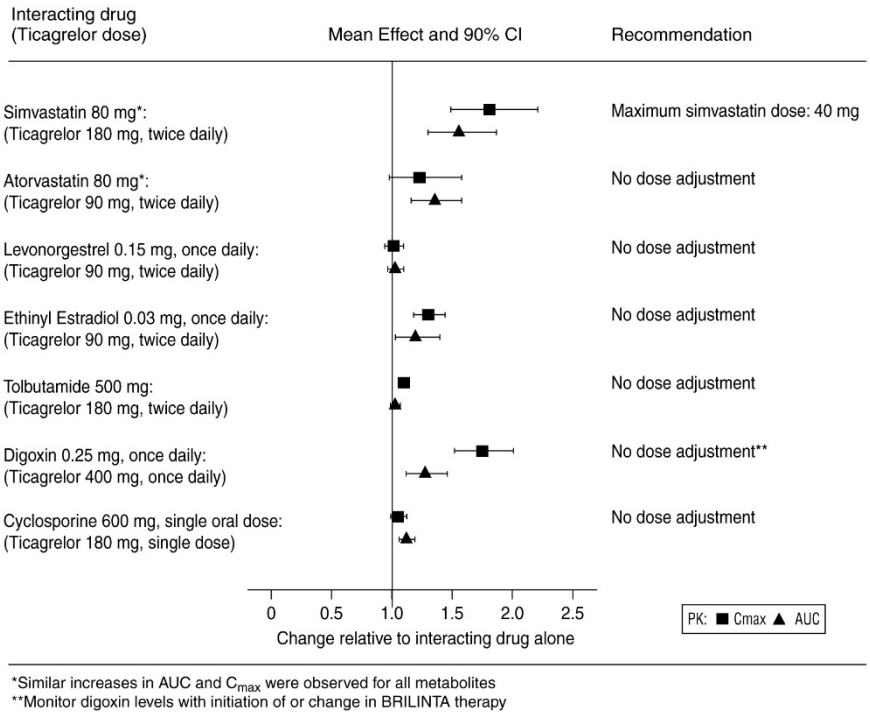
**See Dosage and Administration (2)*

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 8.

Figure 8 – Impact of BRILINTA on the pharmacokinetics of co-administered drugs



*Similar increases in AUC and C_{max} were observed for all metabolites
**Monitor digoxin levels with initiation of or change in BRILINTA therapy

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 (NCT00391872) 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 276 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 7 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 7 – Patients with outcome events (PLATO)

	BRILINTA* **N=9333**	**Clopidogrel N=9291**	**Hazard Ratio (95% CI)**	***p*-value**
	Events / 1000 patient years	**Events / 1000 patient years**		
Composite of CV death, MI, or stroke	111	131	0.84 (0.77, 0.92)	0.0003
CV death	32	43	0.74	
Non-fatal MI	64	76	0.84	
Non-fatal stroke	15	12	1.24	
Secondary endpoints†				

	BRILINTA* N=9333	Clopidogrel N=9291	Hazard Ratio (95% CI)	*p*-value
	Events / 1000 patient years	Events / 1000 patient years		
CV death	45	57	0.79 (0.69, 0.91)	0.0013
MI‡	65	76	0.84 (0.75, 0.95)	0.0045
Stroke‡	16	14	1.17 (0.91, 1.52)	0.22
All-cause mortality	51	65	0.78 (0.69, 0.89)	0.0003

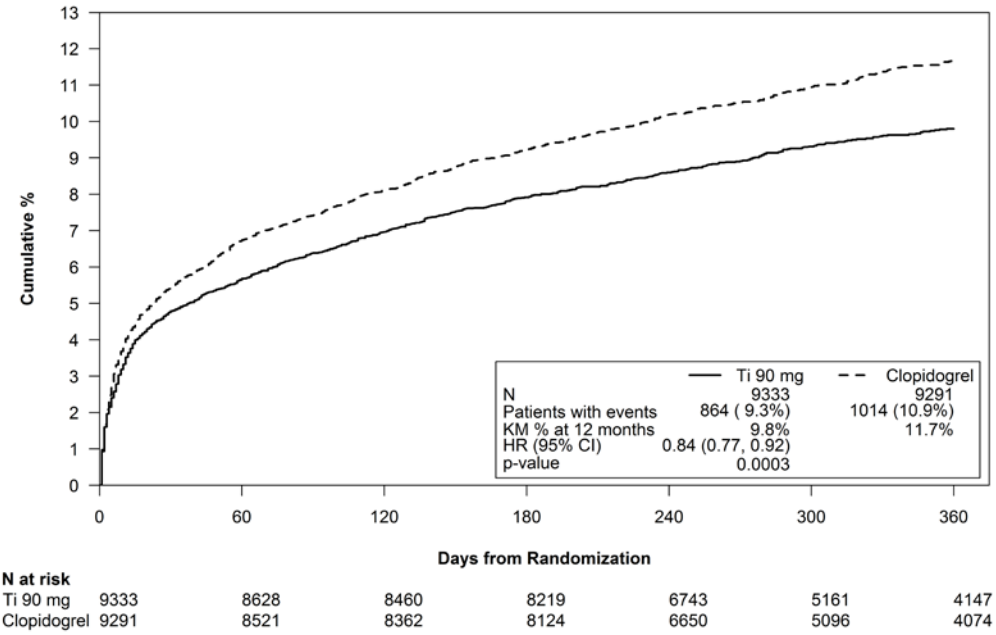
*Dosed at 90 mg bid.

†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.

‡Including patients who could have had other non-fatal events or died.

The Kaplan-Meier curve (Figure 9) 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 9 – Time to first occurrence of CV death, MI, or stroke (PLATO)



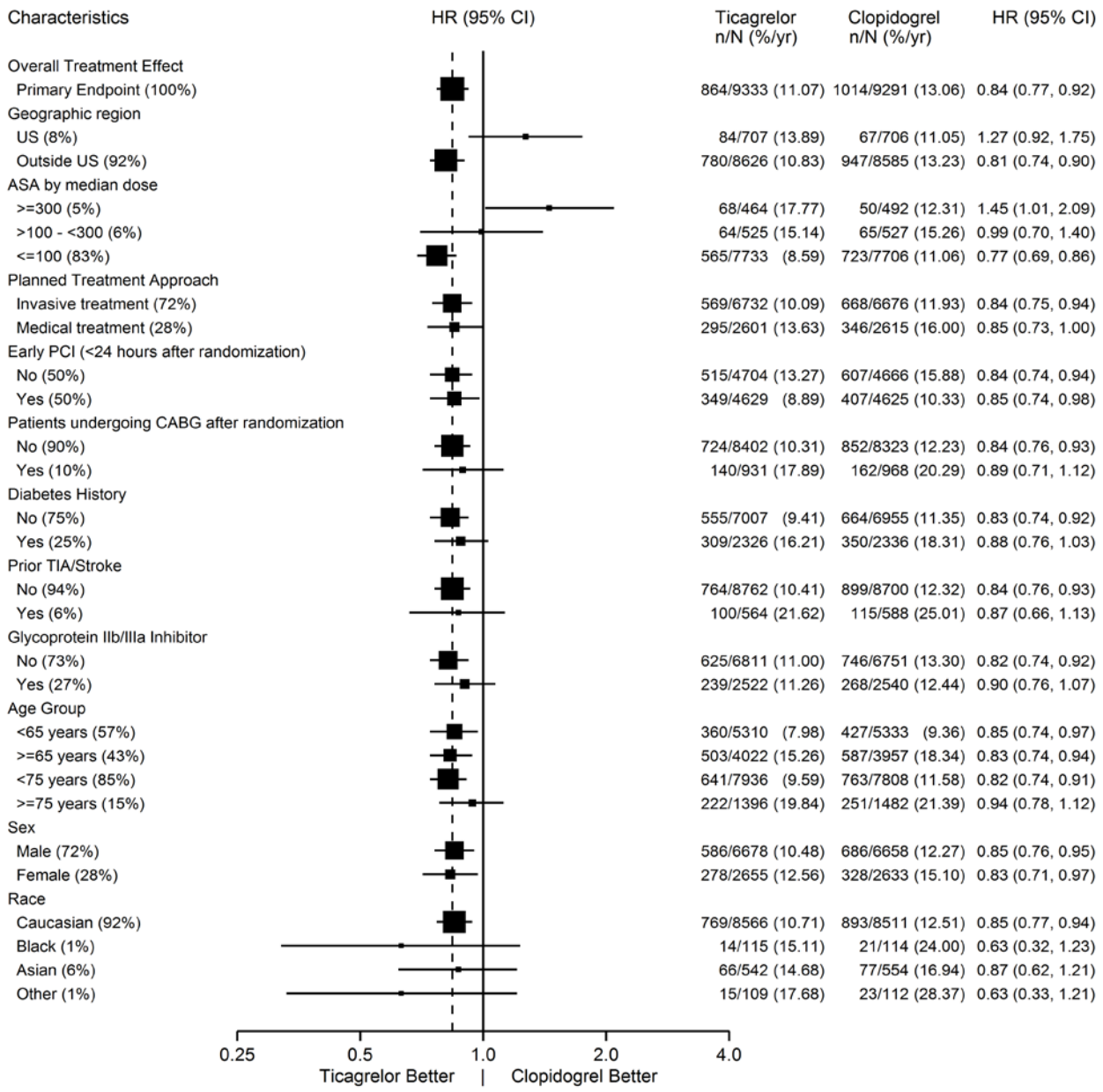
The curves separate by 30 days [relative risk reduction (RRR) 12%] and continue to diverge throughout the 12-month treatment period (RRR 16%).

Among 11,289 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 10. 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 10 – 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

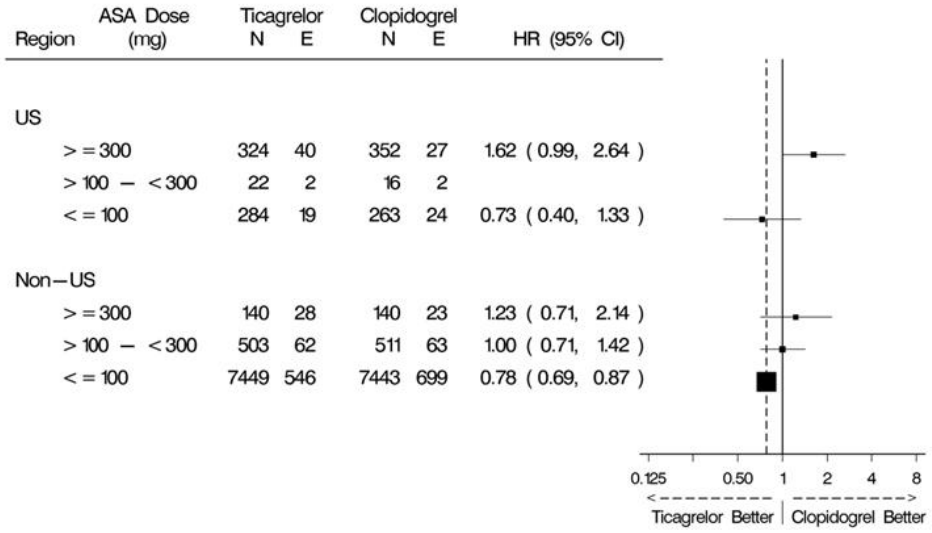
Results in the rest of the world compared to effects in North America (US and Canada) show a smaller effect in North America, numerically inferior to the control and driven by the US subset. The statistical test for the US/non-US comparison is statistically significant (p=0.009), and the same trend is 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 11 shows results by region and dose.

Figure 11 – 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 (NCT01225562) was a 21,162-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.

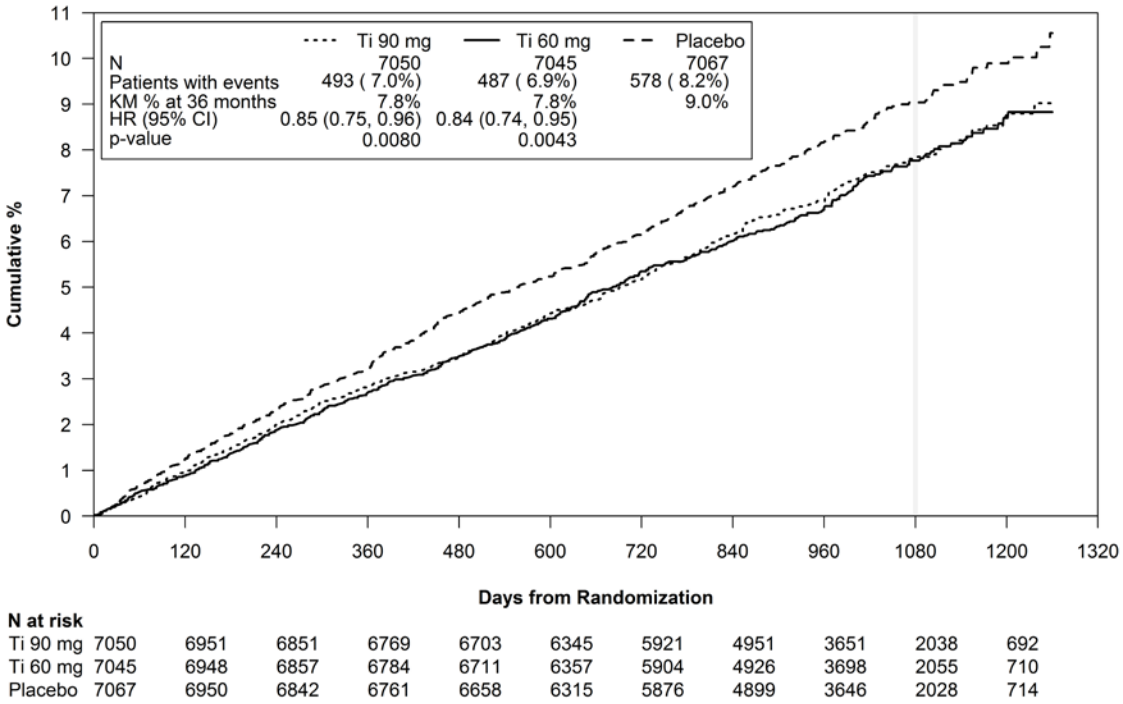
Patients were predominantly male (76%) Caucasian (87%) with a mean age of 65 years, and 99.8% of patients received prior aspirin therapy. See Table 8 for key baseline features.

Table 8 – 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 $P2Y_{12}$ platelet inhibitor therapy	89%
Lipid lowering therapy	94%

The Kaplan-Meier curve (Figure 12) shows time to first occurrence of the primary composite endpoint of CV death, non-fatal MI or non-fatal stroke.

Figure 12 – Time to First Occurrence of CV death, MI or Stroke (PEGASUS)



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

Table 9 – Incidences of the primary composite endpoint, primary composite endpoint components, and secondary endpoints (PEGASUS)

	BRILINTA* **N=7045**	**Placebo N=7067**	**HR (95% CI)**	***p*-value**
	Events / 1000 patient years	**Events / 1000 patient years**		
Time to first CV death, MI, or stroke†	26	31	0.84 (0.74, 0.95)	0.0043
CV Death‡,§	9	11	0.83 (0.68, 1.01)	
Myocardial infarction§	15	18	0.84 (0.72, 0.98)	
Stroke§	5	7	0.75 (0.57, 0.98)	
All-cause mortality‡	16	18	0.89 (0.76, 1.04)	

CI = Confidence interval; CV = Cardiovascular; HR = Hazard ratio; MI = Myocardial infarction; N = Number of patients.

*60 mg BID

† Primary composite endpoint

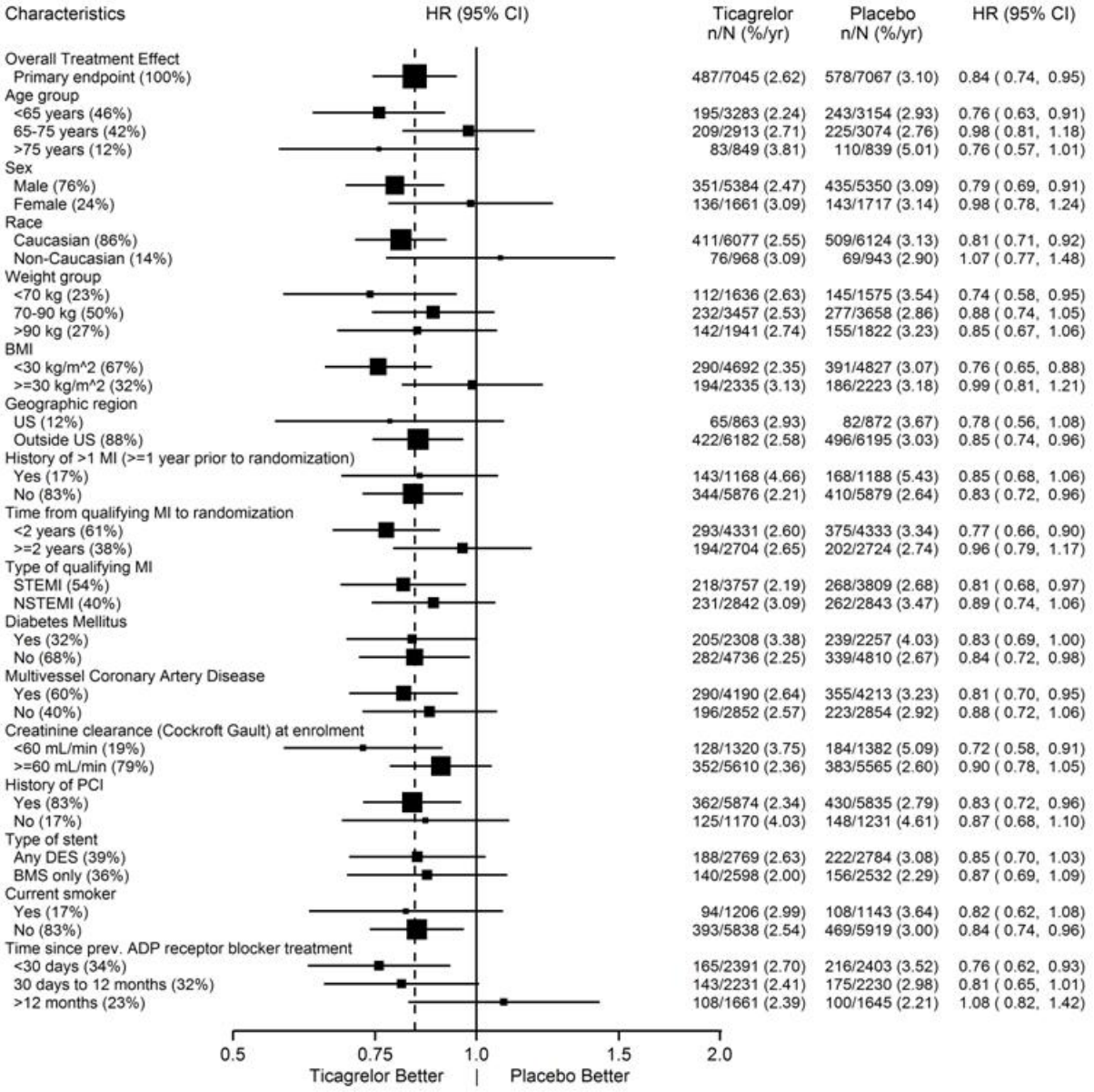
‡ Secondary endpoints

§ The event rate for the components CV death, MI and stroke are calculated from the actual number of first events for each component.

In PEGASUS, the relative risk reduction (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 13.

Figure 13 – 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.

14.2 Coronary Artery Disease but No Prior Stroke or Myocardial Infarction

THEMIS

The THEMIS study (NCT01991795) was a double-blind, parallel group, study in which 19,220 patients with CAD and Type 2 Diabetes Mellitus (T2DM) but no history of MI or stroke were randomized to twice daily BRILINTA or placebo,

on a background of 75-150 mg of aspirin. The primary endpoint was the composite of first occurrence of CV death, MI, and stroke. CV death, MI, ischemic stroke, and all-cause death were assessed as secondary endpoints.

Patients were eligible to participate if they were ≥ 50 years old with CAD, defined as a history of PCI or CABG, or angiographic evidence of ≥ 50% lumen stenosis of at least 1 coronary artery and T2DM treated for at least 6 months with glucose-lowering medication. Patients with previous intracerebral hemorrhage, gastrointestinal bleeding within the past 6 months, known bleeding diathesis, and coagulation disorder were excluded. Patients taking anticoagulants or ADP receptor antagonists were excluded from participating, and patients who developed an indication for those medications during the trial were discontinued from study drug.

Patients were treated for a median of 33 months and up to 58 months.

Patients were predominantly male (69%) with a mean age of 66 years. At baseline, 80% had a history of coronary artery revascularization; 58% had undergone PCI, 29% had undergone a CABG and 7% had undergone both. The proportion of patients studied in the US was 12%. Patients in THEMIS had established CAD and other risk factors that put them at higher cardiovascular risk; see Table 10.

Table 10 – Baseline risk factors (THEMIS)

Risk factor	% Patients
Type 2 Diabetes Mellitus	100%
Hypertension	92%
Dyslipidemia	87%
Multi-vessel CAD	62%
Obesity	43%
Heart failure	16%
Current smoking	11%
Chronic kidney disease	9%

BRILINTA was superior to placebo in reducing the incidence of CV death, MI, or stroke. The effect on the composite endpoint was driven by the individual components MI and stroke; see Table 11.

Table 11 – Primary composite endpoint, primary endpoint components, and secondary endpoints (THEMIS)

	BRILINTA N=9619	Placebo N=9601	HR (95% CI)	*p*-value
	Events / 1000 patient years	Events / 1000 patient years		
Time to first CV death, MI, or stroke*	24	27	0.90 (0.81, 0.99)	0.04
CV death†	12	11	1.02 (0.88, 1.18)	
Myocardial infarction†	9	11	0.84 (0.71, 0.98)	
Stroke†	6	7	0.82 (0.67, 0.99)	
Secondary endpoints				
CV death	12	11	1.02 (0.88, 1.18)	
Myocardial infarction	9	11	0.84 (0.71, 0.98)	
Ischemic stroke	5	6	0.80 (0.64, 0.99)	
All-cause death	18	19	0.98 (0.87, 1.10)	

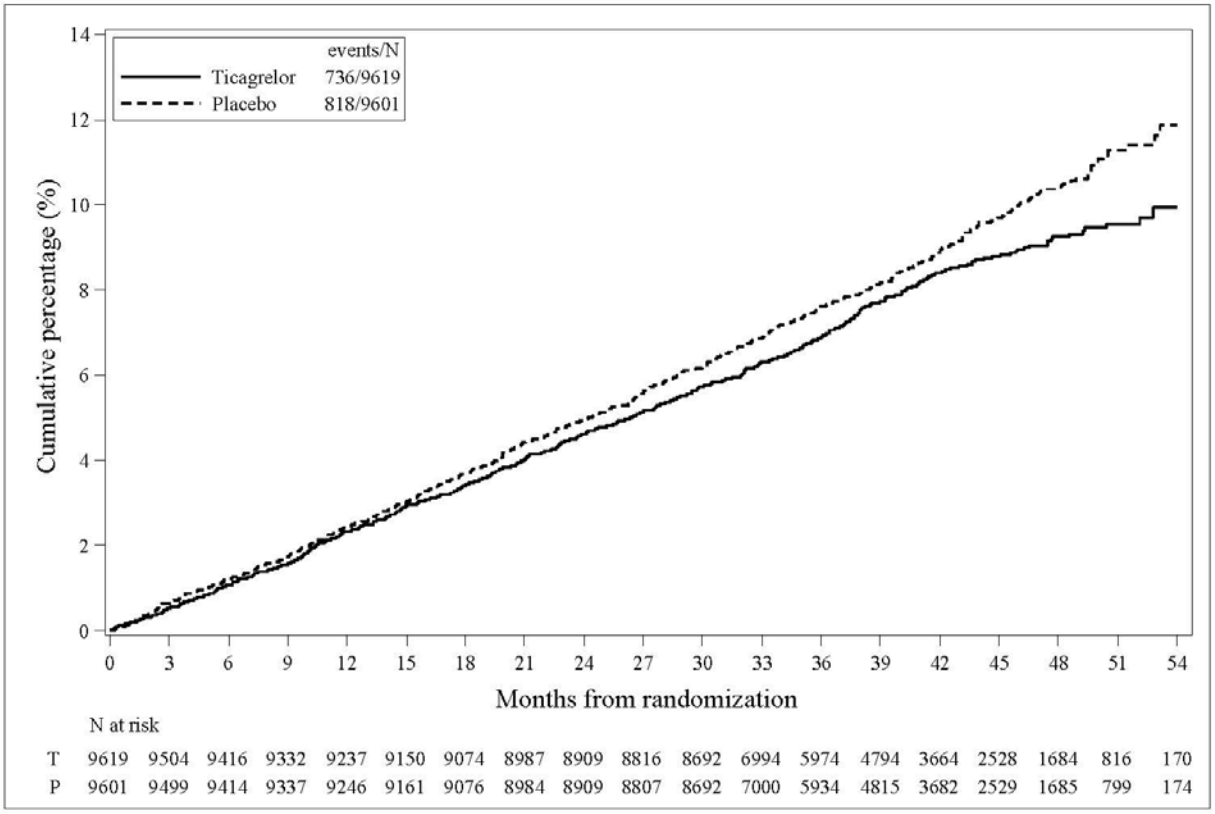
CI = Confidence interval; CV = Cardiovascular; HR = Hazard ratio; MI = Myocardial infarction.

* Primary endpoint

† The event rate for the components CV death, MI and stroke are calculated from the actual number of first events for each component.

The Kaplan-Meier curve (Figure 14) shows time to first occurrence of the primary composite endpoint of CV death, MI, or stroke.

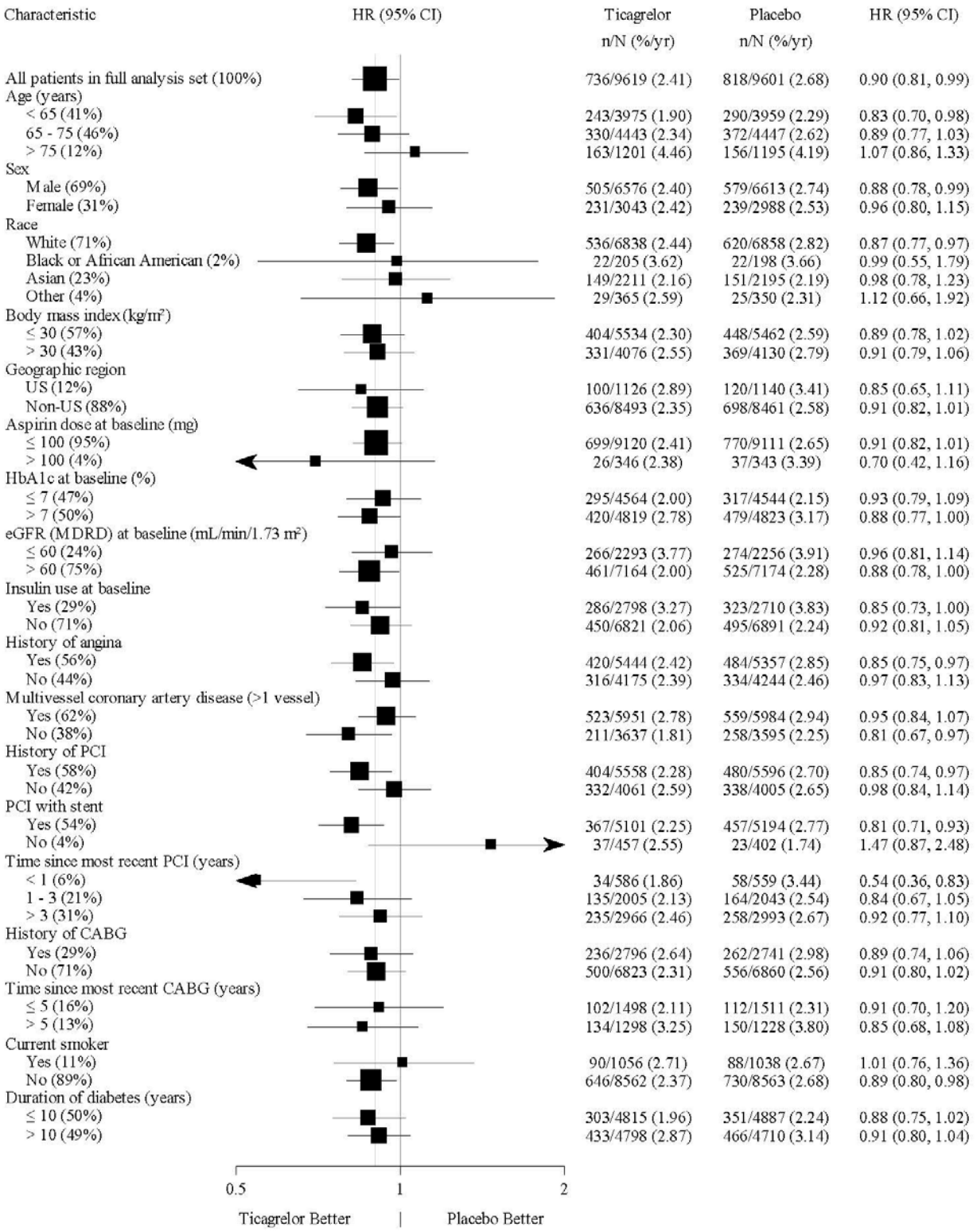
Figure 14 - Time to First Occurrence of CV death, MI or Stroke (THEMIS)



T = Ticagrelor; P = Placebo; N = Number of patients.

The treatment effect of BRILINTA appeared similar across patient subgroups, see Figure 15.

Figure 15 –Subgroup analyses of ticagrelor (THEMIS)



Note: The figure above presents effects in various subgroups all of which are baseline characteristics. 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 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

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.

Advise women that breastfeeding is not recommended during treatment with BRILINTA *[see Use in Specific Populations (8.2)]*.

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

Distributed by: AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850

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:

- decrease your risk of death, heart attack, and stroke in people with a blockage of blood flow to the heart (acute coronary syndrome or ACS) or a history of a heart attack. BRILINTA can also decrease your risk of blood clots in your stent in people who have received stents for the treatment of ACS.
- decrease your risk of a first heart attack or stroke in people who have a condition where the blood flow to the heart is decreased (coronary artery disease or CAD) who are at high risk for having a heart attack or stroke.

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

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.

Before taking BRILINTA, tell your doctor about all of your medical conditions, 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
- medicine used to control pain
- an anti-fungal medicine by mouth
- an antibiotic medicine
- an anti-seizure medicine
- a blood thinner medicine
- rifampin

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.

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 the safe and effective use of 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 Pharmaceuticals 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: 05/2020

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/s/

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022433Orig1s028

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	May 1, 2020
From	Division of Cardiology and Nephrology (DCN): Karen A. Hicks, M.D., Cross-Discipline Team Leader
Subject	Cross-Discipline Team Leader Review
NDA/BLA # and Supplement#	NDA 22433, S-028, eCTD Sequence No.: 0560
Applicant	AstraZeneca
Date of Submission	July 30, 2019 (received on July 31, 2019)
PDUFA Goal Date	May 30, 2020
Proprietary Name	BRILINTA®
Established or Proper Name	Ticagrelor
Dosage Form(s)	60 mg and 90 mg tablets
Applicant's Proposed Indication(s)/Population(s)	"BRILINTA is a $P2Y_{12}$ platelet inhibitor indicated to reduce (b) (4) myocardial infarction (MI), and stroke in patients with coronary artery disease (CAD) and type 2 diabetes mellitus (T2DM) (b) (4)
Applicant's Proposed Dosing Regimen(s)	60 mg tablet orally twice daily
Recommendation on Regulatory Action	*Approval*
Recommended Indication/Population	"BRILINTA is a $P2Y_{12}$ platelet inhibitor indicated to reduce the risk of a first MI or stroke in patients with type 2 diabetes mellitus (T2DM) and coronary artery disease (CAD)."
Recommended Dosing Regimen(s)	60 mg tablet orally twice daily

This memorandum is based on the following reviews and consults:

Discipline	Reviewer(s)
Project Manager	Bridget Kane, M.S.
Clinical and Biometrics	Fred Senatore, M.D., Ph.D., FACC (Efficacy and Safety); Christine Garnett, Pharm.D. (ASCVD Risk Assessment); Lars Johannesen, Ph.D. (ASCVD Risk Assessment); Jialu Zhang, Ph.D. (Biometrics); Karen A. Hicks, M.D. (CDTL)
Decision Support and Analysis Team, Office of Program & Strategic Analysis (OPSA)	Leila Lackey, MHS, DEnv; Graham Thompson, B.S.; and Sara Eggers, Ph.D.
Division of Medication Error Prevention and Analysis	Grace P. Jones, Pharm.D.; Chi-Ming (Alice) Tu, Pharm.D.
Patient Labeling	Morgan Walker, Pharm.D., MBA, CPH
Office of Prescription Drug Promotion (OPDP)	Zarna Patel, Pharm.D.

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

BRILINTA® (ticagrelor) is a $P2Y_{12}$ platelet inhibitor approved in 2011 for the treatment of patients with acute coronary syndrome (ACS) to reduce the rate of cardiovascular (CV) death, myocardial infarction (MI), and stroke. In 2015, BRILINTA® was approved for the same indication in patients with a history of MI. On July 30, 2019, AstraZeneca submitted NDA 22433 to also market BRILINTA® for a primary prevention claim "to reduce (b) (4) MI, and stroke in patients with coronary artery disease (CAD) and type 2 diabetes mellitus (T2DM) (b) (4) ."

Heart disease is the leading cause of death in the United States (US) and globally (1,2). In 2016, the World Health Organization estimated that 17.9 million individuals died from cardiovascular diseases, comprising 31% of all global deaths (2). Approximately 85% of these deaths were due to MI and stroke. To date, no $P2Y_{12}$ inhibitor has been approved in patients to prevent CV events (i.e., primary prevention). Risk factors for ACS include age, hypertension, hyperlipidemia, diabetes mellitus (DM), family history of premature coronary artery disease, smoking history, obesity, lack of physical activity, unhealthy diet, and during pregnancy, a history of high blood pressure, preeclampsia, or diabetes. Patients with T2DM have a 2 to 4-fold increase in the risk of coronary heart disease and stroke as well as a 1.5 to 3.6-fold increase in mortality (3). In patients with T2DM and CAD, the risk of CV death, MI, or stroke is increased 2-fold compared to patients with T2DM and other CV risk factors but no known CAD (4).

The Effect of Ticagrelor on Health outcomes in diabEtes Mellitus patients Intervention Study (THEMIS) (ClinicalTrials.gov NCT01991795) was a double-blind, parallel group study in which 19,220 patients with T2DM and CAD but no history of MI or stroke were randomized 1:1 to twice daily ticagrelor or placebo, on a background of 75-150 mg of aspirin. Results of the study have been published (5). The study was conducted between February 2014 and January 2019 at 1315 centers in 42 countries. Based on the results of the Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis in Myocardial Infarction 54 (PEGASUS-TIMI 54) study which demonstrated similar efficacy for the 90 mg and 60 mg twice daily oral doses, patients on ticagrelor 90 mg (or matching placebo) were switched to ticagrelor 60 mg (or matching placebo) approximately one year after enrollment began according to their previous randomization. The primary endpoint was the time from randomization to the first occurrence of any event from the composite of CV death, MI, or stroke. Endpoints were adjudicated by a blinded committee of experts. The median duration of treatment was 32.5 months for both doses of ticagrelor and 35.4 months for placebo.

Dr. Zhang's analysis of adjudicated and investigator-reported events is summarized for the primary endpoint as follows:

Table 1. Primary Endpoint Events (time to first occurrence of cardiovascular death, myocardial infarction, or stroke), full analysis set (FAS) population

		Ticagrelor (N = 9619)		Placebo (N = 9601)			
		Patients with Events (%)	KM% at 36 Months	Patients with Events (%)	KM% at 36 Months	Hazard Ratio (95% CI)	p-value
Adjudicated	Composite of CV death, MI, and stroke	736 (7.7%)	6.9%	818 (8.5%)	7.6%	0.90 (0.81-0.99)	0.04
	CV death	364 (3.8%)	3.3%	357 (3.7%)	3.0%	1.02 (0.88-1.18)	
	MI	274 (2.8%)	2.6%	328 (3.4%)	3.3%	0.84 (0.71-0.98)	
	Stroke	180 (1.9%)	1.7%	221 (2.3%)	2.1%	0.82 (0.67-0.99)	
Investigator-Reported	Composite of CV death, MI, and stroke	742 (7.7%)	7.0%	823 (8.6%)	7.6%	0.90 (0.82, 1.00)	0.04

Source: Jialu Zhang, Ph.D. (Division of Biometrics I)
CI: confidence interval; CV: cardiovascular; KM: Kaplan-Meier; MI: myocardial infarction;

Ticagrelor significantly reduced the risk of the time to the first occurrence of the primary composite endpoint of CV death, MI, or stroke. This result was largely driven by the effect on MI (HR 0.84, 95% CI: 0.71-0.98) and stroke (HR 0.82, 95% CI: 0.67-0.99). The numerical difference in CV deaths in the treatment groups was negligible. Results for the investigator-reported primary endpoint events were similar (HR 0.90, 95% CI: 0.82-1.00).

No new safety issues have been identified. The incidence of TIMI Major bleeding events was similar in both dose groups and occurred twice as often in the ticagrelor arm (2.2%) compared to placebo (1.0%) at 36 months. The incidence of fatal bleeding events was 0.2% and 0.1% in the ticagrelor and placebo groups, respectively. The incidence of intracranial hemorrhage was also balanced between treatment groups (0.7% ticagrelor vs. 0.5% placebo). In addition, the incidence of TIMI Major bleeding events with ticagrelor in THEMIS was similar to that observed in the PEGASUS-TIMI 54 trial.

The benefit/risk assessment compared the reduction in primary endpoint events to the risk of TIMI Major bleeding events. These analyses demonstrated that to prevent 1 primary endpoint event and to cause 1 TIMI Major bleeding event, 143 patients and 67 patients, respectively, required treatment with ticagrelor for 36 months.

The Decision Support and Analysis Team (DSAT) also performed a multiple criteria decision analysis (MCDA) incorporating quantitative judgments from members of the review team about the relative importance of outcomes. Results of the MCDA were highly dependent on ticagrelor's perceived effect on CV death and whether CV death was included. DSAT concluded that "given the clinical assumptions about CV death . . . the benefit-risk of ticagrelor is likely neither clearly favorable nor clearly unfavorable to the target patient population as a whole." Hence, "DSAT's recommendation is that the analysis should be viewed as an indication that the decision is a close call and relies heavily on the review team's and the signatory's judgment in light of the therapeutic context and the identified uncertainties regarding benefit and risks."

Given the known antiplatelet effects of ticagrelor, the neutral effect on CV death in THEMIS, and the statistically significant reduction in CV death in the Platelet Inhibition and Patient Outcomes (PLATO) trial, the clinical review team concluded that the benefit of ticagrelor narrowly outweighs the risk. Although the treatment effect is small, the clinical review team is in agreement that THEMIS provides substantial evidence of ticagrelor's effectiveness in reducing the risk of a first MI or stroke in patients with T2DM and CAD.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Heart disease is the leading cause of death in the United States (US) and globally (1,2). • In 2016, the World Health Organization (WHO) estimated that 17.9 million individuals died from CV diseases, comprising 31% of all global deaths. Approximately 85% of these deaths were due to MI and stroke. • In 2017, over 647,000 deaths in the US were attributed to diseases of the heart. • Globally, approximately 422 million individuals have diabetes and 1.6 million deaths annually are directly attributed to diabetes. • In the US, approximately 34.2 million individuals have diabetes and 88 million adults have prediabetes (6). Diabetes is the 7th leading cause of death (6). In 2017, over 83,000 deaths were attributed to diabetes. • T2DM accounts for approximately 90 - 95% of all diagnosed cases of diabetes (6). • Patients with T2DM have a 2 to 4-fold increase in the risk of coronary heart disease and stroke as well as a 1.5 to 3.6-fold increase in mortality (3). • In patients with T2DM and CAD, the risk of CV death, MI, or stroke is increased 2-fold compared to patients with T2DM and other CV risk factors but no known CAD (4). • Acute coronary syndrome (ACS) is a medical emergency and includes ST-elevation MIs (STEMIs), non-ST-elevation MIs (NSTEMIs), and unstable angina. • Death from sudden coronary thrombosis (MI) occurs from 3 main causes: 1) plaque rupture (65%); plaque erosion (30%); and calcified nodule (5%).	Heart disease is the leading cause of death globally. Heart disease and T2DM are serious and life-threatening diseases.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• To date, no $P2Y_{12}$ inhibitor has been approved in patients to prevent CV events (i.e., primary prevention). • The following therapies are used to treat CAD. Whether a therapy is appropriate is based on presentation (ACS or stable ischemic heart disease [SIHD]) or whether a patient has had a prior MI. o Primary percutaneous coronary intervention (PCI) or thrombolytic therapy (STEMI). o PCI o Coronary artery bypass graft (CABG) surgery o Antiplatelet agents ▪ Aspirin ▪ $P2Y_{12}$ platelet inhibitors ➢ Thienopyridines ✓ Ticlopidine ✓ Clopidogrel ✓ Prasugrel ➢ Nonthienopyridines ✓ Ticagrelor ✓ Cangrelor o Glycoprotein IIb/IIIa receptor inhibitors ▪ Abciximab ▪ Eptifibatide ▪ Tirofiban o Unfractionated heparin o Low molecular weight heparin ▪ Enoxaparin o Direct thrombin inhibitors ▪ Bivalirudin ▪ Argatroban o Factor Xa inhibitor ▪ Fondaparinux ▪ Rivaroxaban	BRILINTA® (ticagrelor) is already approved for the treatment of patients with ACS (2011) and for the treatment of patients with a prior MI (2015) to reduce the rate of CV death, MI, and stroke. The applicant now seeks approval of BRILINTA® for the same indication in patients with CAD and T2DM but no prior stroke or MI (b) (4)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	o Vitamin K antagonist ▪ Warfarin o Protease-activated receptor-1 (PAR-1) antagonist ▪ Vorapaxar o Angiotensin converting enzyme inhibitors, angiotensin receptor blockers beta blockers, calcium channel blockers, nitrates, and ranolazine	
Benefit	• In THEMIS, ticagrelor significantly reduced the risk of time to the first occurrence of the primary composite endpoint of CV death, MI, or stroke (HR 0.90, 95% CI: 0.81-0.99). • This result was largely driven by the effect on MI (HR 0.84, 95% CI: 0.71-0.98) and stroke (HR 0.82, 95% CI: 0.67-0.99). • The numerical difference in CV deaths in the treatment groups was negligible. • Results for the investigator-reported primary endpoint events were similar (HR 0.90, 95% CI: 0.82-1.00).	Although the treatment effect is small, the clinical review team is in agreement that THEMIS provides substantial evidence of ticagrelor's effectiveness in reducing the risk of a first MI or stroke in patients with T2DM and CAD.
Risk and Risk Management	• Safety findings were consistent with the known safety profile of ticagrelor. • There was no significant imbalance of serious adverse events or adverse events of specific interest (i.e., kidney impairment, slow hear rate, gout, pneumonia, shortness of breath, and bleeding) in treatment groups except for bleeding and dyspnea. • The incidence of TIMI Major bleeding events was similar in each dose group and occurred twice as often in the ticagrelor arm (2.2%) compared to placebo (1.0%) at 36 months. • The incidence of fatal bleeding events was 0.2% and 0.1% in the ticagrelor and placebo groups, respectively. • The incidence of intracranial hemorrhage was balanced between treatment groups (0.7% ticagrelor vs. 0.5% placebo). • The incidence of TIMI Major bleeding events in THEMIS was similar to that observed in the previous trial (PEGASUS-TIMI 54). • Compared to placebo, dyspnea occurred 3x as often in the ticagrelor arm. Dyspnea event rates observed in THEMIS were similar to the event rates observed in PEGASUS-TIMI 54.	These risks are included in existing labeling.

2. Background

BRILINTA® (ticagrelor) is a $P2Y_{12}$ platelet inhibitor and inhibits platelet activation and aggregation mediated by the $P2Y_{12}$ ADP-receptor. On July 20, 2011, BRILINTA® received US marketing approval "to reduce the rate of thrombotic cardiovascular (CV) events in patients with acute coronary syndrome (ACS)" (unstable angina, non-ST elevation myocardial infarction, or ST elevation myocardial infarction) based on the results of the Platelet Inhibition and Patient Outcomes (PLATO) trial. Specifically, BRILINTA® reduced the risk of a combined endpoint of CV death, MI, or stroke compared to clopidogrel. The difference between treatments was driven by CV death and MI with no difference in stroke. In patients with PCI, BRILINTA® also reduced the rate of stent thrombosis.

On September 3, 2015, BRILINTA® received approval for the same indication (to reduce the rate of CV death, MI, and stroke) in patients with a history of a MI based on the results of the Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis in Myocardial Infarction 54 (PEGASUS-TIMI 54) trial.

On July 30, 2019, AstraZeneca submitted NDA 22433 to also market BRILINTA® for the same indication in patients with CAD and T2DM (but no prior stroke or MI) (b) (4). The application was filed and classified as a standard review. The principal support for safety and efficacy was provided by The Effect of Ticagrelor on Health outcomes in diabEtes Mellitus patients Intervention Study (THEMIS). The study was conducted between February 2014 and January 2019 at 1315 centers in 42 countries.

For this indication, the applicant proposes to market BRILINTA® as tablets for oral administration in a strength of 60 mg. The recommended dose is 60 mg twice daily with a daily maintenance dose of aspirin of 75-100 mg.

3. Product Quality

There was no proposed change in the drug substance supplier, drug product formulation/ process, and manufacturing site for the drug product.

4. Nonclinical Pharmacology/Toxicology

This submission contained no additional nonclinical studies, and none were expected.

5. Clinical Pharmacology

This submission contained no additional clinical pharmacology studies, and none were expected.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Principal support for efficacy is provided by one phase 3 study, THEMIS. For additional information, see the clinical and statistical review.

The THEMIS Trial – Design and Objectives:

The Effect of Ticagrelor on Health outcomes in diabEtes Mellitus patients Intervention Study (ClinicalTrials.gov NCT01991795) was a multinational, randomized, double-blind, placebo-controlled phase 3b trial to evaluate the effect of ticagrelor on the incidence of CV death, MI, or stroke. Results of the study have been published (5). Patients ≥ 50 years of age with T2DM and CAD were randomized 1:1 to either twice daily ticagrelor or placebo. The original dosing regimen was ticagrelor 90 mg twice daily. Approximately 1 year after enrollment began, the protocol was amended to provide subjects already randomized to ticagrelor 90 mg BID or matching placebo with ticagrelor 60 mg BID or matching placebo according to their previous randomization. Patients with a history of MI or stroke were excluded.

The primary objective was to compare the effect of long-term treatment with ticagrelor twice daily vs. placebo for the prevention of major CV events (composite of CV death, MI, or stroke) in patients with T2DM at high risk of CV events, but without a medical history of previous MI or stroke. Endpoints were adjudicated by a blinded committee of experts.

Inclusion Criteria:

1) Men or women ≥ 50 years of age
2) Diagnosed with T2DM and treated for at least 6 months with glucose-lowering medication prior to screening/enrollment (Visit 1)
3) At high risk of CV events, defined as a history of PCI or CABG or angiographic evidence of ≥ 50% lumen stenosis in at least 1 coronary artery

Key Exclusion Criteria:

1) Previous MI[1] (with the exception of definite secondary MI [e.g., due to coronary revascularization procedure, profound hypotension, hypertensive emergency, tachycardia, or profound anemia])
2) Previous stroke (transient ischemic attack [TIA] is not included in the stroke definition)

[1]Previous MI herein refers to a documented hospitalization with a final diagnosis of spontaneous MI

3) Planned use of ADP receptor antagonists (e.g., clopidogrel, ticlopidine, prasugrel), dipyridamole, or cilostazol. Planned use of aspirin (ASA) treatment at doses > 150 mg qd.
4) Planned coronary, cerebrovascular, or peripheral arterial revascularization
5) Anticipated concomitant oral or intravenous therapy with strong cytochrome P450 3A4 (CYP3A4) inhibitors or CYP3A4 substrates with narrow therapeutic indices that cannot be stopped for the course of the study
6) Need for chronic oral anticoagulant therapy or chronic low-molecular-weight heparin (at venous thrombosis treatment not prophylaxis doses)
7) Known bleeding diathesis or coagulation disorder, or with uncontrolled hypertension (systolic blood pressure ≥ 180 mm Hg and/or diastolic blood pressure ≥ 100 mm Hg)
8) History of previous intracerebral bleed at any time, gastrointestinal bleed within the past 6 months prior to randomization, or major surgery within 30 days prior to randomization
9) Severe liver disease or renal failure requiring dialysis

Study Procedures:

Visit 1 (Day -7 ±7 days) was the screening/enrollment visit. Randomization occurred at Visit 2 (Day 0). The planned visits included a telephone contact (TC) at days 7 and 30, clinic visits at 3 and 6 months, and alternating clinic visits or TCs every 3 months. There was also a Study Closure Visit (or TC in exceptional cases).

Endpoints and Statistical Considerations:

The primary efficacy endpoint was the time from randomization to the first occurrence of any event from the composite of CV death, MI, or stroke (ischemic, hemorrhagic, or unknown etiology).

In hierarchical order, secondary efficacy endpoints were 1) CV death; 2) MI; 3) ischemic stroke; and 4) all-cause death.

Only positively adjudicated events were included in the analyses.

According to the statistical analysis plan (SAP), the primary analysis was intent-to-treat (ITT) using the full analysis set (FAS), defined as all subjects who have been randomized to study treatment irrespective of their protocol adherence and continued participation in the study. The primary analysis was conducted irrespective of dose (90 mg or 60 mg) based on a previous agreement with the United States Food and Drug Administration (FDA). Treatments were compared using a Cox proportional hazards model with a factor for treatment group, using the Efron method for ties.

One interim analysis was performed by the Data Monitoring Committee (DMC) following the accrual and confirmation of 517 adjudicated primary endpoint events.

Planned sample size was 17,000 randomized subjects to collect 750 adjudicated primary endpoint events. Amendments to the SAP increased 1) the sample size to 19,000 randomized subjects; 2) the expected number of primary endpoint events to 1385; 3) the assumed Hazard Ratio from 0.80 to 0.84; 4) maximum treatment duration from 35 to 58 months; 5) minimum follow-up period from 15 to 29 months; 6) mean follow-up period from 24 to 40 months; and 7) enrollment period from 18 to 28 months. Assuming a true hazard ratio (HR) of 0.84 between ticagrelor and placebo, 1385 primary endpoint events would provide a power of 90%.

RESULTS:

Subject Demographics:

Subject demographics are displayed in Table 2. The mean age of subjects enrolled in the trial was 66 years (standard deviation = 8 years), and 12% of the subjects were older than 75 years. Approximately 31% of subjects were women. The subjects were mostly white (71%) and Asian (23%). Only 2% of subjects were black or African American.

Table 2. Subject Demographics

Demographic Parameters	Ticagrelor	Placebo	Total
	N=9619	N=9601	N=19220
Sex n (%)			
Male	6567 (68%)	6613 (69%)	13189 (69%)
Female	3043 (32%)	2988 (31%)	6031 (31%)
Age			
Mean years (SD)	66.3 (7.8)	66.3 (7.8)	66.3 (7.8)
Median (years)	66	66	66
Min, max (years)	46, 92	50, 95	46, 95
Age Group n (%)			
< 50 years	2 (0%)	0 (0%)	2 (0%)
50—64 years	3973 (41%)	3959 (41%)	7932 (41%)
65—75 years	4443 (46%)	4447 (46%)	8890 (46%)
> 75 years	1201 (12%)	1195 (12%)	2396 (12%)
Race			
White	6838 (71%)	6858 (71%)	13696 (71%)
Black or African American	205 (2%)	198 (2%)	403 (2%)
Asian	2211 (23%)	2195 (23%)	4406 (23%)
American Indian or Alaska Native	161 (2%)	152 (2%)	313 (2%)
Native Hawaiian or Other Pacific Islander	7 (0.1%)	7 (0.1%)	14 (0.1%)
Other	197 (2%)	191 (2%)	388 (2%)
Ethnicity			
Hispanic or Latino	1408 (15%)	1368 (14%)	2776 (14%)
Not Hispanic or Latino	8211 (85%)	8233 (86%)	16444 (86%)
Region			
United States of America	1126 (12%)	1140 (12%)	2266 (12%)
Rest of the World			
Canada	364 (4%)	365 (4%)	729 (4%)
Central and South America	1100 (11%)	1078 (11%)	2178 (11%)

Demographic Parameters	Ticagrelor	Placebo	Total
Europe	4884 (51%)	4875 (51%)	9759 (51%)
Asia	2145 (22%)	2143 (22%)	4288 (22%)
Source: Clinical and Statistical Review, Table 10, pages 49-50.			

Approximately 51% of subjects were from Europe. As discussed in the clinical and statistical review, countries not usually considered to be part of Europe, such as Saudi Arabia and South Africa, were included in this classification. Only 12% of subjects were from the US.

Baseline Disease Characteristics:

Baseline disease characteristics are displayed in Table 3 and were balanced between treatment groups. All subjects in the FAS population had T2DM and CAD. Sixty-two percent of subjects had multivessel disease. Ninety-three percent of subjects had hypertension, and 87% of subjects had dyslipidemia. Fifty-eight percent and 29% of subjects had a history of prior PCI or CABG, respectively.

Table 3. Baseline Disease Characteristics

Baseline Disease Characteristics	Ticagrelor	Placebo	Total
	N=9619	N=9601	N=19220
Coronary Artery Disease	9600 (100%)	9592 (100%)	19192 (100%)
-Single Vessel	3637 (38%)	3595 (37%)	7232 (38%)
-Multiple Vessel	5951 (62%)	5984 (62%)	11935 (62%)
Diabetes Mellitus	9613 (100%)	9597 (100%)	19210 (100%)
-Duration: mean years (SD)	11.8 (8.7)	11.7 (8.6)	11.7 (8.6)
-Duration: median years (1st, 3rd quartile)	10 (5, 16)	10 (5, 16)	10 (5, 16)
Complications of Diabetes	2480 (26%)	2430 (25%)	4910 (25%)
-Retinopathy	1023 (11%)	976 (10%)	1999 (10%)
-Autonomic Neuropathy	223 (2%)	202 (2%)	425 (2%)
-Peripheral Neuropathy	1425 (15%)	1416 (15%)	2841 (15%)
-Nephropathy	828 (9%)	847 (9%)	1675 (9%)
Clinical Diagnoses			
-Angina Pectoris	5444 (57%)	5357 (56%)	10810 (56%)
-Myocardial Infarction	72 (1%)	81 (1%)	153 (1%)
-Atrial Fibrillation/Flutter	351 (4%)	356 (4%)	707 (4%)
-Congestive Heart Failure	1543 (16%)	1600 (17%)	3143 (16%)
-Carotid Artery Stenosis	611 (6%)	615 (6%)	1226 (6%)
-Ischemic Stroke	13 (0.1%)	19 (0.2%)	32 (0.2%)
-Transient Ischemic Attack	140 (2%)	164 (2%)	304 (2%)
-Hemorrhagic Stroke	0 (0%)	0 (0%)	0 (0%)
-Peripheral Arterial Disease	827 (9%)	860 (9%)	1687 (9%)

Baseline Disease Characteristics	Ticagrelor	Placebo	Total
-Hypertension	8909 (93%)	8867 (92%)	17776 (93%)
-Dyslipidemia	8386 (87%)	8367 (87%)	16753 (87%)
-Chronic Obstructive Pulmonary Disease	570 (6%)	597 (6%)	1167 (6%)
-Chronic Kidney Disease	853 (9%)	901 (9%)	1754 (9%)
-Liver Disease	367 (4%)	336 (4%)	703 (4%)
-Malignant Neoplasm (not specified)	359 (4%)	351 (4%)	710 (4%)
History of Procedures			
-PCI	5558 (58%)	5596 (58%)	11154 (58%)
-CABG	2796 (29%)	2741 (29%)	5537 (29%)
Source: Clinical and Statistical Review, Table 11, page 51. CABG: coronary artery bypass graft surgery; PCI: percutaneous coronary intervention; SD: standard deviation.			

Key Baseline Medications:

Key baseline medications are displayed in Table 4 and were balanced between treatment groups.

Table 4. Key Baseline Medications

Baseline Medications	Ticagrelor	Placebo	Total
	N=9619	N=9601	N=19220
Anti-Platelet Agents (excluding heparin)	9527 (99%)	9507 (99%)	19034 (99%)
-Aspirin	8907 (93%)	8942 (93%)	17849 (93%)
-Clopidogrel	178 (2%)	184 (2%)	362 (2%)
-Ticagrelor	21 (0.2%)	11 (0.1%)	28 (0.1%)
Anti-Diabetic Agents	9586 (100%)	9571 (100%)	19157 (100%)
-Insulin / Insulin Analogues	2801 (29%)	2717 (28%)	5518 (29%)
-Biguanides	6552 (68%)	6568 (68%)	13120 (68%)
-Alpha Glucosidase Inhibitors	452(5%)	461 (5%)	913 (5%)
-Thiazolidinediones	257 (3%)	279 (3%)	536 (3%)
-Dipeptidyl Peptidase Inhibitors	1248 (13%)	1234 (13%)	2482 (13%)
-Glucagon-Like Peptide-1 Analogues	203 (2%)	209 (2%)	412 (2%)
-Sodium-Glucose Co-Transporter 2 Inhibitors	180 (2%)	169 (2%)	349 (2%)
-Sulfonylureas	3119 (32%)	3185 (33%)	6304 (33%)
Antiarrhythmic Agents			
-Class I (combined A, B, C; mostly propafenone)	38 (0.4%)	36 (0.4%)	74 (0.4%)
-Class III (mostly amiodarone)	97 (1%)	106 (1%)	203 (1%)
Anti-hypertensive Agents	594 (6%)	623 (7%)	1217 (6%)
Alpha Blockers	279 (3%)	296 (3%)	575 (3%)
Beta Blockers	7058 (73%)	7134 (74%)	14192 (74%)
Diuretics	2910 (30%)	2972 (31%)	5882 (31%)
-Thiazides	856 (9%)	830 (9%)	1686 (9%)
-Sulfonamides	1210 (13%)	1206 (13%)	2416 (13%)
-Aldosterone Antagonists	488 (5%)	545 (6%)	1033 (5%)
Calcium Channel Blockers	3286 (34%)	3208 (33%)	6494 (34%)
Renin Angiotensin Aldosterone Agents	7563 (79%)	7563 (79%)	15126 (79%)
-Angiotensin Converting Enzyme Inhibitors	3511 (37%)	3526 (37%)	7037 (37%)
-Angiotensin II Receptor Antagonists	2798 (29%)	2819 (29%)	5617 (29%)
Anti-Lipid Agents	8841 (92%)	8832 (92%)	17673 (92%)
-HMG CoA Reductase Inhibitors	8417 (88%)	8443 (88%)	16860 (88%)
Testosterone	36 (0.4%)	34 (0.4%)	70 (0.4%)

Source: Clinical and Statistical Review, Table 12, page 52.
HMG CoA Reductase Inhibitor: 3-hydroxy-3-methyl-glutaryl-coenzyme reductase inhibitor (i.e., statin)

Efficacy Results – Primary Endpoint:

Dr. Zhang's analysis of adjudicated and investigator-reported events is summarized for the primary endpoint as follows:

Table 5. Primary Endpoint Events (time to first occurrence of cardiovascular death, myocardial infarction, or stroke), full analysis set (FAS) population (FDA Analysis)

	PEP	Ticagrelor		Placebo			
		N=9619		N=9601		α = 0.0496	
		Number of Patients with PEP		Number of Patients with PEP			
		Patients with Event (%)	KM% at 36 M	Patients with Event (%)	KM% at 36 M	HR (95%CI)	p-value
Adjudicated	Composite	736 (7.7%)	6.9%	818 (8.5%)	7.6%	0.90 (0.81-0.99)	0.04
	CV Death	364 (3.8%)	3.3%	357 (3.7%)	3.0%	1.02 (0.88-1.18)	
	MI	274 (2.8%)	2.6%	328 (3.4%)	3.3%	0.84 (0.71-0.98)	
	Stroke	180 (1.9%)	1.7%	221 (2.3%)	2.1%	0.82 (0.67-0.99)	
Investigator-Reported	Composite	742 (7.7%)	7.0%	823 (8.6%)	7.6%	0.90 (0.82, 1.00)	0.04

Source: Jialu Zhang, Ph.D., Division of Biometrics I
CI: confidence interval; CV: cardiovascular; HR: hazard ratio; KM: Kaplan-Meier; M: months; MI: myocardial infarction; PEP: primary endpoint

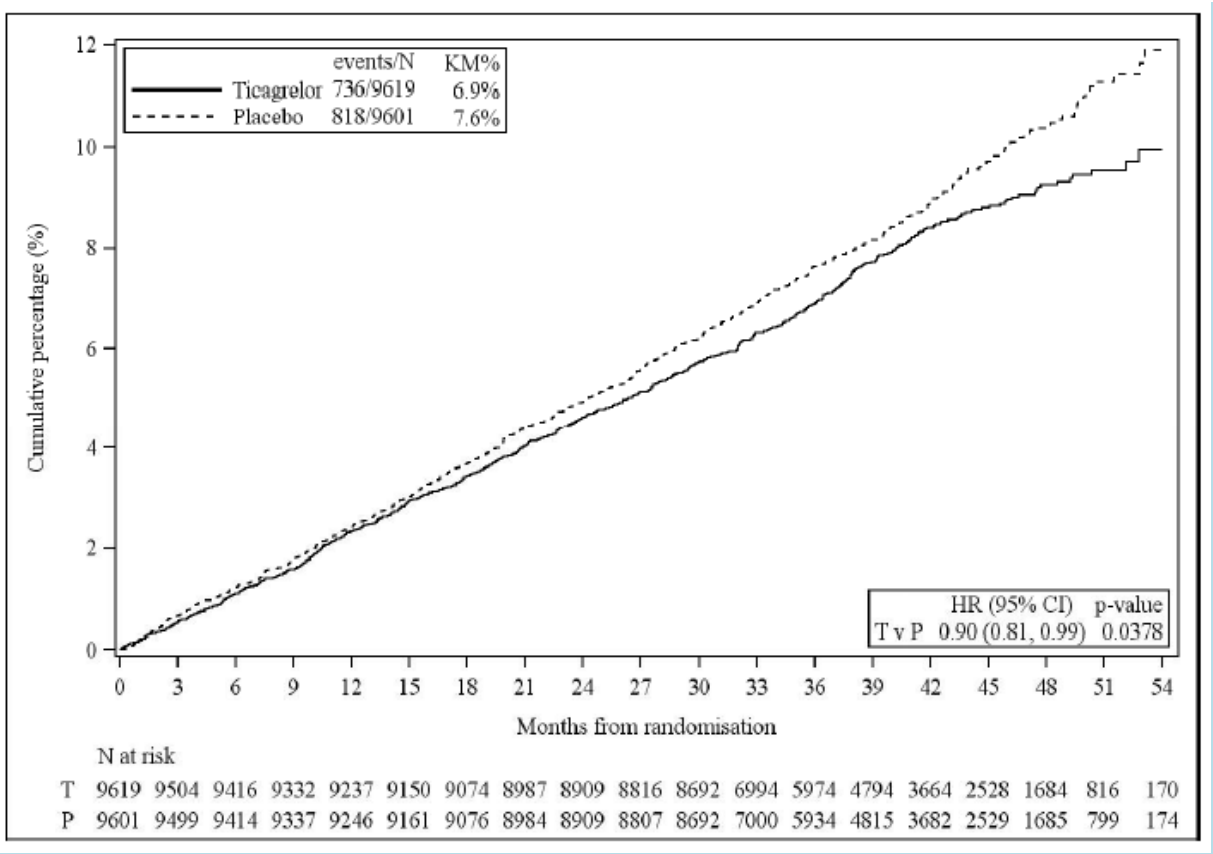
Ticagrelor significantly reduced the risk of the time to the first occurrence of the primary composite endpoint of CV death, MI, or stroke (HR 0.90, 95% CI: 0.81-0.99). This result was largely driven by the effect on MI (HR 0.84, 95% CI: 0.71-0.98) and stroke (HR 0.82, 95% CI: 0.67-0.99). The majority of adjudicated MIs in each treatment group were type 1 MIs (2.4% ticagrelor vs. 2.9% placebo). The majority of adjudicated strokes in each treatment group were primary ischemic strokes (1.6% ticagrelor vs. 2.0% placebo). Primary hemorrhagic strokes comprised 0.3% of all strokes in each treatment group. The numerical difference in CV deaths in the treatment groups was negligible.

Results for the investigator-reported primary endpoint events were similar (HR 0.90, 95% CI: 0.82-1.00).

The Kaplan-Meier (KM) plot of the primary efficacy endpoint is displayed in Figure 1. The benefit of ticagrelor was apparent at 12-15 months when the curves began to separate. For those who were randomized to ticagrelor 60 mg or matching placebo following the protocol

amendment, the KM plot was similar.

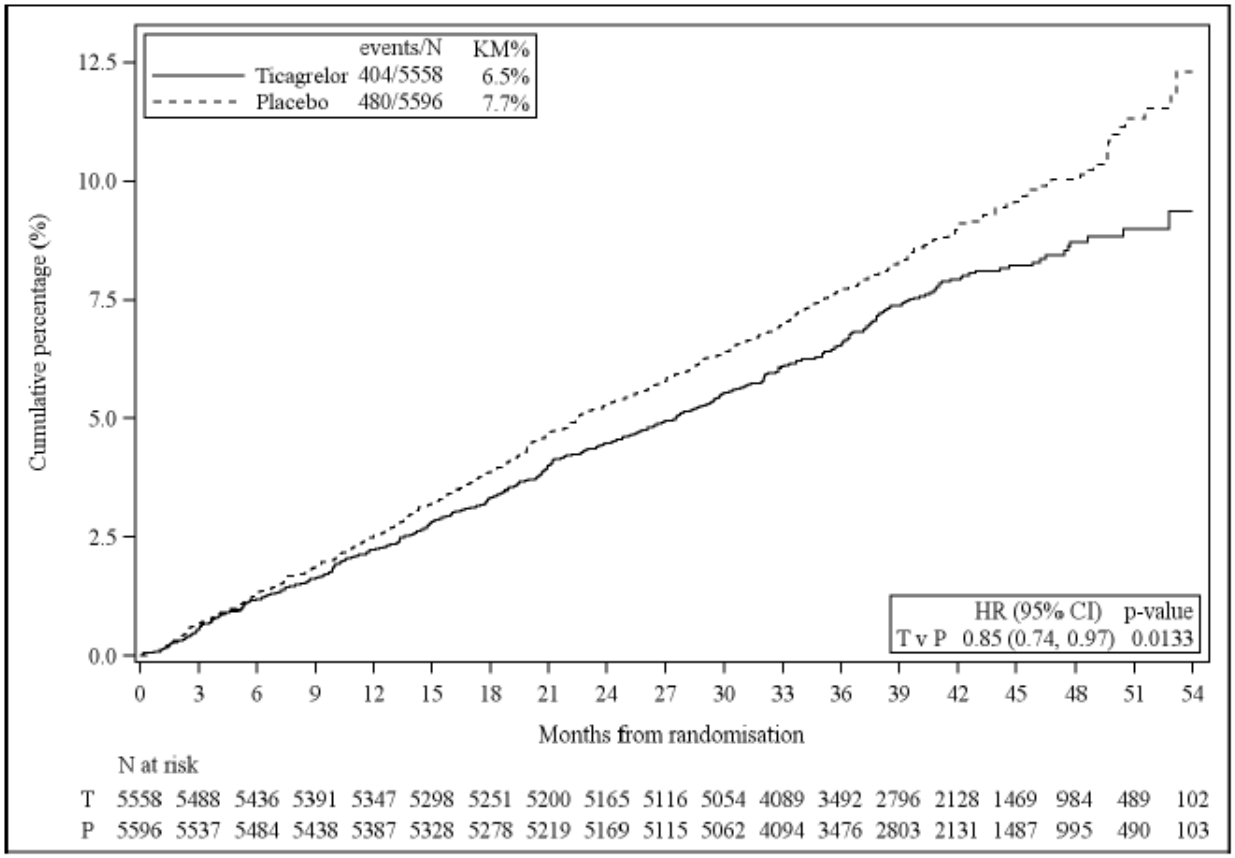
Figure 1. Kaplan-Meier Plot of Primary Efficacy Variable – Both Doses (FAS)



(Source: Clinical and Statistical Review, Figure 4, page 57)

The K-M plot for the primary endpoint in the subgroup of subjects who underwent PCI is displayed in Figure 2. The benefit of ticagrelor was apparent earlier at 6-9 months when the curves began to separate.

Figure 2. Kaplan-Meier Plot of Primary Efficacy Variable – both doses (FAS) in Subjects who had PCI

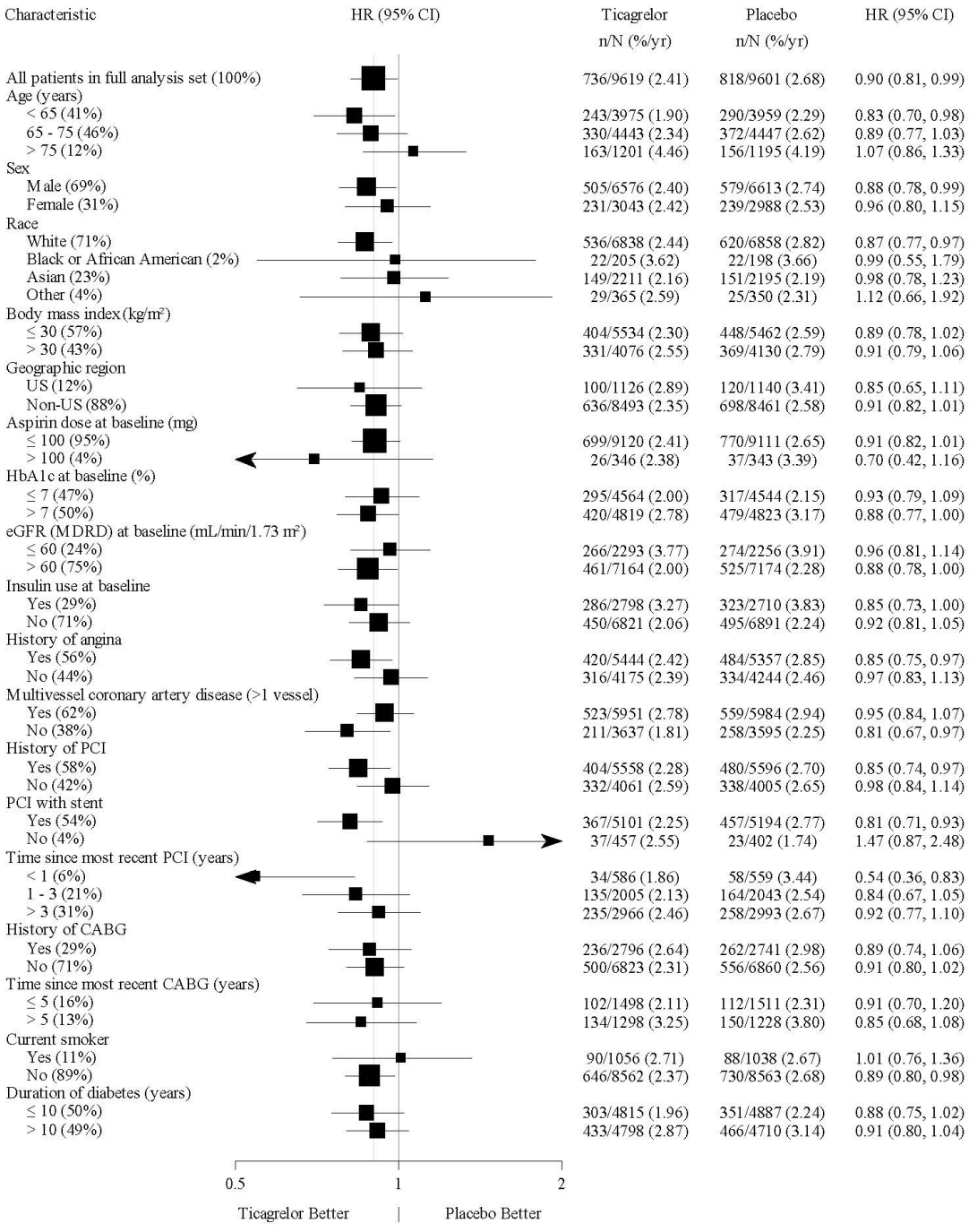


(Source: Clinical and Statistical Review, Figure 6, page 59)

A number of sensitivity analyses were conducted to evaluate dose and dose response in the FAS and Safety populations for the primary endpoint. These analyses generally demonstrated similar hazard ratios and confidence intervals with the exception of the 60 mg dose (HR 0.87, 95% CI 0.69-1.11). The lack of statistical significance was likely related to the small sample size in this subgroup (2492 ticagrelor vs. 2532 placebo).

The treatment effect of ticagrelor was durable over 36 months and was consistent across pre-specified subgroups, as shown in Figure 3.

Figure 3. Subgroup Analyses Baseline Characteristics (FAS)



(Source: Prescribing Information)

Secondary Efficacy Endpoints:

Table 6 summarizes the results of the hierarchical analysis of the secondary efficacy endpoints. Because there was no difference between ticagrelor and placebo in the incidence of CV death, no further secondary efficacy endpoints were tested.

Table 6. Secondary Endpoint Hierarchical Analysis (FAS)

	BRILINTA® N=9619		Placebo N=9601		HR (95% CI)
	Patients with event (%)	KM%	Patients with event (%)	KM%	
CV death	364 (3.8%)	3.3%	357	3.0%	1.02 (0.88, 1.18)
Myocardial infarction	274 (2.8%)	2.6%	328	3.3%	0.84 (0.71, 0.98)
Ischemic stroke	152 (1.6%)	1.5%	191	1.8%	0.80 (0.64, 0.99)
All-cause death	579 (6.0%	5.1%	592	4.9%	0.98 (0.87, 1.10)
Source: Prescribing Information CI: confidence interval; CV: cardiovascular; KM: Kaplan-Meier					

Efficacy Conclusion – Provides Substantial Evidence of Effectiveness:

Ticagrelor significantly reduced the risk of the time to the first occurrence of the primary composite endpoint of CV death, MI, or stroke (HR 0.90, 95% CI: 0.81-0.99). This result was largely driven by the effect on MI (HR 0.84, 95% CI: 0.71-0.98) and stroke (HR 0.82, 95% CI: 0.67-0.99). Although the treatment effect is small, the clinical review team is in agreement that THEMIS provides substantial evidence of ticagrelor's effectiveness in reducing the risk of a first MI or stroke in patients with T2DM and CAD.

Benefit Risk Discussion:

See Section 1, page 5.

Discussion of Indication:

Although the clinical review team is in agreement that this application should be approved, there has been substantial discussion regarding the indication. I summarize the proposed indications below:

Proposal	Source	Proposed Indication
A	Applicant (Original Proposal)	BRILINTA® is a $P2Y_{12}$ platelet inhibitor indicated to reduce (b) (4) MI, and stroke in patients with CAD and T2DM (b) (4)
B	CDTL	BRILINTA® is a $P2Y_{12}$ platelet inhibitor indicated to reduce the risk of a first MI or stroke in patients with type 2 diabetes mellitus (T2DM) and coronary artery disease (CAD).
C	Other Members of the Review Team	BRILINTA® is indicated to reduce the risk of a first MI or stroke in patients with coronary artery disease (CAD) at high risk for such events. While use is not limited to this setting, the benefit of BRILINTA was established in a population with type 2 diabetes mellitus (T2DM).
CDTL: Cross-Discipline Team Leader		

The argument against proposal A was this was a subgroup analysis that had not been controlled for type-1 error. Hence, this application should be approved for the overall population, not a subgroup.

My argument for proposal B is that it accurately reflects the population and setting in which the study was conducted.

Arguments made in favor of proposal C were: 1) T2DM as an inclusion criterion was used as an enrichment strategy to increase the number of events in the trial; hence, given that subjects typically had other CV risk factors (e.g., hypertension, hyperlipidemia), results could translate to other settings; 2) this drug product should be made available to those with CAD and cardiac risk factors other than T2DM so that the use of this product will be covered by the Centers for Medicare & Medicaid Services (CMS).

First, that T2DM was used as an enrichment criterion in THEMIS is not a matter of dispute. In THEMIS, all subjects had T2DM and CAD and most of them had two additional cardiac risk factors, hypertension and hyperlipidemia. Despite these CV risk factors, ticagrelor's treatment effect in THEMIS was small. Given that the clinical review team also believes that the benefit of ticagrelor narrowly outweighs the risks, I would be inclined to define the population studied in the indication carefully to discourage off-label use.

Second, this situation is clearly different from a trial that has a large treatment effect for which one would strive to make the drug product available to all patients who were eligible.

Third, this trial had only 3 inclusion criteria: 1) age ≥ 50; 2) T2DM treated for at least 6 months

with glucose-lowering medication; and 3) at high risk of CV events, defined as a history of PCI or CABG or angiographic evidence of ≥ 50% lumen stenosis of at least 1 coronary artery. My sense is that in THEMIS, T2DM had everything to do with the results because these patients were almost guaranteed to have at least two other CV risk factors (hypertension, hyperlipidemia), thereby increasing their risk for CV events.

Fourth, I am not convinced that this trial would be positive or that the benefit of ticagrelor would outweigh the risk in, for example, a study population with only hypertension and CAD. This warrants another trial. Although these patients are also at increased risk, it is unclear whether the benefit of therapy would outweigh the risk in this population.

Fifth, it does not seem reasonable to use CMS considerations to make decisions about whether a drug product should be approved or what the indication should be. I believe the indication should be based on the population and setting in which ticagrelor was studied (i.e., patients with T2DM and CAD).

Sixth, the indication should be clear so health care providers use ticagrelor in the correct patient population. As proposed, option C is unclear because it does not define "high risk" and the text, "While not limited to this setting," is vague.

For the reasons discussed above, I recommend approval of this application for the following indication:

> BRILINTA® is a $P2Y_{12}$ platelet inhibitor indicated to reduce the risk of a first MI or stroke in patients with type 2 diabetes mellitus (T2DM) and coronary artery disease (CAD).

8. Safety

For additional information, see the clinical and statistical review, Appendix 12.6 (ASCVD Risk Assessment) in the clinical review, and the Decision Support and Analysis Memorandum.

Safety analyses were conducted with respect to the safety population, defined as all subjects who received at least 1 dose of randomized ticagrelor or placebo, and for whom post-dose data are available.

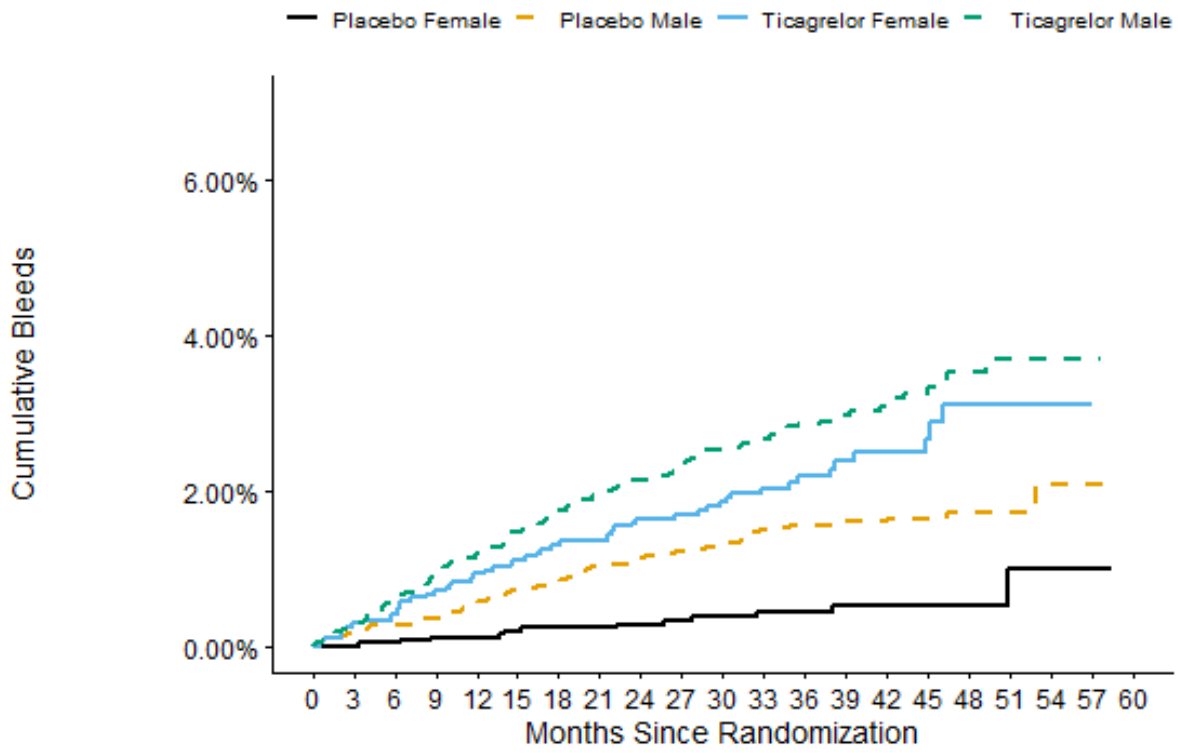
No new safety issues have been identified with ticagrelor. With the exception of bleeding and dyspnea, there was no significant imbalance in the incidence of death, serious adverse events, or adverse events of specific interest (i.e., kidney impairment, slow heart rate, gout, pneumonia, shortness of breath, and bleeding) in the two treatment groups. The incidence of TIMI Major bleeding events was similar in each dose group and occurred twice as often in the ticagrelor arm (2.2%) compared to placebo (1.0%) at 36 months, as displayed in Table 7. The difference in overall intracranial hemorrhages (ICHs) was due to an imbalance in traumatic ICHs (11 ticagrelor, 7 placebo cases).

Table 7. Bleeding Events (THEMIS)

	BRILINTA® N=9562		Placebo N=9531	
	n (%) patients with event	**Events / 1000 pt yrs**	**n (%) patients with event**	**Events / 1000 pt yrs**
TIMI Major	206 (2.2%)	9	100 (1.0%)	4
TIMI Major or Minor	285 (3.0%)	12	129 (1.4%)	5
TIMI Major or Minor or Requiring medical attention	1072 (11.2%)	46	485 (5.1%)	18
Fatal bleeding	17 (0.2%)	1	10 (0.1%)	0
Intracranial hemorrhage	70 (0.7%)	3	46 (0.5%)	2
Source: Prescribing Information **pt: patient; yrs: years**				

Figure 4 displays the Kaplan-Meier plot of TIMI Major bleeding events by sex. Compared to placebo, the risk of TIMI Major bleeding events was increased in male and female subjects receiving ticagrelor. Although the relative risk of bleeding was higher in females (interaction p-value: 0.007), the event rates were lower, as shown in Table 8.

Figure 4. Kaplan-Meier plot of TIMI major bleeds by sex (safety population)



(Clinical and Statistical Review, Figure A-18, page 110)
Table 8. TIMI Major Bleeding Events by Sex

Subgroup	Subjects with Events n (%)		Event Rate (per 1000 PY)		HR (95% CI)	Interaction p-value
	Ticagrelor	Placebo	Ticagrelor	Placebo		
Female	53 (1.7%)	12 (0.4%)	7.6	1.5	5.0 (2.7,9.3)	0.007
Male	153 (2.3%)	88 (1.3%)	9.6	4.9	2.0 (1.5, 2.5)	

(Clinical and Statistical Review, page 211)

Compared to placebo (7.3%), dyspnea occurred 3x as often in the ticagrelor group (21.4%).

In the ticagrelor group, there were twice as many adverse events leading to discontinuation, largely because of dyspnea.

9. Advisory Committee Meeting

The Division determined that an advisory committee was not necessary. We identified no controversial/difficult approvability or safety issues that would have benefited from a public discussion with experts in the field.

10. Pediatrics

On February 18, 2020, the Pediatric Review Committee met to discuss this application and agreed with granting the full waiver as outlined in the Agreed Initial Pediatric Study Plan because necessary studies are impossible or highly impracticable.

11. Other Relevant Regulatory Issues

- *Financial disclosures and Good Clinical Practice:* According to the clinical review, the Applicant has adequately disclosed financial arrangements with clinical investigators. The submitted information does not raise concern about the integrity of the data. As also noted in the clinical review, the applicant has provided attestation that the THEMIS trial was conducted in compliance with U.S. regulations pertaining to Good Clinical Practice (GCP).

- *Office of Scientific Investigations (OSI) audits:* No investigations were conducted because there were no sites that were likely to have influenced the outcome of this study.

- *Proprietary Name Review:* Not applicable.

12. Labeling

Labeling has been reviewed by the clinical and statistical reviewers, and also by reviewers from the Division of Medication Error Prevention and Analysis, Patient Labeling, and the Office of Prescription Drug Promotion. Labeling has also been reviewed by Mike Monteleone, the Associate Director for Labeling, and Dr. Mary Ross Southworth, the Deputy Director for Safety.

13. Postmarketing Recommendations

None.

14. Recommended Comments to the Applicant

None.

References

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3. Sarwar N, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet* 2010;375(9733):2215-22.

4. Cavender MA, et al. Impact of Diabetes Mellitus on Hospitalization for Heart Failure, Cardiovascular Events, and Death. Outcomes at 4 Years From the Reduction of Atherothrombosis for Continued Health (REACH) Registry. *Circulation* 2015;132:923-931.

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6. National Diabetes Statistics Report 2020. Estimates of Diabetes and its Burden in the United States. Centers for Disease Control and Prevention. https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf

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KAREN A HICKS
05/01/2020 02:54:42 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022433Orig1s028

CLINICAL REVIEW(S)

DIVISION OF CARDIOLOGY AND NEPHROLOGY

Divisional Memo

NDA: 22433 S028 BRILINTA (ticagrelor) for primary prevention of cardiovascular events.

Sponsor: AstraZeneca

Review date: 17 May 2020

Reviewer: N. Stockbridge, M.D., Ph.D.

This memo conveys the Division's decision to approve this application.

This application has been the subject of clinical reviews (Senatore, Zhang [OB], and Garnett) and decision support review (Lakey and Thompson). There is also a CDTL memo (Hicks), with which I am in general agreement.

THEMIS was a study in which 19220 subjects with age >50 years, coronary artery disease, and type 2 diabetes—but no prior history of myocardial infarction or stroke—were randomized to placebo or ticagrelor (initially 90 mg bid, later amended to 60 mg bid). The primary endpoint was the composite of cardiovascular death, myocardial infarction, or stroke. The study was powered based on a presumed risk reduction of 15% and required observing 1385 events.

In actuality, there were 1554 events over about 3 years, which is fortunate as the risk reduction was only 10%; p=0.038. Event rates (per 1000 patient-years) are shown below:

	Placebo	Ticagrelor	Difference
Composite	25	23	-2
Cardiovascular death	10	11	+1
MI	11	9	-2
Stroke	6	5	-1
All-cause mortality	16	17	+1
Fatal bleeding	0.4	0.7	+0.3
Intracranial hemorrhage	2	3	+1
TIMI Major bleeding	4	9	+5

Studies with major cardiovascular claims and a limited set of adverse consequences lend themselves to quantitative benefit-risk assessment, and a considerable number of person-hours went into this. Results varied predictably because of differences among review team members in the relative weights attached to various outcomes, but a key issue was what to do with the observed cardiovascular and all-cause mortality observation. Although the analyses took into consideration the confidence limits around this observation, we concluded that this did not adequately address the likelihood of this being a reliable finding, given beneficial effects seen in secondary prevention settings of acute coronary syndrome or acute MI.

I have attempted to craft labeling that makes it clear what the risks and benefits were in a way that would be useful and interpretable by all stakeholders.

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/s/

NORMAN L STOCKBRIDGE
05/17/2020 05:17:32 PM

CLINICAL and STATISTICAL REVIEW

Application Type	505(b)(1) NDA
Application Number(s)	022433 /S-028
Priority or Standard	Standard
Submit Date(s)	30 July 2019
Received Date(s)	31 July 2019
PDUFA Goal Date	30 May 2020
Division/Office	Division of Cardiology and Nephrology (DCN) / Office of Cardiology, Hematology, Endocrinology, and Nephrology (OCHEN) / Office of New Drugs (OND)
Reviewer Name(s)	Clinical Fred Senatore, MD, PhD, FACC Christine Garnett, Pharm D. Statistics Jialu Zhang, PhD
Review Completion Date	30 March 2020
Established/Proper Name	Ticagrelor
(Proposed) Trade Name	BRILINTA®
Applicant	AstraZeneca
Dosage Form(s)	Tablets
Applicant Proposed Dosing Regimen(s)	60 mg or 90 mg tablet orally twice daily
Applicant Proposed Indication(s)/Population(s)	To reduce (b) (4) myocardial infarction, and stroke in patients with coronary artery disease and T2DM mellitus (b) (4)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Ticagrelor is indicated to reduce the risk of a first myocardial infarction or stroke in patients diagnosed with coronary artery disease at high risk for such events. While use is not limited to this setting, the benefit of ticagrelor was established in a population also diagnosed with type 2 diabetes mellitus.

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Glossary

AC	advisory committee
ACS	acute coronary syndrome
AE	adverse event
AR	adverse reaction
BARC	Bleeding Academic Research Consortium
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CABG	Coronary Artery Bypass Surgery
CAD	Coronary Artery Disease
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CEC	Clinical Endpoint Committee
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
CV	Cardiovascular
DMC	Data Monitoring Committee
EC	Executive Committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FAS	full analysis dataset (full analysis set)
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GP IIb/IIIa	glycoprotein IIb/IIIa
GRMP	good review management practice

ICH	International Council for Harmonization
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
LMWH	low molecular weight heparin
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NSTEMI	non-ST-segment elevation myocardial infarction
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PACD	primary analysis censoring date
PBRER	Periodic Benefit-Risk Evaluation Report
PCI	Percutaneous Coronary Intervention
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	post marketing commitment
PMR	post marketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
STEMI	ST-segment elevation myocardial infarction
TEAE	treatment emergent adverse event
TIMI	Thrombolysis in Myocardial Infarction

TTP	Thrombotic Thrombocytopenic Purpura
T2DM	Type 2 Diabetes Mellitus
UAP	Unstable Angina Pectoris

1. Executive Summary

1.1. Product Introduction

Ticagrelor (BRILINTA®), a cyclopentyltriazolopyrimidine, is an orally active, reversibly-binding $P2Y_{12}$ receptor antagonist that prevents adenosine diphosphate (ADP)-mediated platelet activation and aggregation. Ticagrelor is currently approved for patients presenting with acute coronary syndrome (ACS) and patients with a history of myocardial infarction (MI).

The current dosing regimen, in conjunction with aspirin 75-100 mg, is a 180 mg loading dose followed by 90 mg twice daily for the first year after an ACS event. After one year, ticagrelor is administered 60 mg twice daily.

The applicant's proposed indication is to reduce (b) (4) MI, and stroke in patients with coronary artery disease and T2DM mellitus (T2DM) (but without a history of MI or stroke) (b) (4)

The proposed dosing regimen is 60 mg orally twice daily in conjunction with a daily maintenance dose of aspirin 75-100 mg.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Pursuant to §21 CFR 314.126, it can fairly and responsibly be concluded that the applicant presented substantial evidence of effectiveness from the THEMIS trial to support approval for the following indication: to reduce the risk of myocardial infarction and stroke in patients at high risk but no prior stroke or MI.

The THEMIS trial was adequate, well-controlled, and well-conducted with a paucity of protocol violations or conflicts of interest amongst investigators. The evidence demonstrated a statistically significant reduction in the rate of the composite primary efficacy endpoint of CV death, MI, and stroke (*Hazard Ratio 0.90, 95% Confidence Interval 0.81-0.99)*. This result was driven by statistically significant reductions in the rate of MI and stroke.

The evidence of effectiveness is clinically meaningful to the extent that it expanded the spectrum of benefit to include a primary prevention population of high-risk patients.

1.3. Benefit-Risk Assessment

APPEARS THIS WAY ON ORIGINAL

Benefit-Risk Integrated Assessment

The THEMIS study was a double-blind, two-arm, randomized, placebo-controlled trial designed to evaluate ticagrelor in patients who were at high risk, defined as having type 2 diabetes mellitus (T2DM), established coronary artery disease, and other risk factors (i.e., hypertension and hypercholesterolemia) but without a history of MI or stroke. The trial was designed to evaluate whether ticagrelor can reduce the incidence of the primary endpoint comprised of first-time heart attack or stroke (i.e., primary prevention) and death due to cardiac causes.

A total of 19,220 patients were randomized to receive ticagrelor 90 or 60 mg (most of the subjects were taking 60 mg) by mouth twice daily or corresponding placebo (50% of the patients in each arm). The study was well conducted, using the same clinical guidelines globally.

Efficacy analysis showed a statistically significant absolute reduction of 0.8% in the risk of the composite primary endpoint favoring ticagrelor (either dose) over placebo. This corresponded to a relative reduction of 10% (hazard ratio 0.90; 95% confidence interval 0.81-0.99). Hence, the benefit was small for this patient population. The results were driven by MI and stroke. There was no statistical difference between the arms for CV death. The severity of heart attacks varied from mild to severe and were evenly distributed in both arms, showing no bias towards degree of severity for which a ticagrelor benefit was observed. The strokes that were prevented were all mild with little or no sequalae as determined by the Rankin scores provided, but there was a significant amount of missing stroke severity data. The benefit of ticagrelor over placebo was noticeable at 12-15 months from the start of treatment for the entire trial population; and 6-9 months from the start of treatment for those subjects who had a percutaneous coronary intervention (PCI). The benefit was durable over a 36-month follow-up period.

Safety analysis showed no difference between ticagrelor (either dose) versus placebo for: 1) serious adverse events by any organ class; and for 2) adverse events of specific interest (i.e., kidney impairment, slow heart rate, gout, pneumonia, shortness of breath, and bleeding) except for shortness of breath (dyspnea) and bleeding that occurred more frequently in the ticagrelor arm.

There were twice as many adverse events leading to discontinuation in the ticagrelor arm compared to the placebo arm, mostly due to dyspnea. The dyspnea event rates observed in the THEMIS trial were comparable to that observed in a previous trial PEGASUS-TIMI 54 that led to a previous approval of ticagrelor in patients who already experienced a heart attack.

TIMI Major bleeding occurred twice as often in the ticagrelor arm (206 of 9562 subjects: 2.2%; similar between the two doses) compared to the placebo arm (100 of 9531 subjects: 1.0%) at 36 months. There was a very low incidence of fatal bleeds: 17 subjects in the ticagrelor arm (0.2%) and 10 subjects in the placebo arm (0.1%). Fatal bleeds by system organ class were balanced between the two arms with the exception of the class that described procedural complications or injury (7 cases in the ticagrelor arm and 2 cases in the placebo arm). There was also a low incidence of intracranial hemorrhage that were balanced between the two arms (ticagrelor: 70 [0.7%] vs placebo: 46 [0.5%]). The incidence of TIMI-major bleeds in the THEMIS trial was similar to that observed in the previous study (PEGASUS-TIMI 54). The risk of a TIMI major bleed began immediately upon initiation of ticagrelor.

Dyspnea and bleeding are described in the current label, the latter as a warning.

The benefit/risk assessment compared the reduction of the primary endpoint to the risk of TIMI Major bleeds. A simple calculation showed that 143 patients required treatment with ticagrelor to prevent 1 primary endpoint event. Similarly, 67 patients required treatment with ticagrelor to cause 1 TIMI major bleed. From this strict numerical perspective, the risk outweighed the benefit.

An additional benefit/risk evaluation was performed using multiple criteria decision analysis (MCDA) that incorporated the relative importance of outcomes (i.e., primary endpoint components and TIMI major bleed). The results of this analysis exhibited variability and fragility. A minor change in relative importance for the different outcomes led to a major change in the benefit/risk with some assumptions showing a greater overall benefit from ticagrelor and other assumptions showing a greater risk. It is reasonable to assume that some patients may determine the benefit-risk profile of ticagrelor to be favorable, based on their individual views and risk factors. Subgroup analysis showed a potentially more favorable benefit/risk for patients with a history of PCI, in particular PCI with stent placement. However, as these analyses were not controlled for type-1 error, we cannot conclude that the indication should be limited to these subgroups.

Results from the MCDA were very sensitive to whether cardiovascular death was included. Despite a very small increase in the number of cardiovascular deaths in the ticagrelor arm (364, 3.8%) vs the placebo arm (357, 3.7%), incorporation of this numerical increase into the benefit/risk analysis contributed greatly to the risk of ticagrelor. However, the clinical team determined that the numerical difference in cardiovascular death between the two arms was negligible. Additionally, antecedent trials showed a statistically significant reduction in cardiovascular death. Excluding cardiovascular death from the MCDA led to a more favorable benefit/risk for ticagrelor.

The 6-15-month delay in benefit vs the immediate risk of a major bleed upon the start of treatment also impacted the benefit/risk evaluation. However, given the sequalae of heart attack (heart failure) and stroke (evolution of disability from expansion of index stroke or secondary stroke), the benefit-risk assessment deemed the aggregate benefit of preventing heart attack and stroke to be greater than the increased risk of a TIMI major bleed (mostly falls in hemoglobin $\geq$ 5 g/dL) that can be clinically managed. Individual patients and providers should have the option to use ticagrelor if the expected benefits and risks are acceptable to them. Therefore, the clinical team recommends approval.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Coronary artery disease (CAD) results from a constriction of blood flow through the coronary arteries that usually progresses and ultimately leads to myocardial infarction (MI). The mechanism causing CAD involves plaque build-up, mostly due to cholesterol infiltration into the walls of the coronary vessels. This leads to an inflammatory response that further exacerbates plaque buildup. Plaques eventually erode and rupture, consequently leaking cholesterol-laden inflammatory material into the blood stream. The interaction of plaque material with flowing blood leads to platelet activation and blood clot formation, thus blocking blood flow	The therapeutic context of this sNDA focuses on a high-risk population based on diabetes mellitus and a history of CAD but without a history of MI or stroke (i.e., primary prevention population).

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	in the coronary arteries. Blocking the coronary arteries is a medical emergency called acute coronary syndrome (ACS). • The combination of CAD and diabetes mellitus in the absence of a previous MI is associated with a risk of thrombotic events similar to that with a history of MI and no diabetes.	
Current Treatment Options	• Patients who present with ACS, including those who had a MI, are treated with a medical regimen designed 1) keep arteries open for blood flow; 2) keep the heart rate from rising thus limiting stress on the heart; and 3) keep platelets from clumping and consequently activating the blood clot mechanism. Antiplatelet agents include: 1) aspirin; 2) inhibitors of the P2Y12 receptor on the platelet (clopidogrel, prasugrel, ticagrelor, and cangrelor); and 3) inhibitors of the GPIIbIIIa receptor on the platelet (abciximab, eptifibatide, and tirofiban). Ticagrelor, the subject of this application, has already been approved for the treatment of patients who present with an ACS and for the treatment of patients who have a history of MI. • The use of antiplatelet agents in patients with established CAD, or patients who are at high risk without an established diagnosis of CAD, (i.e., primary prevention) is controversial (https://www.ncbi.nlm.nih.gov/pubmed/27917712). • The current application requests approval of ticagrelor in combination with aspirin for a high-risk primary prevention population. Thus, this application explores a treatment paradigm	This drug application seeks to expand the spectrum of patients who would benefit from ticagrelor: ACS→history of MI→ primary prevention of MI in high risk patients. There are currently no anti-platelet agents approved for primary prevention.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	still being formulated.	
Benefit	• The THEMIS trial demonstrated that, compared to placebo, ticagrelor (combined 90 mg or 60 mg twice daily) statistically significantly reduced the composite endpoint of CV death, MI and stroke in subjects with diabetes mellitus and a history of CAD but without a history of MI or stroke. These results were driven by MI and stroke. There was no difference in CV death between ticagrelor and placebo. • The results were consistent in patients who took only the 60 mg dose, and those who initially took 90 mg and then 60 mg at some time point in the trial. • The results were durable over a 36-month follow-up period of time. • The results were consistent across pre-specified subgroups (e.g., age, duration of diabetes, diabetic complications, geographic location, presence of kidney disease, active smoking, use of statins for elevated cholesterol). • The overall results were similar to those of other clinical trials that led to previous approvals of ticagrelor for patients who presented with an ACS or patients with a history of MI.	The applicant has met the evidentiary standard described in the code of federal regulations (§21 CFR 314.126) to support the following indication: *to reduce the rate of myocardial infarction and stroke in patients with type 2 diabetes mellitus (T2DM), coronary artery disease, and no prior stroke or MI.*

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• There were no differences between the ticagrelor arm and the placebo arm for 1) serious adverse events by any organ class; and for 2) adverse events of specific interest (i.e., kidney impairment, slow heart rate, gout, pneumonia, shortness of breath, and bleeding) except for shortness of breath (dyspnea) and bleeding that occurred more frequently in the ticagrelor arm. • Dyspnea occurred 3x as often in the ticagrelor arm compared to the placebo arm; major bleeding by several criteria occurred approximately 2x as often in the ticagrelor arm compared to the placebo arm. • The majority of any bleeding events were mostly subcutaneous, followed by gastrointestinal bleeds, nose bleeds, and genitourinary bleeds. • Brain bleeds were balanced between the two groups (0.7% ticagrelor, 0.5% placebo). • There was a low incidence of fatal bleeds: 17 subjects in the ticagrelor arm (0.2%) and 10 subjects in the placebo arm (0.1%). Fatal bleeds were balanced between the two groups in every system organ class with the exception of the classification called *Injury / Poisoning / Procedural* (7 cases in the ticagrelor arm and 2 cases in the placebo arm). In this classification, there were 11 cases of fatal brain bleeds caused by trauma in the ticagrelor arm and 7 cases in the placebo arm. • There was 1 case of a fatal brain bleed not classified as due to	The risk of ticagrelor was generally not different from placebo except for dyspnea and bleeding. Dyspnea is already carried as a warning the ticagrelor label. Bleeding events in the THEMIS trial were similar to previous trials. The risk of bleeding is based on ticagrelor's mechanism of action and already carries a warning in the label. The safety data did not demonstrate a new risk or an increase in known risk.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	trauma in the ticagrelor arm and 4 cases in the placebo arm. • The major bleeding event rate was consistent with previous studies that led to previous approvals of ticagrelor for ACS or history of MI and appeared to be independent of dose (60 mg or 90 mg).	

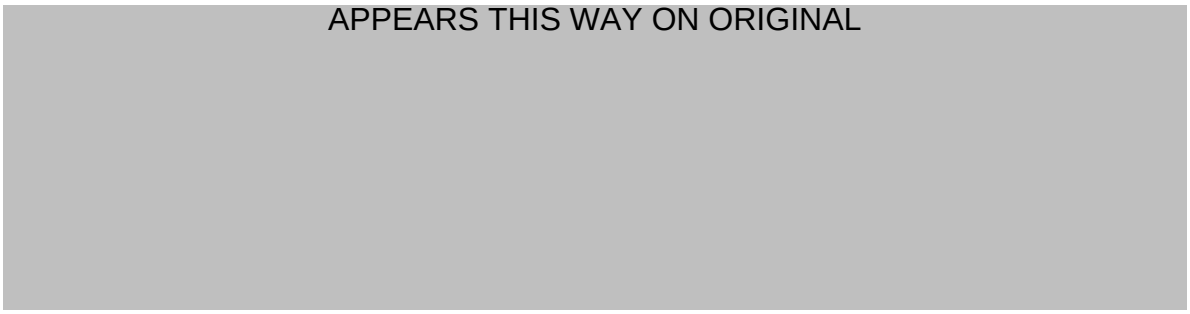
1.4. Patient Experience Data

Patient experience data was not part of this application.

Patient Experience Data Relevant to this Application (check all that apply)

□	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
	□ Clinical outcome assessment (COA) data, such as	[e.g., Sec 6.1 Study endpoints]
	□ Patient reported outcome (PRO)	
	□ Observer reported outcome (ObsRO)	
	□ Clinician reported outcome (ClinRO)	
	□ Performance outcome (PerfO)	
	□ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Sec 2.1 Analysis of Condition]
	□ Observational survey studies designed to capture patient experience data	
	□ Natural history studies	
	□ Patient preference studies (e.g., submitted studies or scientific publications)	
	□ Other: (Please specify)	
□	Patient experience data that were not submitted in the application, but were considered in this review:	
	□ Input informed from participation in meetings with patient stakeholders	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
	□ Observational survey studies designed to capture patient experience data	
	□ Other: (Please specify)	
X	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context



2.1 Analysis of Condition

Coronary artery disease (CAD) results from a constriction of blood flow through the coronary arteries that usually progresses and ultimately leads to angina pectoris and myocardial infarction (MI). The pathophysiology of CAD involves plaque build-up, mostly due to cholesterol infiltration into the walls of the coronary vessels. This leads to an inflammatory response that further exacerbates plaque buildup. Plaques eventually erode and rupture, consequently extruding cholesterol-laden inflammatory material into the blood stream. The interaction of plaque exudate with flowing blood leads to platelet activation and thrombus formation, thus occluding the coronary lumen.

The presence of a stable plaque is clinically manifested as stable angina pectoris (stable threshold of exertion beyond which chest pain occurs and is relieved by maintaining exertion below the threshold). Plaque build-up leads to clinical symptoms with lesser amounts of physical exertion (i.e., unstable angina pectoris (UAP)). Plaque erosion/rupture and subsequent platelet activation / thrombus formation is clinically manifested as an ACS, presenting as either UAP, non-ST segment elevation myocardial infarction (NSTEMI) or ST segment elevation myocardial infarction (STEMI).

Risk factors for CAD leading to ACS include hypertension, diabetes mellitus, hypercholesterolemia, age, male gender, smoking history, family history, stress, and a chronic inflammatory state.

The presence of T2DM and concomitant CAD doubles the risk of CV death and MI (Daly, 2006), and is associated with a 2-fold increase in the rates of CV death, MI, or stroke compared to a patients with type 22 diabetes mellitus and cardiac risk factors without known CAD (Cavender, 2015). The combination of CAD and type 2 diabetes mellitus is associated with a risk of thrombotic events similar to a history of MI and no diabetes (Bhatt, 2010; Olesen, 2019).

An epidemiological study of 260,000 Swedish patients (Jernberg, 2019) with T2DM with or without known CAD showed that about two thirds of patients with CAD did not have a history of MI. The 3-year cumulative incidence of CV events in diabetic patients with CAD and a previous MI was 19%; the 3-year event rate in diabetic patients with CAD without a history of MI was 13%; and the 3-year event rate in diabetic patients without known CAD was 6%. This data showed an elevated risk of cardiovascular events in patients with T2DM and known CAD compared to those with T2DM without known CAD.

The therapeutic context of this sNDA focuses on a high-risk population based on diabetes mellitus and a history of CAD (b) (4)

but without a history of MI or stroke.

2.2 Analysis of Current Treatment OptionsAntiplatelet therapy is the cornerstone of treatment for patients presenting with ACS and scheduled for PCI (Angiolillo, 2008).

Two classes of antiplatelet agents have been developed since 1978 based on antagonizing specific platelet receptors: the $P2Y_{12}$ and the glycoprotein (GP) IIb/IIIa receptor (Table 1). An essential mechanism in platelet activation is the interaction of adenosine diphosphate (ADP) with the $P2Y_{12}$ receptor. The $P2Y_{12}$ receptor is the predominant receptor in the ADP-stimulated activation of the GP IIb/IIIa receptor. Activation of the GP IIb/IIIa receptor precipitates platelet degranulation, thromboxane production, and platelet aggregation, the latter which plays a key role in thrombosis resulting in ACS (Damman, 2012).

Platelet inhibitors include thromboxane inhibitors (aspirin); $P2Y_{12}$ receptor antagonists such as thienopyridines (ticlopidine, clopidogrel and prasugrel) and nonthienopyridines (ticagrelor and cangrelor); and GP IIb/IIIa receptor antagonists (abciximab, eptifibatide, and tirofiban).

Thienopyridines covalently and irreversibly bind to platelet receptors, thus permanently deactivating them. The nonthienopyridines are reversible binders to the $P2Y_{12}$ receptor.

Ticlopidine was considered the 1st generation $P2Y_{12}$ inhibitor, but serious side effects (neutropenia, agranulocytosis, thrombotic thrombocytopenic purpura {TTP}) prompted the development of the 2nd generation $P2Y_{12}$ inhibitor (clopidogrel). Clopidogrel requires metabolism for activation, thereby prolonging the time to a pharmacodynamic response that was considered suboptimal in the setting of ACS. Further, clopidogrel produces a diminished response based on genetic variations, and can cause TTP. Consequently, the 3rd generation $P2Y_{12}$ inhibitors were developed (prasugrel, ticagrelor, cangrelor) that were shown to be superior compared to clopidogrel in reducing major cardiac events when administered to patients with ACS managed by PCI. Ticagrelor's efficacy was further expanded to include subjects with a history of MI outside of the spectrum of ACS. Cangrelor was shown to be superior to clopidogrel in preventing peri-procedural MI in the cardiac catheterization laboratory.

GP IIb/IIIa receptor antagonists underwent an independent parallel track development. The three approved GP IIb/IIIa receptor antagonists are parentally administered. Oral GP IIb/IIIa receptor antagonists were shown to be paradoxically thrombotic for reasons that remain speculative. Abciximab, an antibody and irreversible inhibitor of the GP IIb/IIIa receptor, was shown to confer a significant long-term mortality benefit in patients undergoing PCI. Both

eptifibatide and tirofiban, small molecules and short acting reversible inhibitors of the GP IIb/IIIa receptor, were also shown to decrease ischemic events in subjects undergoing medical management of ACS (tirofiban) and in subjects undergoing either medical management of ACS or elective PCI (eptifibatide). The benefit of the three GP IIb/IIIa receptors seemed to be amplified in the setting of diabetes mellitus, both in the context of PCI and ACS. Despite these benefits, their further development was halted but encouraged (Bhatt & Topol, 2003).

Table 1: Current Treatment Options: $P2Y_{12}$ and GP IIb/IIIa receptor antagonists

Product Name	Relevant Indication	Year Approved	Route and Frequency of Administration	Key Safety Issues
FDA Approved $P2Y_{12}$ Receptor Antagonists				
Ticlopidine	Reduce risk of thrombotic stroke in patients who had a stroke or stroke precursors.	1978	250 mg PO BID	Neutropenia/agranulocytosis; (TTP); bleeding
Clopidogrel	Reduce rate of atherothrombotic events in patients with a recent MI, stroke, established PAD, or ACS.	1997	In combination with ASA, 75 mg PO QD. For ACS, 300 mg PO loading dose followed by 75 mg PO QD.	Diminished response based on genetic variation; TTP; bleeding
Prasugrel	Reduce rate of thrombotic CV events including ST in patients with ACS managed with PCI.	2009	In combination with ASA, 60 mg PO loading dose followed by 10 mg PO QD. For patients < 60 kg, 5 mg PO QD.	Bleeding (in patients ≥ 75 years, increased risk of fatal or intracranial bleeding with uncertain benefit)
Ticagrelor	Reduce rate of CV death, MI and stroke in patients with ACS; reduce the rate of ST in patients stented for ACS.	2011	In combination with ASA, 180 mg PO loading dose followed by 90 mg PO BID for the 1st year after ACS, followed by 60 mg PO BID.	Significant, sometimes fatal bleeding
Ticagrelor	Reduce rate of CV death, MI and stroke in patients with a history of MI.	2015	Same as above.	Same as above
Cangrelor	As an adjunct to PCI, reduce the risk of periprocedural MI, repeat coronary revascularization, and ST in patients who have not been treated with a $P2Y_{12}$ inhibitor and are not being given a GP IIb/IIIa inhibitor.	2015	30 ug/kg IV bolus prior to PCI followed by 4 ug/kg/min IV infusion for at least 2 hours or duration of PCI, whichever is longer.	Significant bleeding.
FDA Approved GPIIbIIIa Receptor Antagonists				
Abciximab	As an adjunct to PCI and with concomitant ASA and heparin, for the prevention of cardiac ischemic complications.	1997	0.25 mg/kg IV bolus 10-60 minutes prior to PCI followed by 0.125 ug/kg/min (max 10 ug/min) for 12 hours	Serious bleeding.
Eptifibatide	With concomitant ASA and heparin, to reduce the rate of death and new MI in patients with ACS; reduce rate of death, new MI, and need for urgent intervention in patients undergoing PCI.	1998	ACS: 180 ug/kg IV bolus followed by 2.0 ug/kg/min until hospital discharge. PCI: same as above but add 2nd 180 ug/kg IV bolus 10 minutes after 1st IV bolus.	Major TIMI bleeding.
Tirofiban	With concomitant ASA and heparin, to reduce the rate of death, new MI, refractory ischemia, and repeat cardiovascular procedure in patients with ACS.	1999	0.4 ug/kg/min IV 30-minute infusion followed by 0.1 ug/kg/min 24-48 hours. High dose bolus regimen approved in 2013: 25 ug/kg over 3 minutes followed by 0.15 ug/kg/min up to 18 hours.	Major TIMI bleeding.
Source: Labels from Drugs@FDA.gov. *TIMI = thrombolysis in myocardial infarction*; $P2Y_{12}$ = chemoreceptor for adenine diphosphate; GPIIbIIIa = glycoprotein IIbIIIa inhibitor				

2. Regulatory Background

2.1. U.S. Regulatory Actions and Marketing History

Based on the PLATO trial, ticagrelor was approved by the US FDA in July 2011 for the reduction of CV death, MI, or stroke in patients presenting with ACS.

Based on the PEGASUS TIMI-54 trial, ticagrelor was approved by the US FDA in September 2015 for the same indication in patients with a history of MI.

The labeled dosing instruction is 180 mg PO load followed by 90 mg PO twice daily during the first year after ACS. After 1 year, the dose is reduced to 60 mg PO twice daily. Ticagrelor is to be used concomitantly with aspirin 75 mg-100mg PO daily.

The current sNDA for the proposed indication in patients with T2DM mellitus and CAD is based on the THEMIS trial.

2.2. Summary of Presubmission/Submission Regulatory Activity

The Division held two meetings with the Applicant: a pre-NDA meeting on 14 November 2018 and a top-line meeting on 09 April 2019.

At the pre-NDA meeting, the Division agreed that the proposed primary analysis to compare ticagrelor irrespective of dose to the control was appropriate. This agreement was made because the original ticagrelor dose in the THEMIS trial was 90 mg PO BID. The protocol was amended to reduce the dose to 60 mg PO BID 1.25 years after the first patient was randomized. The dose reduction was based on an observation of similar efficacy and better tolerability regarding dyspnea for the lower dose evaluated in the PEGASUS TIMI 54 trial. The Division also agreed that exploratory sensitivity analyses including dose were appropriate to investigate whether there was a difference in effect between doses.

At the topline meeting, the Division requested the following:

- Conduct on an-treatment assessment of benefit-risk.
- Characterize the subgroup of subjects who had a PCI < 1 year from randomization (e.g., how many had PCI within 30 days, how many were eligible for dual antiplatelet therapy).
- Characterize stroke events based on severity and type based on Rankin score.

- Segment the population by stage of chronic kidney disease in forest plots.
- Provide TIMI major bleeding and intracranial hemorrhage events by dose and provide a listing of how long the subject was on 90 mg BID vs 60 mg BID.

The Applicant did not request an expedited review pathway /designation but argued that there is an unmet medical need for intensified antiplatelet therapy in the patient population covered by this sNDA (i.e., diabetics with CAD but without a history of MI or stroke). The PLATO trial (N=18,624) included a total of 4662 subjects (25%) with diabetes mellitus and only 3824 subjects (21%) with a history of MI. Stroke was not listed. The PEGASUS TIMI-54 trial (N= 21,162) included a total of 6808 subjects (32%) with diabetes mellitus and 21,135 (99.9%) with a history of MI. Stroke was not listed. Therefore, high risk patients based on documented CAD and diabetes but without a history of MI have been studied as a significant subgroup in the PLATO trial that led to approval for ACS.

2.3. Foreign Regulatory Actions and Marketing History

Ticagrelor is approved in the EU (all 28 EU member countries plus Iceland, Norway, and Liechtenstein) for the same indications (ACS and post-MI) as in the USA and based on the same pivotal trials.

Foreign data is included in the THEMIS trial, and the sNDA package contained documentation justifying the use of foreign data to support the sNDA. Key justifying points were:

- The design of the THEMIS trial followed the relevant guidelines: American Heart Association/American College of Cardiology Foundation, the European Society of Cardiology, and the American Diabetes Association/European Association for the Study of Diabetes.
- There were similar baseline characteristics between US and non-US subjects. An exception to this was race distribution between the US (80% white, 13% black, 5% Asian) and non-US (66% white, 1% black, and 30% Asian). Another exception was the baseline history of angina pectoris: 35% in the US and 63% in the non-US regions.
- The exposure to ticagrelor was similar between the two regions: 32 months US and 35 months non-US.

3. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

3.1. Office of Scientific Investigations (OSI)

In a joint meeting between Clinical, Statistics and OSI, each site was evaluated for enrollment, protocol violations, site-specific treatment effect, and imbalances between treatment arms. This was accomplished by the site-selection tool designed to display outliers and thus facilitate site selection for inspection.
The evaluation showed no site or cluster of sites with a significant difference in enrollment, protocol violations, treatment effect, or significant imbalances that would have impacted the overall results of the THEMIS trial. Hence, the review team concluded that routine or for-cause site inspections would not be informative and were not required.

3.2. Product Quality

Not applicable.

3.3. Clinical Microbiology

Not applicable.

3.4. Nonclinical Pharmacology/Toxicology

Not applicable.

3.5. Clinical Pharmacology

Not applicable.

3.6. Devices and Companion Diagnostic Issues

Not applicable.

3.7. Consumer Study Reviews

Not applicable.

4. Sources of Clinical Data and Review Strategy

4.1. Table of Clinical Studies

The THEMIS trial served as the sole basis for supporting the proposed indication in this sNDA (Table 2).

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Table 2: Clinical Trial(s) Supporting sNDA

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
THEMIS D513BC00001	01991795	Randomized, Double-Blind, Placebo Controlled	90 mg PO BID. Protocol amended to 60 mg PO BID	Time to event: composite of CV death, MI, or stroke	Treatment duration for an individual subject: anticipated 58 months. Follow-up period: 40 months	20,108	Subjects with T2DM and documented CAD who had PCI, but no history of MI or stroke	42 countries in North America, South America, Asia, Africa, Australia, and Europe; 1315 sites

Source: Applicant's CSR. *PO BID=By mouth twice per day*

4.2. Review Strategy

The efficacy analysis from the Applicant was confirmed by the team statistician. An independent efficacy analysis was conducted on subjects who were on 90 mg / 60 mg BID for various periods of time, in order to explore consistency of treatment effect between the doses.

Safety evaluation focused on adverse events of specific interest: dyspnea, renal impairment, bradyarrhythmia, gout, pneumonia and bleeding based on BARC, TIMI, and PLATO criteria. Safety data was compared to published safety results from PEGASUS-TIMI 54 and PLATO to ascertain the development of a new safety signal or exacerbation of known safety issues that are already described in the label or stated as a warning.

A benefit-risk evaluation was performed in collaboration with Dr. Christine Garnett (supervisory pharmacologist, DCaRP) and Dr. Leila Lackey (Operations Research Analysis from the Benefit/Risk Team).

Sections of the review template (i.e., Section 3) were deemed not applicable to this clinical review because ticagrelor is a marketed product whereby key review features were already evaluated in antecedent reviews.

5. Review of Relevant Individual Trials Used to Support Efficacy

5.1. THEMIS

5.1.1. Study Design

Overview and Objective

The primary objective of the THEMIS trial (Effect of Ticagrelor on Health Outcomes in Diabetes Mellitus Patients Intervention Study) was to compare the effect of long-term treatment with ticagrelor versus placebo for the prevention of major CV events (i.e., composite of CV death, MI, or stroke).

Secondary objectives were to compare the effect of long-term treatment with ticagrelor versus placebo for the 1) prevention of death; 2) prevention of MI; 3) prevention of stroke; and 4) prevention of all-cause death.

Trial Design

THEMIS was a multinational, randomized, double-blind, placebo controlled, 2-arm parallel group study.

The study was conducted in 1315 sites across 42 countries in North and South America, Asia, Africa, Australia, and Europe. Of the 1315 sites, 369 were from the USA.

The countries participating in THEMIS were: Argentina, Australia, Austria, Belgium, Brazil, Bulgaria, Canada, Chile, China, Colombia, Czech Republic, Denmark, Finland, France, Germany, Hong Kong, Hungary, India, Israel, Italy, Japan, Mexico, Netherlands, Norway, Peru, Philippines, Poland, Romania, Russia, Saudi Arabia, Slovakia, South Africa, South Korea, Spain, Sweden, Taiwan, Thailand, Turkey, UK, Ukraine, USA, and Vietnam.

This was an event-driven trial and was planned to continue until the pre-estimated number of primary events had been reached. It was estimated that 19,000 randomized subjects with a median follow-up of 40 months (minimum 29 months and maximum 58 months) would be needed to ensure the collection of a minimum of 1385 primary events based on a 28-month recruitment period.

Eligible patients were $\geq$ 50 years of age with CAD and T2DM without a history of MI or stroke. CAD was defined as a history of PCI, coronary bypass grafting or with angiographic evidence of $\geq$ 50% lumen stenosis of at least 1 coronary artery. The diagnosis of T2DM required ongoing anti-diabetic medication since at least 6 months prior to screening/enrollment. All subjects were on a background of standard of care including aspirin 75-150 mg PO QD.

Key exclusion criteria were: 1) previous MI or stroke; 2) planned use of $P2Y_{12}$ antagonists; 3) planned revascularization procedures (coronary, cerebrovascular, peripheral); 4) need for anticoagulant therapy; 5) known bleeding diathesis or coagulation disorder; 6) history of bleeding (intracerebral or GI); 7) major surgery in last 6 months; and 8) severe liver disease or renal failure requiring dialysis.

The trial design is shown in Figure 1 and the schedule of trial events is shown in Table 3. Visit # 1 constituted screening/enrollment; randomization occurred on Visit # 2. Subjects were randomized (1:1) to either ticagrelor or matching placebo. The Applicant generated the randomization codes using their in-house global randomization (G-Rand) computerized system and loaded them on to the interactive voice or web response system (IVRS or IWRS). Randomization codes were generated in blocks to ensure approximate balance (1:1) between the 2 arms. The IVRS/IWRS allocated randomization codes sequentially within each center as subjects became eligible for randomization.

The planned visits included a telephone contact (TC) at day 7 and day 30, clinic visits at 3 months and 6 months, and alternating clinic visits or TCs every 3 months.

The dosing regimen was ticagrelor 90 mg PO BID or matching placebo but was amended to ticagrelor 60 mg PO BID or matching placebo approximately 1 year after enrollment began. When the protocol amendment was locally approved, subjects already randomized to ticagrelor 90 mg BID or matching placebo were provided with ticagrelor 60 mg BID or matching placebo tablets in accordance with their previous randomization to either ticagrelor or placebo. The dosing change occurred at the next planned visit or at an extra visit. A planned telephone contact visit was rescheduled as an on-site visit to make the dose change.

All subjects received dietary and lifestyle advice during the study (e.g., smoking cessation).

Concomitant medications were generally allowed (e.g., for the treatment of diabetes, dyslipidemia, and hypertension). Use of non-steroidal anti-inflammatory drugs (NSAIDs) were allowed as per investigator discretion. Treatment with selective cyclooxygenase-2 inhibitors was permitted. When pain management was needed, acetaminophen/paracetamol was preferred. Short term treatment with GP IIb/IIIa receptor antagonists (up to 7 days) was allowed. Short term treatment (up to 7 days) with parenteral anticoagulants (e.g., unfractionated heparin, low molecular-weight heparin (LMWH), bivalirudin, fondaparinux) was permitted.

Long-term treatment with LMWH or fondaparinux at venous thrombosis or atrial fibrillation doses was not allowed. If it was necessary to use LMWH or fondaparinux long-term, study medication was discontinued. Except for aspirin, antiplatelet agents other than study drug were not allowed. Long-term maintenance of aspirin > 150 mg QD was not permitted. Concomitant treatment with oral anticoagulants (i.e., warfarin, direct thrombin inhibitors, factor X inhibitors) was not permitted. Other prohibited concomitant medications were simvastatin or lovastatin at doses higher than 40 mg daily, CYP3A4 Inhibitors (e.g., ketoconazole, itraconazole), and strong inducers of CYP3A4 (i.e., rifampin / rifampicin, rifabutin, phenytoin, carbamazepine, phenobarbital, dexamethasone). The use of dipyridamole was not allowed and if it was needed, study drug would be discontinued for the duration of dipyridamole use. If fibrinolytics were required, study drug would be discontinued and restarted no earlier than 24 hours after completion of fibrinolytic therapy and when the risk of bleeding was deemed to be low as per investigator judgment.

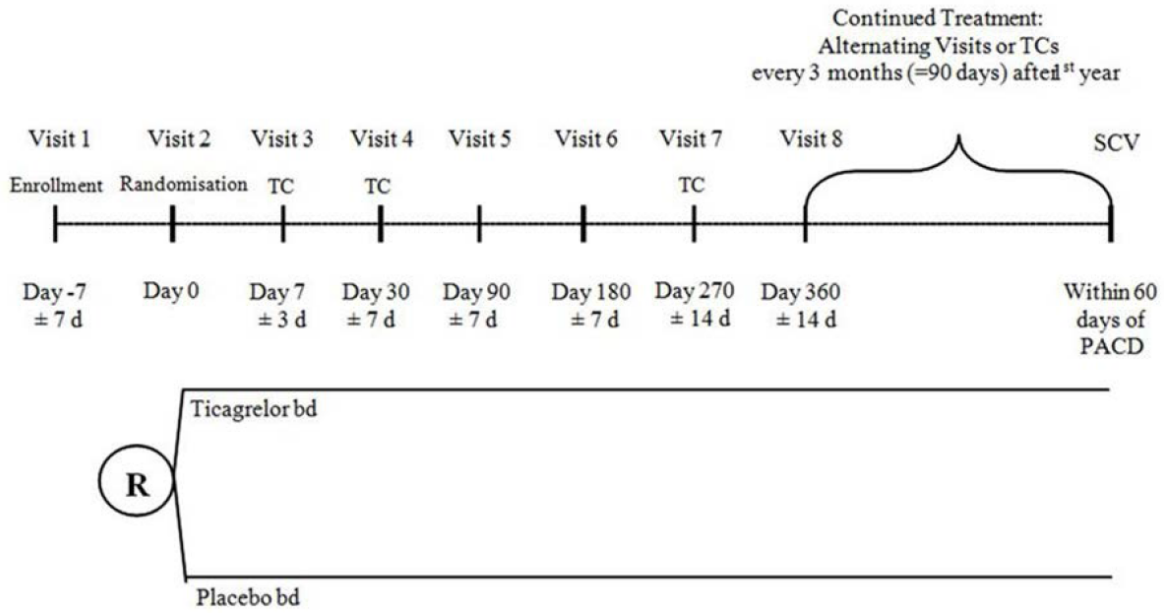
Subjects were temporarily discontinued from study drug for severe thrombocytopenia (< 50,000 /uL), surgery or procedures associated with major bleeding, actual major bleeding, and the need to treat with a prohibited concomitant medication.

Subjects were permanently discontinued from study medication if they met any exclusion criteria or experienced an adverse event that placed them at risk, if they showed "severe" non-compliance with the protocol, or if pregnancy occurred.

The Applicant assumed that the number of subjects lost to follow-up would be negligible. Therefore, it was not considered in sample size determination. All randomized subjects were included in the full analysis dataset (FAS) irrespective of protocol compliance or continued participation in the study. Subjects who withdrew consent were included up to the date of their study termination except for use of public records with regard to all-cause mortality.

The investigators were responsible for treatment compliance. All data, including study drug treatment and interruption, were recorded in the case report form.

Figure 1: THEMIS Trial Design



Source: Applicant's CSR. *R=randomization; PACD= Primary efficacy Analysis Censoring Date: the date by which the executive committee estimated that the pre-determined number of primary adjudicated events would have been accrued; SCV= Study Closure Visits; TC= telephone contact.*

Table 3: THEMIS Schedule of Events

	V1	V2	V3	V4	V5	V6	V7	V8	V9, 11, 13, etc.	V10, 12, 14, etc.	PTDV	SCV
	D -7	D 0	D +7 TC	D +30 TC	D +90	D +180	D +270	D +360	15, 21, 27…mos TC	18, 24, 30…mos	≤ 15 d since last dose	≤ 60 d after PACD
IC	X											
Eligibility	X	X										
Hx	X											
Dem	X											
VS	X	X									X	X
Wt/Ht	X											
Pregnancy	X	X										
Labs		X										
ECG		X										
HEA		X				X		X		X	X	X
Drug		X			x	X		X		X		
Drug Ret					X	X		X		X	X	X
Account					X	X		X		X	X	X
Compl.			X	X	x	X	X	X	X	X		
Life Adv	X	X			X	X		X		X	X	
Concom meds		X	X	X	X	X	X	X	X	X	X	X
AEI			X	X	X	X	X	X	X	X	X	X
PEP events			X	X	X	X	X	X	X	X	X	X
SAE		X	X	X	X	X	X	X	X	X	X	X

Source: Applicant's Protocol. *Account= accountability assessment; compl= compliance reminder; Life Adv= lifestyle including dietary advice; AEI= adverse event of interest; D=Day; Dem=demographics; Drug= drug dispense; Drug Ret= drug return; HEA= health economic assessment; IC=informed consent; PACD= primary analysis censoring date; PEP=primary endpoint event assessment, including bleeding; PTDV=premature treatment discontinuation visit; SCV=study closure visit; TC= telephone contact; V=visit.*

The THEMIS trial governance is shown in Figure 2. Governance membership in key committees (Executive, Data Monitoring, and Clinical Endpoint) is located in appendix 12.5.

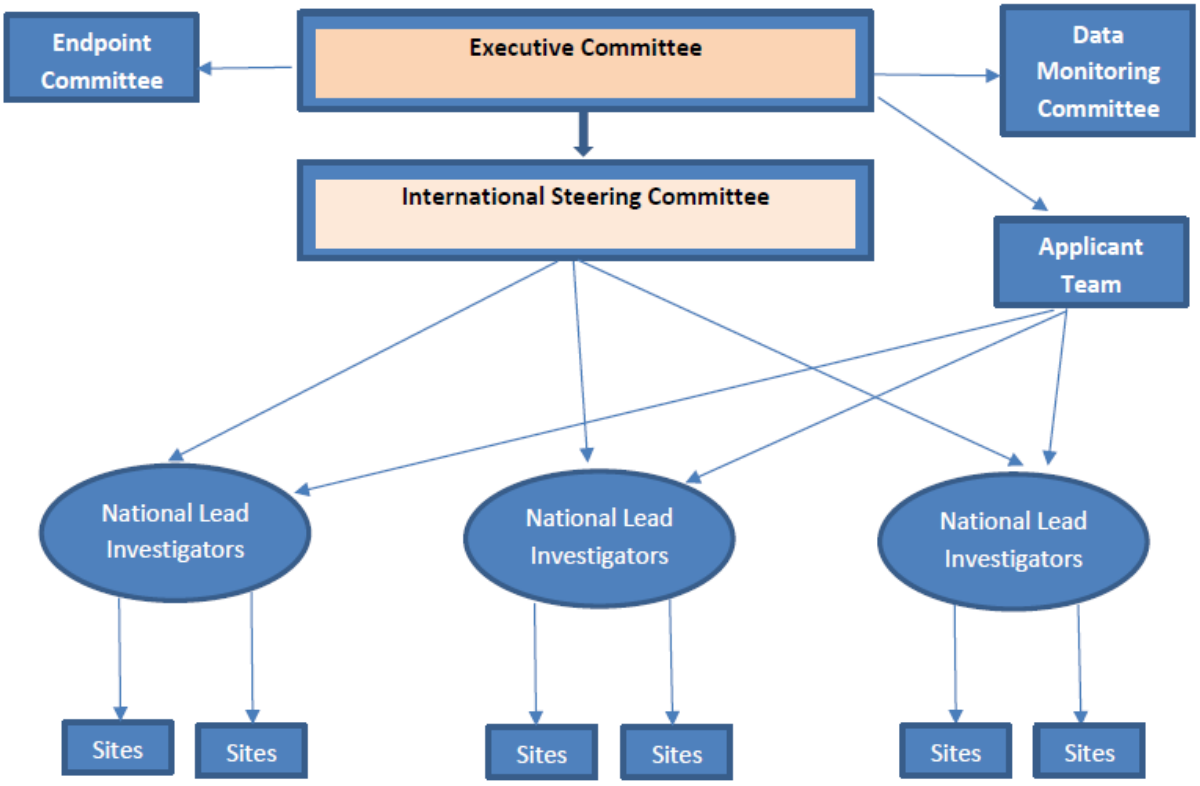
The Executive Committee (EC) was responsible for the overall design of THEMIS, the protocol and protocol amendments, data interpretation, reporting, and publication. The EC was also responsible for making recommendations to the Applicant with regard to early stopping or modifications of the trial based on information received from the data monitoring committee.

The International Steering Committee comprised of national lead investigators from each country where the study was conducted. These investigators were responsible for providing clinical guidance on study implementation and conduct in their respective country. The International Steering Committee was supervised by the EC but also interacted with the Applicant.

The Clinical Endpoint Committee (CEC) was independent, blinded, and responsible for the adjudication of all potential endpoint events.

The Data Monitoring Committee (DMC) was independent and responsible for the unblinded evaluation of safety data. The DMC also performed an interim analysis for efficacy. The DMC reported to the EC.

Figure 2: THEMIS Trial Study Governance



Source: Reviewer Drawing of CSR section 2.3 description of study governance

A total of 20,108 subjects were enrolled in THEMIS of which 19,220 were randomized 1:1 (ticagrelor arm: 9619; placebo arm: 9601).

Study Endpoints

The primary efficacy endpoint was time from randomization to the first occurrence of any event from the composite of CV death, MI or stroke (ischemic, hemorrhagic, or unknown etiology).

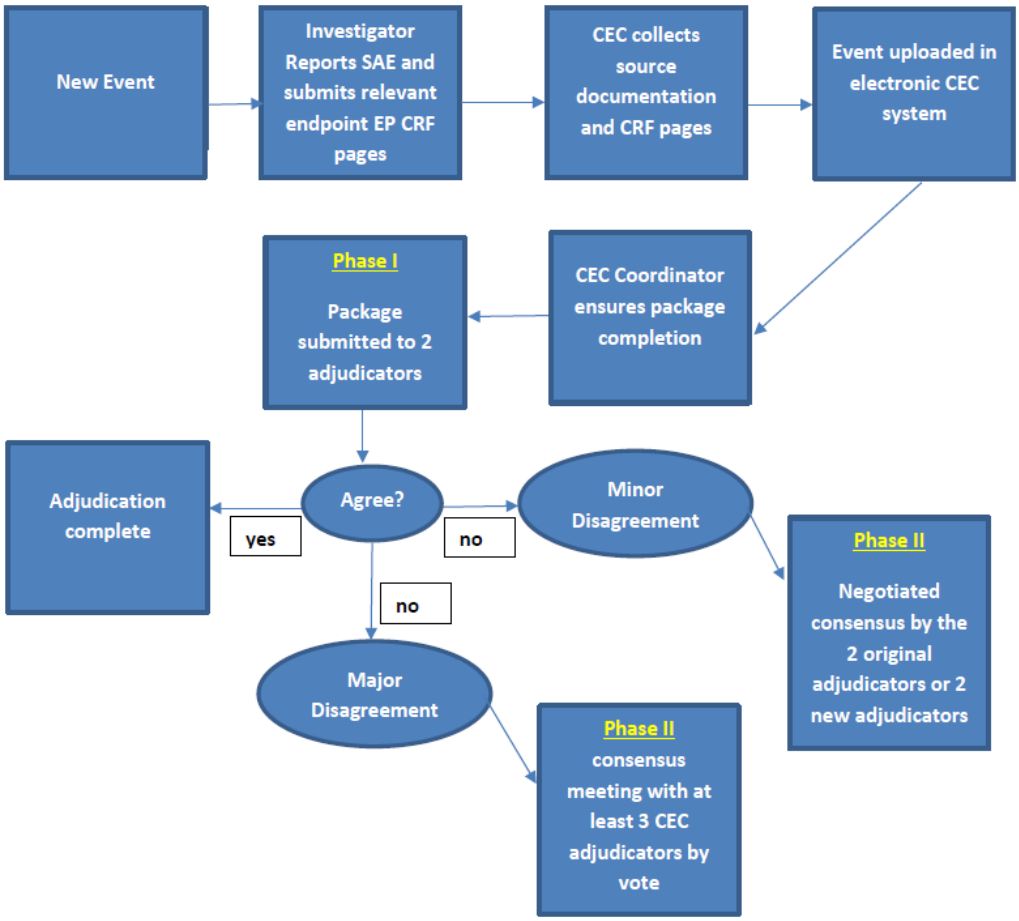
Secondary efficacy endpoints in hierarchical order were 1) CV death; 2) MI; 3) ischemic stroke; and 4) and all-cause death.

All potential endpoints were adjudicated. The adjudication process is illustrated in Figure 3 and the required documentation for endpoint adjudication is specified in Table 4. The adjudication process comprised of 2 phases. In Phase I, an adjudication package for a potential endpoint was

dispatched to 2 adjudicators. If there was a disagreement between the 2 adjudicators, Phase II was initiated where either a consensus was achieved between the 2 original or 2 new adjudicators if the disagreement was minor, or a consensus meeting with at least 3 adjudicators with adjudication by vote if the disagreement was major.

If an investigator provided additional data warranting a re-adjudication, then the committee would proceed to re-adjudicate the event and update the database.

Figure 3: Clinical Endpoint Committee Adjudication Process



Source: Reviewer Drawing based on CEC Charter d513bc00001

Table 4: Endpoints for Adjudication and Required Documentation

Endpoint	Required Source Documentation	Required eCRF
Cardiac Ischemic Event including MI and unstable angina	• Discharge Summary • ECGs (randomization, peri-event, post event) • Angiography report • Revascularization Report • Cardiac Lab Report	• Event log • SAE Report • Cardiac Ischemic Event • Biomarker Results • Coronary Revascularization • Hospitalization Log
Stroke / Transient Ischemic Attack	• Discharge Summary • Neurological Consult Report • Reports of CT / MRI scans	• Event log • SAE Report • Modified Rankin Scale prior to stroke, during stroke hospitalization, and at current visit or 90 days after stroke • Non-coronary vascular intervention • Hospitalization Log
Death	• Discharge Summary • Consult Reports (if done) • Autopsy Report (if done) • Police/EMS reports • Lab reports	• Event Log • SAE Report • Death event • Hospitalization Log
Bleeding Event	• Discharge Summary • Report(s) from procedures related to event • Lab report	• Event Log • SAE Report • Bleeding vent • Hemoglobin / Hematocrit Results Log • Transfusion • Hospitalization Log

Source: CEC Charter d513bc00001. *eCRF= electronic case report form.*

Statistical Analysis Plan

The original statistical analysis plan (SAP) was finalized on 31 January 2014 prior to enrollment of the first subject into the THEMIS trial (10 Feb 2014).

The SAP was amended on 27 March 2017 when 20,108 subjects were enrolled. The key amendment was the change from "*Ticagrelor 90 mg twice daily*" to "*Ticagrelor twice daily*" to reflect the THEMIS protocol amendment that reduced the ticagrelor dose from 90 mg BID to 60 mg BID. Additional changes were: 1) an increase in the expected number of primary endpoint events from 750 to 1385; 2) an increase in the assumed Hazard Ratio from 0.80 to 0.84.; 3) an increase in the maximum study duration of treatment from 35 to 58 months; 4) an increase in the minimum follow-up period from 15 to 29 months; a mean follow-up period from 24 to 40 months, and enrollment period from 18 to 28 months. These changes led to 90% power for an assumed relative risk reduction of 16%.

The SAP was amended again on 17 September 2017. The key amendment was the clarification that strokes defined as "unknown type of stroke / no image performed" would be included in the analysis of ischemic stroke.

The FAS was defined as all subjects who have been randomized to study treatment irrespective of protocol compliance and continued participation in the study. The safety analysis dataset comprised of all subjects who received at least 1 dose of study drug and for whom post-dose data were available.

The primary analysis was based on the FAS including all randomized patients. Patients requiring anti-platelet therapy other than low dose ASA were excluded at study entry.

Subjects who withdrew consent were included in the analysis up to the date of study termination. If a patient received study drug from the wrong kit and then switched to the randomized kit later on, the treatment group assigned to the subject was that with the longest exposure. Protocol violators were not excluded from the analysis.

Bleeding events that were self-limited and did not prompt medical evaluation or intervention were not reported.

Clinical events reported after database lock were not included in the primary efficacy and safety analysis.

Time-to-event variables were compared between treatment groups by a Cox proportional hazards model. Kaplan-Meier estimates of the cumulative portion of subjects with events per treatment group were estimated and plotted.

The EC monitored accrual of the number of primary endpoint events. Based on the accrual rate, a date on which the pre-defined target number of primary endpoint events will have occurred

was predicted and consequently defined as the primary analysis censoring date (PACD). On the PACD, subjects who were event-free and have not withdrawn consent were censored in the efficacy time-to-event analyses. Primary events that occurred after the PACD but before closure of the study site were collected, adjudicated and included only in a sensitivity analysis but not the primary analysis. Primary events occurring after study site closure were tabulated descriptively.

Subgroup analyses on the composite endpoint and its components were performed to evaluate treatment effect on a variety of characteristics: age, race, gender, state of obesity, geographic region, use of aspirin and/or insulin, background medical history, and time to most recent PCI.

The primary efficacy analysis was irrespective of dose (90 mg or 60 mg) as per agreement with the FDA. Sensitivity analyses were conducted to explore consistency of treatment effect between the two doses. Sensitivity analyses included:

- Overall treatment effect in patients randomized to ticagrelor 60 mg and matching placebo.
- Overall treatment effect in patients randomized to ticagrelor 90 mg and matching placebo; events occurred after switching to 60 mg were included in the analysis.
- On treatment analysis in patients randomized to ticagrelor 60 mg and matching placebo; events with onset date from randomization to 7 days after the last dose of study drug 60 mg were included.
- On treatment analysis in patients randomized to ticagrelor 90 mg and matching placebo; events with onset date from randomization to 7 days after the last dose of study drug 90 mg were included.
- On treatment analysis in patients randomized to either 60 mg or 90 mg; the latter were event-free up to the day the dose was reduced to 60 mg; events occurred within 7 days after the last dose of study drug 60 mg were included.
- Overall treatment effect in patients randomized to either ticagrelor 60 mg or 90 mg, the latter were event-free up to the day the dose was reduced to 60 mg, which was counted as onset date.

One interim analysis was performed by the DMC following confirmation of 517 adjudicated primary events. The stopping boundary at the interim analysis was a 2-sided p value < 0.001 for both the primary efficacy endpoint event and for CV death (the 1st secondary efficacy variable). The interim p-value was considered to be small enough for the final analysis to be conducted at a significance of 4.96%, with the family-wise error rate controlled at 5.00%.

Protocol Amendments

There were 3 protocol amendments dated 11 May 2015, 23 September 2015, and 7 February 2017. As described in Table 5, the amendments involved 1) changing the ticagrelor dose from 90 mg BID to 60 mg BID; 2) hierarchically changing the order of the secondary efficacy endpoints; and 3) increasing the number of subjects, the number of requisite primary endpoints to be collected, and duration of study to ensure 90% power to detect the assumed Hazard Ratio of 0.84.

As a consequence of the May 2015 amendment, 26% of the subjects were randomized directly to the 60 mg BID dose. For those subjects starting on 90 mg BID and switching to 60 mg BID, 76% of the total exposure time to ticagrelor was at the dose of 60 mg BID.

Table 5: Protocol Amendments

Date	Amendment	Rationale
MAY 2015	1) Ticagrelor dose changed from 90 mg to 60 mg. 2) Secondary endpoints changed from comparing effect of ticagrelor vs placebo for a) composite of all cause death, MI or stroke; b) CV death; and c) all-cause death; *to* a) CV death; b) MI; c) ischemic stroke; and d) all-cause death.	1) One year after THEMIS initiation, the PEGASUS study showed similar efficacy profiles for ticagrelor at the 90 and 60 mg BID doses when administered with low-dose aspirin. The 60 mg dose had better tolerability regarding dyspnea and less risk of bleeding, leading to fewer discontinuations. Subjects with diabetes did not differ from the ITT population regarding safety or efficacy. Hence, the dose in THEMIS was changed to 60 mg BID. 2) The components of the primary efficacy endpoint were planned to be analyzed individually as secondary endpoints in hierarchical testing sequence.
SEP 2015	1) Increase the number of subjects to be enrolled and increase the length of the study.	1) The estimated annual event rate for the composite primary endpoint was 2.5% in the target population; the initial sample size was 17,000 subjects based on an accrued 750 primary events and a true HR of 0.8 between ticagrelor and placebo. In the PEGASUS study, the observed HR for ticagrelor 60 mg vs placebo was 0.84 (95%CI 0.74-0.95). To ensure 80% power to detect a similar HR in THEMIS, the requisite number of primary endpoints was increased from 750 to 1034 and the maximum duration of study drug treatment was increased from 35 to 48 months.
FEB 2017	1) Increase in anticipated length of study by 10 months and increasing the requisite number of primary endpoints.	1) To further increase the confidence of a conclusive finding in THEMIS, the requisite number of primary endpoints was increased from 1034 to 1385 to ensure 90% power assuming an HR of 0.84. This would be achieved by prolonging the study duration by ~ 10 months.

Source: Applicant's CSR. *HR=Hazard Ratio*.

5.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant stated that the THEMIS trial was conducted in accordance with the ethical principles from the Declaration of Helsinki that were consistent with the International Council for Harmonization / Good Clinical Practice (GCP) and applicable regulatory requirements. The Applicant instituted a GCP audit program to ensure GCP compliance.

Since the THEMIS trial contained a significant number of foreign subjects, the Applicant provided assurance of compliance with the requirements of 21 CFR 312.120 regarding foreign clinical studies, although it was conducted under an IND. Justification for the use of foreign data was provided and was based on regional similarity in disease burden and treatment guidelines as well as regional consistency in efficacy and safety.

Independent ethics committees and Institutional Review Boards (IRBs) approved the study protocol, including the informed consent form and subject recruitment advertising prior to enrollment of any subject.

Reviewer Assessment: The study was conducted in accordance with the CFR governing protection of human subjects (21 CFR 50), IRBs (21 CFR 56), and obligations of clinical investigators (21 CFR 312.50 to 312.70).

Financial Disclosure

The Applicant adequately disclosed financial interests/arrangements with clinical investigators as per guidance for the industry *Financial Disclosure by Clinical Investigators*.

There were 6248 investigators of which 1461 were designated as principle investigators. A total of 19 investigators were reported to have participated in financial arrangements or held financial interests that were required to be disclosed (see Table 6). Most of these investigators received "significant payment of other sorts" such as honoraria or consultation fees exceeding $25,000 USD. Three investigators had significant equity interest. One investigator was reported to have financial arrangements with the Applicant whereby the value of the compensation could be influenced by the outcome. The detail of this financial arrangement was reported as the investigator receiving a speaker fee from the Applicant and participating in advisory board meetings.

The number of investigators with a financial interest was a small fraction of the total number of investigators (0.3%). The number of evaluable subjects recruited at the sites of the 19 investigators with financial interest was low, thereby rendering a low probability that any potential bias could have affected the outcome of the study.

There were 31 investigators (0.5% of the total number of investigators) who did not provide financial disclosures. The Applicant provided form 3454 due diligence (box 3) certification testifying to have acted with due diligence to obtain from these 31 investigators the information required under 21 CFR part 54.4. There is a low likelihood that the outcome of the study would have been affected if all 31 non-disclosing investigators had a financial interest.

In conclusion, financial arrangements with investigators did not impact the clinical review.

Table 6: Investigators with Disclosed Financial Interest

Investigator	Financial arrangement that could be influenced by the outcome	Significant payment of other sorts (e.g., honoraria, consultation)	Proprietary interest in product	Significant equity interest
(b) (6)		X		
		X		X
		X		
		X		
		X		
		X		
		X		
		X		
	X			
		X		
		X		X
		X		
		X		
		X		
		X		
		X		
		X		
		X		
		X		
				X

Source: Submission number 0427, module 1

Patient Disposition

The disposition of non-randomized subjects is shown in Table 7; the disposition of randomized subjects is shown in Table 8.

A total of 20,108 subjects were enrolled (i.e. signed informed consent). Of these, 847 subjects (4%) were not randomized for various reasons: not meeting eligibility criteria, withdrawing consent, 1 death, and “other” (i.e., not defined). Subjects who were not randomized may have had more than one documented reason for not being randomized.

A total of 19,220 subjects (96% of enrolled subjects) were randomized (i.e., 9619 to ticagrelor and 9601 to placebo). In the ticagrelor arm, 7127 (74%) were randomized to 90 mg BID and 2492 (26%) were randomized to 60 mg BID. The same percentage of subjects in the placebo

arm were randomized to 90 mg BID and 60 mg BID placebo images, respectively. Ninety-nine percent (99%) of all randomized subjects received treatment. Of the subjects randomized, 65% in the ticagrelor arm completed treatment and 74% in the placebo arm completed treatment. This discrepancy in treatment completion between the arms was attributed to a higher rate of premature discontinuations due to adverse events in the ticagrelor arm compared to the placebo arm.

Table 7: Disposition of Non-Randomized Subjects

Disposition Pre-Randomization	Number of Patients (%)
Subjects Enrolled	20108
Subjects not randomized	837 (4%)
Subjects not meeting eligibility criteria	454 (2%)
Subjects withdrawing consent	256 (1%)
Subjects who died	1 (0 %)
Other (not defined)	131 (0.7%)
Patients randomized by a site prematurely closed by the Applicant	51 (26 ticagrelor; 25 placebo)

Source: Table 11.1.1.1 Applicant's CSR

Table 8: Disposition of Randomized Subjects

Disposition at Randomization	Number of Subjects (%)		
	Ticagrelor	Placebo	Total
Subjects enrolled			20108
Subjects randomized (FAS)	9619	9601	19220 (96%)
Subjects randomized to 90 mg	7127 (74%) *	7069 (74%)	14196 (74%)
Subjects randomized to 60 mg	2492 (26%)	2532 (26%)	5024 (26%)
Subjects not receiving treatment	58 (0.6%)	69 (0.7%)	127 (0.7%)
-Withdrew consent	35 (0.4%)	40 (0.4%)	75 (0.4%)
-Adverse event	3 (0%)	1 (0%)	4 (0%)
-Protocol violation	7 (0.1%)	7 (0.1%)	14 (0.1%)
-Other (not defined)	11 (0.1%)	13 (0.1%)	24 (0.1%)
Subjects receiving treatment	9561 (99%)	9532 (99%)	19093 (99%)
Subjects prematurely discontinued	3303 (34%)	2426 (25%)	5729 (30%)
-Withdrawal by subject	1425 (15%)	1122 (12%)	2547 (13%)
-Adverse event	1618 (17%)	986 (10%)	2604 (14%)
-Protocol violation	30 (0.3%)	44 (0.5%)	74 (0.4%)
-Other (not defined)	227 (2%)	269 (3%)	496 (3%)
-Not specified	3 (0%)	5 (0.1%)	8 (0%)
Patients who withdrew consent at any time during study	117 (1.2%)	94 (1.1%)	211 (1.1%)
Subjects completing treatment	6258 (65%)	7106 (74%)	13364 (70%)

Source: Table 11.1.1.1 Applicant's CSR. FAS=full analysis dataset. (** Of the 7127 subjects randomized to 90 mg BID, 7080 were instructed to change to 60 mg BID-source: section 8.1 CSR*)

Protocol Violations/Deviations

Key protocol violations were defined as: 1) subjects who were randomized but violated eligibility criteria; 2) subjects who were randomized but did not take study drug; 3) subjects who received the wrong study drug at any visit during the study; 4) subjects who received prohibited concomitant medications*; 5) subjects who met discontinuation criteria but continued taking study drug; and 6) compliance < 50%.

**Prohibited concomitant medications were: 1) antiplatelet therapy other than low-dose aspirin; 2) aspirin at a dose > 150 mg per day; 3) PDE3 Inhibitors (e.g., cilostazol); 4) oral anticoagulants;*

5) CYP3A4 Inhibitors (e.g., ketoconazole, itraconazole); and 5) CYP3A4 substrates or inducers (e.g., rifampin/rifampicin, phenytoin).

Subjects with protocol violations were not excluded from efficacy or safety analyses.

A total of 13% of the randomized subjects in each arm had at least 1 key protocol violation (Table 9). The bulk of the violations were in the category of receiving prohibited concomitant medication (5.2% in the ticagrelor arm and 6.2% in the placebo arm) and study drug compliance (5.8% in the ticagrelor arm and 4.5% in the placebo arm). The most common prohibited medication administered in violation of the protocol were $P2Y_{12}$ inhibitors (mostly clopidogrel) and aspirin at doses exceeding 150 mg. Given the relatively low percentage of individual key violations that occurred at similar incidences between the arms, it was unlikely that such violations significantly impacted the study results.

Table 9: Protocol Violations

Important Protocol Violations	Number (%) of subjects		
	Ticagrelor	Placebo	Total
	N=9619	N=9601	N=19220
Number of subjects with at least 1 key violation	1247 (13.0%)	1233 (12.8%)	2480 (12.9%)
-randomized but violated eligibility criteria	234 (2.4%)	229 (2.4%)	463 (2.4%)
-randomized but took no study drug	59 (0.6%)	70 (0.7%)	129 (0.7%)
-received incorrect study drug at any visit	23 (0.2%)	7 (0.1%)	30 (0.2%)
-received prohibited concomitant medication*	498 (5.2%)	599 (6.2%)	1097 (5.7%)
-discontinuation criteria met but subject continued	6 (0.1%)	6 (0.1%)	12 (0.1%)
-study drug compliance < 50%	557 (5.8%)	430 (4.5%)	987 (5.1%)

Source: root/cdar/d513/d513bc00001/ar/csr/tlf/dev/program/s1101p003.sas; * Source listing of disallowed concomitant medications: root/cdar/d513/d513bc00001/ar/csr/tlf/dev/programs/s1101p012.sas

Demographic Characteristics

Subject demographics were evenly distributed between the two arms of the trial (Table 10). The THEMIS trial consisted of 69% male. The mean age was 66.3 years (median age 66 years). The youngest and oldest subjects were 46 and 95 years, respectively. The majority of the subjects were between 50-75 years (87% of the FAS). Twelve percent (12%) of the subjects were older than 75 years.

The subjects were mostly white (71% of the FAS); 23% were Asian; 2% were black or African American; and 2% were not identified.

Half (51%) of the enrolled subjects came from Europe. Subjects from the USA comprised 12% of the FAS population; 4% were from Canada; 22% were from Asia; and 11% were from Central and South America.
Some countries categorized as coming from Europe are not usually considered to be part of Europe. Countries listed as coming from Europe were Austria, Belgium, Bulgaria, Czech Republic, Denmark, Finland, France, Germany, Hungary, Israel, Italy, Netherlands, Norway, Poland, Romania, Russian Federation, *Saudi Arabia*, Slovakia, *South Africa*, Spain, Sweden, Turkey, Ukraine, and the United Kingdom.

Asia is comprised of Australia, China, Hong Kong, India, Japan, Philippines, South Korea, Taiwan, Thailand, and Vietnam.

Central and South America is comprised of Argentina, Brazil, Chile, Colombia, Mexico, and Peru.

Table 10: Demographic Characteristics

Demographic Parameters	Ticagrelor	Placebo	Total
	N=9619	N=9601	N=19220
Sex n (%)			
Male	6567 (68%)	6613 (69%)	13189 (69%)
Female	3043 (32%)	2988 (31%)	6031 (31%)
Age			
Mean years (SD)	66.3 (7.8)	66.3 (7.8)	66.3 (7.8)
Median (years)	66	66	66
Min, max (years)	46, 92	50, 95	46, 95
Age Group n (%)			
< 50 years	2 (0%)	0 (0%)	2 (0%)
50—64 years	3973 (41%)	3959 (41%)	7932 (41%)
65—75 years	4443 (46%)	4447 (46%)	8890 (46%)
> 75 years	1201 (12%)	1195 (12%)	2396 (12%)
Race			
White	6838 (71%)	6858 (71%)	13696 (71%)
Black or African American	205 (2%)	198 (2%)	403 (2%)
Asian	2211 (23%)	2195 (23%)	4406 (23%)
American Indian or Alaska Native	161 (2%)	152 (2%)	313 (2%)
Native Hawaiian or Other Pacific Islander	7 (0.1%)	7 (0.1%)	14 (0.1%)
Other	197 (2%)	191 (2%)	388 (2%)
Ethnicity			
Hispanic or Latino	1408 (15%)	1368 (14%)	2776 (14%)
Not Hispanic or Latino	8211 (85%)	8233 (86%)	16444 (86%)
Region			
United States of America	1126 (12%)	1140 (12%)	2266 (12%)

Demographic Parameters	Ticagrelor	Placebo	Total
Rest of the World			
Canada	364 (4%)	365 (4%)	729 (4%)
Central and South America	1100 (11%)	1078 (11%)	2178 (11%)
Europe	4884 (51%)	4875 (51%)	9759 (51%)
Asia	2145 (22%)	2143 (22%)	4288 (22%)

Source: Table 11.1.3.1 Applicant's CSR: root/cdar/d513bc00001/ar/csr/tlf/dev/program/s1101p006.sas

Baseline Disease Characteristics

Baseline disease characteristics were evenly divided between the two arms of the trial (Table 11). One hundred percent (100%) of the subjects in the FAS population had both coronary artery disease (62% with multivessel disease) and diabetes mellitus (mean duration 11.7 years).

A total of 25% of the FAS population had diabetic complications, mostly peripheral neuropathy (15%), retinopathy (10%) and nephropathy (9%).

A total of 56% of the FAS population had angina pectoris; 16% had congestive heart failure; 9% had peripheral arterial disease; 4% had atrial fibrillation/flutter; 1% had a baseline history of myocardial infarction (*i.e. protocol violation*); 58% had a PCI and 29% had coronary artery bypass surgery.

A total of 93% of the FAS population had hypertension; 87% with dyslipidemia; 9% with chronic kidney disease; 6% with chronic obstructive pulmonary disease; and 4% with liver disease.

Key Baseline Medications

Key baseline medications were evenly divided between the two arms of the trial (Table 12).

A total of 99% of the FAS population were on anti-platelet agents at baseline (*93% aspirin, 28% ticagrelor, and 2% clopidogrel*); 100% were on anti-diabetic agents (*68% biguanides, 29% insulin / insulin analogues, 13% dipeptidyl peptidase inhibitors, 5% alpha glucosidase inhibitors, 3% thiazolidinediones, 2% glucagon-like peptide-1 analogues, and 2% sodium-glucose co-transporter 2 inhibitors*).

A total of 92% of the FAS population were on anti-lipid agents (mostly statins: 88%); 79% were on renin-angiotensin-aldosterone agents; 74% were on beta blockers; 34% on calcium channel blockers; 31% on diuretics; 0.3% on testosterone.

Table 11: Baseline Disease Characteristics

Baseline Disease Characteristics	Ticagrelor	Placebo	Total
	N=9619	N=9601	N=19220
Coronary Artery Disease	9600 (100%)	9592 (100%)	19192 (100%)
-Single Vessel	3637 (38%)	3595 (37%)	7232 (38%)
-Multiple Vessel	5951 (62%)	5984 (62%)	11935 (62%)
Diabetes Mellitus	9613 (100%)	9597 (100%)	19210 (100%)
-Duration: mean years (SD)	11.8 (8.7)	11.7 (8.6)	11.7 (8.6)
-Duration: median years (1st, 3rd quartile)	10 (5, 16)	10 (5, 16)	10 (5, 16)
Complications of Diabetes	2480 (26%)	2430 (25%)	4910 (25%)
-Retinopathy	1023 (11%)	976 (10%)	1999 (10%)
-Autonomic Neuropathy	223 (2%)	202 (2%)	425 (2%)
-Peripheral Neuropathy	1425 (15%)	1416 (15%)	2841 (15%)
-Nephropathy	828 (9%)	847 (9%)	1675 (9%)
Clinical Diagnoses			
-Angina Pectoris	5444 (57%)	5357 (56%)	10810 (56%)
-Myocardial Infarction	72 (1%)	81 (1%)	153 (1%)
-Atrial Fibrillation/Flutter	351 (4%)	356 (4%)	707 (4%)
-Congestive Heart Failure	1543 (16%)	1600 (17%)	3143 (16%)
-Carotid Artery Stenosis	611 (6%)	615 (6%)	1226 (6%)
-Ischemic Stroke	13 (0.1%)	19 (0.2%)	32 (0.2%)
-Transient Ischemic Attack	140 (2%)	164 (2%)	304 (2%)
-Hemorrhagic Stroke	0 (0%)	0 (0%)	0 (0%)
-Peripheral Arterial Disease	827 (9%)	860 (9%)	1687 (9%)
-Hypertension	8909 (93%)	8867 (92%)	17776 (93%)
-Dyslipidemia	8386 (87%)	8367 (87%)	16753 (87%)
-Chronic Obstructive Pulmonary Disease	570 (6%)	597 (6%)	1167 (6%)
-Chronic Kidney Disease	853 (9%)	901 (9%)	1754 (9%)
-Liver Disease	367 (4%)	336 (4%)	703 (4%)
-Malignant Neoplasm (not specified)	359 (4%)	351 (4%)	710 (4%)
History of Procedures			
-PCI	5558 (58%)	5596 (58%)	11154 (58%)
-CABG	2796 (29%)	2741 (29%)	5537 (29%)

Source: Table 11.1.3.2 Applicant's CSR (Note: CABG = Coronary Artery Bypass Surgery)

Table 12: Key Baseline Medications

Baseline Medications	Ticagrelor	Placebo	Total
	N=9619	N=9601	N=19220
Anti-Platelet Agents (excluding heparin)	9527 (99%)	9507 (99%)	19034 (99%)
-Aspirin	8907 (93%)	8942 (93%)	17849 (93%)
-Clopidogrel	178 (2%)	184 (2%)	362 (2%)
-Ticagrelor	21 (0.2%)	11 (0.1%)	28 (0.1%)
Anti-Diabetic Agents	9586 (100%)	9571 (100%)	19157 (100%)
-Insulin / Insulin Analogues	2801 (29%)	2717 (28%)	5518 (29%)
-Biguanides	6552 (68%)	6568 (68%)	13120 (68%)
-Alpha Glucosidase Inhibitors	452(5%)	461 (5%)	913 (5%)
-Thiazolidinediones	257 (3%)	279 (3%)	536 (3%)
-Dipeptidyl Peptidase Inhibitors	1248 (13%)	1234 (13%)	2482 (13%)
-Glucagon-Like Peptide-1 Analogues	203 (2%)	209 (2%)	412 (2%)
-Sodium-Glucose Co-Transporter 2 Inhibitors	180 (2%)	169 (2%)	349 (2%)
-Sulfonylureas	3119 (32%)	3185 (33%)	6304 (33%)
Antiarrhythmic Agents			
-Class I (combined A, B, C; mostly propafenone)	38 (0.4%)	36 (0.4%)	74 (0.4%)
-Class III (mostly amiodarone)	97 (1%)	106 (1%)	203 (1%)
Anti-hypertensive Agents	594 (6%)	623 (7%)	1217 (6%)
Alpha Blockers	279 (3%)	296 (3%)	575 (3%)
Beta Blockers	7058 (73%)	7134 (74%)	14192 (74%)
Diuretics	2910 (30%)	2972 (31%)	5882 (31%)
-Thiazides	856 (9%)	830 (9%)	1686 (9%)
-Sulfonamides	1210 (13%)	1206 (13%)	2416 (13%)
-Aldosterone Antagonists	488 (5%)	545 (6%)	1033 (5%)
Calcium Channel Blockers	3286 (34%)	3208 (33%)	6494 (34%)
Renin Angiotensin Aldosterone Agents	7563 (79%)	7563 (79%)	15126 (79%)
-Angiotensin Converting Enzyme Inhibitors	3511 (37%)	3526 (37%)	7037 (37%)
-Angiotensin II Receptor Antagonists	2798 (29%)	2819 (29%)	5617 (29%)
Anti-Lipid Agents	8841 (92%)	8832 (92%)	17673 (92%)
-HMG CoA Reductase Inhibitors	8417 (88%)	8443 (88%)	16860 (88%)
Testosterone	36 (0.4%)	34 (0.4%)	70 (0.4%)
Note: HMG CoA Reductase Inhibitor = 3-hydroxy-3-methyl-glutaryl-coenzyme reductase inhibitor (i.e., statin)			

Source: root/cdar/d513/d513bc00001/ar/csr/tlf/dev/program/s1101p011.sas (Table 11.1.4.1 CSR)

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Recordings of concomitant medications were made at the randomization visit, and at the study closure visit. Updates of other concomitant medications were recorded in conjunction with serious adverse events and potential endpoint events. Standard-of-care medications were permitted as per investigator discretion.

Key concomitant medications at study closure were evenly divided between the two arms of the trial (Table 13). There was no significant difference between baseline medications (Table 12) and concomitant medications at study closure, thus inferring no significant impact of concomitant medications on study outcome.

At study closure compared to baseline, non-impactful observations included a 7% absolute decrease in the use of aspirin; a 2% absolute increase in the use of clopidogrel; a 10-fold use of ticagrelor (i.e., 0.1% to 1.0%); and a 6% absolute decrease in the use of sulfonamides. No clinical relevance was attributed to these differences.

Compliance with study drug administration was evenly distributed between the two arms of the trial (Table 14). The mean compliance was 90% (standard deviation 46%). Seventy-eight percent (78%) of the safety analysis population were > 80% compliant with study drug; 63% were > 90% compliant with study drug.

Table 13: Concomitant Medications at Study Closure

Drug Class at Study Closure Visit	Ticagrelor	Placebo	Total
	N=9619	N=9601	N=19220
Anti-Platelet Agents (excluding heparin)	9001 (94%)	9070 (95%)	18071 (94%)
-Aspirin	8212 (85%)	8369 (87%)	16581 (86%)
-Clopidogrel	395 (4%)	361 (4%)	756 (4%)
-Ticagrelor	104 (1%)	123 (1%)	227 (1%)
Anti-Diabetic Agents	9263 (96%)	9306 (97%)	18569 (97%)
-Insulin / Insulin Analogues	3009 (31%)	3020 (32%)	6029 (31%)
-Biguanides	6267 (65%)	6224 (65%)	12491 (65%)
-Alpha Glucosidase Inhibitors	421 (4%)	458 (5%)	879 (5%)
-Thiazolidinediones	252 (3%)	270 (3%)	522 (3%)
-Dipeptidyl Peptidase Inhibitors	1298 (14%)	1306 (14%)	2604 (14%)
-Glucagon-Like Peptide-1 Analogues	278 (3%)	291 (3%)	569 (3%)
-Sodium-Glucose Co-Transporter 2 Inhibitors	567 (6%)	572 (6%)	1139 (6%)
-Sulfonylureas	2898 (30%)	3003 (31%)	5901 (31%)
Antiarrhythmic Agents			
-Class I (combined A, B, C; mostly propafenone)	43 (0.5%)	44 (0.5%)	87 (0.5%)
-Class III (mostly amiodarone)	161 (2%)	184 (2%)	345 (2%)
Anti-hypertensive Agents	664 (7%)	692 (7%)	1356 (7%)
Alpha Blockers	303 (3%)	332 (4%)	635 (3%)
Beta Blockers	6945 (72%)	7068 (74%)	14013 (73%)
Diuretics	3155 (33%)	3265 (34%)	6420 (33%)
-Thiazides	868 (9%)	820 (9%)	1688 (9%)
-Sulfonamides	630 (7%)	637 (7%)	1267 (7%)
-Aldosterone Antagonists	625 (7%)	703 (7%)	1328 (7%)
Calcium Channel Blockers	3361 (35%)	3286 (34%)	6647 (35%)
Renin Angiotensin Aldosterone Agents	7349 (76%)	7400 (77%)	14749 (77%)
-Angiotensin Converting Enzyme Inhibitors	3277 (34%)	3310 (35%)	6587 (34%)
-Angiotensin II Receptor Antagonists	2830 (29%)	2897 (30%)	5727 (30%)
Anti-Lipid Agents	8655 (90%)	8724 (91%)	17379 (90%)
-HMG CoA Reductase Inhibitors	8156 (85%)	8264 (86%)	16420 (85%)
Testosterone	36 (0.4%)	32 (0.3%)	68 (0.4%)
Note: HMG CoA Reductase Inhibitor = 3-hydroxy-3-methyl-glutaryl-coenzyme reductase inhibitor (i.e., statin)			

Source: root/cdar/d513/d513bc00001/ar/csr/tlf/dev/program/s1101p011.sas (Table 11.1.4.2 CSR)

Table 14: Compliance Data (Safety Dataset).

Compliance	Ticagrelor	Placebo	Total
Safety Analysis Set	N=9562	9531	19093
n	*9382*	*9389*	*18771*
Mean %(SD%)	89 (43)	90 (49)	90 (46)
Median %	94	95	95
Compliance > 80% n (%)	7335 (77%)	7564 (79%)	14899 (78%)
Compliance > 90% n (%)	5867 (61%)	6145 (65%)	12012 (63%)

Source: root/cdar/d513/d513bc00001/ar/csr/tlf/dev/program/s1101p016.sas (Table 11.1.5.1 CSR)

Efficacy Results – Primary Endpoint

In the FAS population, 736 subjects (7.7%) in the ticagrelor arm and 818 subjects (8.5%) in the placebo arm experienced a primary endpoint (see Table 15) for a Hazard Ratio (HR) of 0.90 (95%CI 0.81-0.99), p-value 0.04. This result was driven by MI (HR 0.84, 95%CI 0.71-0.98) and stroke (HR 0.82, 95% CI 0.67-0.99). The component of the composite endpoint, cardiovascular death, was neutral (HR 1.02, 95%CI 0.88-1.18). The Kaplan-Meier (KM) estimate for subjects in the FAS population with a primary endpoint at month 36 was 6.9% in the ticagrelor arm and 7.6% in the placebo arm.

Table 15: Primary Efficacy Results (FAS)

PEP	Ticagrelor		Placebo			
	N=9619		N=9601		$\alpha = 0.0496$	
	Number of Pts with PEP		Number of Pts with PEP			
	Pt with Events (%)	KM% at 36 M	Pt with Events (%)	KM% at 36 M	HR (95%CI)	p-value
Composite	736 (7.7%)	6.9%	818 (8.5%)	7.6%	0.90(0.81-0.99)	0.04
CV Death	364 (3.8%)	3.3%	357 (3.7%)	3.0%	1.02 (0.88-1.18)	
MI	274 (2.8%)	2.6%	328 (3.4%)	3.3%	0.84 (0.71-0.98)	
Stroke	180 (1.9%)	1.7%	221 (2.3%)	2.1%	0.82 (0.67-0.99)	

Source: root/cdar/d513/d513bc00001/ar/csr/tlf/dev/program/s1102p001.sas (Table 11.2.1.1 CSR).
PEP=primary endpoint; Composite = CV death / MI / Stroke; FAS=Full Analysis Set
[verified by the statistical reviewer]

In the FAS population, there were 879 primary endpoint events in the ticagrelor arm and 967 primary endpoint events in the placebo arm (Table 16). Of the 736 subjects experiencing a primary endpoint in the ticagrelor arm, 286 (39%) had CV death as the first event; 273 (37%) had an MI as the first event and 177 (24%) had a stroke as the first event. Of the 818 subjects

experiencing a primary endpoint in the placebo arm, 280 (34%) had CV death as a first event; 325 (40%) had an MI as a first event and 213 (26%) had a stroke as a first event (Table 16).

Table 16: Primary Efficacy Events- Number of Events and Number of Subjects with Events

PEP	Total Number of Events		Number of Pts with PEP		Number of Pts with 1st event	
	Ticagrelor	Placebo	Ticagrelor	Placebo	Ticagrelor	Placebo
			N=9619	N=9601	N=9619	N=9601
Composite	879	967	736 (7.7%)	818 (8.5%)	736	818
CV Death	364	357	364 (3.8%)	357 (3.7%)	286 (38.9%)	280 (34.2%)
MI	322	371	274 (2.8%)	328 (3.4%)	273 (37.1%)	325 (39.7%)
Stroke	193	239	180 (1.9%)	221 (2.3%)	177 (24.0%)	213 (26.0%)

Source: root/cdar/d513/d513bc00001/ar/csr/tlf/dev/program/s1102p008.sas (Table 11.2.3.1 CSR).
[verified by the statistical reviewer]

The majority of adjudicated CV deaths were classified as "presumed cardiovascular death" (unknown) cause. This was followed by sudden cardiac death (Table 17).

Type 1 MI comprised the majority of the adjudicated MI subtype as classified according to the Third Universal MI definition (Thygesen, 2012) (Table 18). The severity of the Type 1 MIs as measured by troponin (Table 19) and CKMB (Table 20) suggested the severity of heart attacks varied from mild to severe and were evenly distributed in both arms, showing no bias towards degree of severity for which a ticagrelor benefit was observed.

The majority of adjudicated strokes were classified as ischemic (Table 21).

Table 17: Adjudicated CV Death Classifications (FAS)

Adjudicated CV Death Component	Number of Pts with PEP	
	Ticagrelor	Placebo
	N=9619	N=9601
CV Death	372 (3.9%)	364 (3.8%)
Sudden Cardiac Death	93 (1.0%)	90 (0.9%)
Death due to Acute MI	23 (0.2%)	28 (0.3%)
Death due to Heart Failure or Cardiogenic Shock	37 (0.4%)	30 (0.3%)
Death due to other cardiovascular cause	29 (0.3%)	23 (0.2%)
Presumed CV death (unknown cause)	182 (1.9%)	178 (1.9%)

Source: root/cdar/d513/d513bc00001/ar/csr/tlf/dev/program/s1102p009.sas (Table 11.2.3.2 CSR).
Note: the data in this table presents all adjudicated events including those reported post-PACD.

Table 18: Adjudicated MI Sub-Type (FAS)

Adjudicated MI Component (FAS)	Total Number of Events		Number of Pts with PEP	
	Ticagrelor	Placebo	Ticagrelor	Placebo
			N=9619	N=9601
MI	323	375	275 (2.9%)	331 (3.4%)
Acute MI	322	375	274 (2.8%)	331 (3.4%)
Type 1 (spontaneous)	265	315	233 (2.4%)	280 (2.9%)
Type 2 (Due to Ischemic Imbalance)	42	29	36 (0.4%)	27 (0.3%)
Type 3 (Death when Biomarkers Unavailable)	6	7	6 (0.1%)	7 (0.1%)
Type 4a (Related to PCI ≤ 48 hours post PCI)	3	8	3 (0.0%)	8 (0.1%)
Type 4b (Related to Stent Thrombosis)	6	16	6 (0.1%)	16 (0.2%)
Type 5 (Related to CABG ≤ 48 hours post CABG)	1	0	1 (0.0%)	0 (0.0%)

Source: root/cdar/d513/d513bc00001/ar/csr/tlf/dev/program/s1102p010.sas (Table 11.2.3.3 CSR).
Note: the data in this table presents all adjudicated events including those reported post-PACD. CABG = Coronary Artery Bypass Surgery

Table 19: Troponin I measurements in adjudicated Type 1 MI Events (FAS)

Adjudicated MI Component (FAS)	Total Number of Events		Number (%) of Pts with Event	
	Ticagrelor	Placebo	Ticagrelor	Placebo
			N=233	N=250
Acute MI Type 1 (spontaneous)	265	315	233 (100%)	280 (100%)
(Note: Peak values cannot be confirmed)				
> 5xULN	97	108	88 (38%)	99 (35%)
> 10xULN	81	94	74 (32%)	88 (31%)
> 40xULN	44	60	39 (17%)	56 (20%)
> 70xULN	37	39	33 (14%)	36 (13%)
Samples not available	126	160	107 (46%)	143 (51%)
Median-fold Increase vs ULN (1st, 3rd quartile)	16 (4, 72)	21 (4, 75)	16 (4, 71)	23 (4, 85)

Source: root/cdar/d513/d513bc00001/ar/fda/req04_20200310/dev/program/r04p001.sas (Response to Information Request)

Table 20: CK-MB measurements in adjudicated Type 1 MI Events (FAS)

Adjudicated MI Component (FAS)	Total Number of Events		Number (%) of Pts with Event	
	Ticagrelor	Placebo	Ticagrelor	Placebo
			N=233	N=250
Acute MI Type 1 (spontaneous)	265	315	233 (100%)	280 (100%)
(Note: Peak values cannot be confirmed)				
> 5xULN	13	24	12 (5%)	24 (9%)
> 10xULN	6	15	6 (3%)	15 (5%)
> 40xULN	1	2	1 (0.4%)	2 (0.7%)
> 70xULN	0	1	0 (0%)	1 (0.4%)
Samples not available	187	225	164 (70%)	196 (70%)
Median-fold Increase vs ULN (1st, 3rd quartile)	1.2 (0.8, 3.4)	2.0 (0.7, 5.3)	1.2 (0.9, 3.4)	2.1 (0.9, 6.5)

Source: root/cdar/d513/d513bc00001/ar/fda/req04_20200310/dev/program/r04p001.sas (Response to Information Request)

Table 21: Adjudicated Stroke by Sub-type (FAS)

Adjudicated Stroke Component (FAS)	Total Number of Events		Number of Pts with PEP	
	Ticagrelor	Placebo	Ticagrelor	Placebo
			N=9619	N=9601
Stroke	197	239	184 (1.9%)	221 (2.3%)
Primary Ischemic Stroke	162	206	153 (1.6%)	189 (2.0%)
Primary Hemorrhagic Stroke	32	31	29 (0.3%	31 (0.3%)
Unknown type of Stroke	3	2	3 (0.0%)	2 (0.0%)

Source: root/cdar/d513/d513bc00001/ar/csr/tlf/dev/program/s1102p011.sas (Table 11.2.3.4 CSR).
Note: the data in this table presents all adjudicated events including those reported post-PACD.

An analysis of subjects taking aspirin (99.4% of the FAS population) was expectedly not different from the primary analysis (Table 22).

Table 22: Primary Efficacy Results with ASA Usage at Randomization (FAS)

PEP	Ticagrelor		Placebo			
	N=9556		N=9548		α = 0.0496	
	Number of Pts with PEP		Number of Pts with PEP			
	Pt with Events (%)	KM% at 36 M	Pt with Events (%)	KM% at 36 M	HR (95%CI)	p-value
Composite	729 (7.6%)	6.9%	811 (8.5%)	7.6%	0.90(0.81-0.99)	0.04
CV Death	359 (3.8%)	3.3%	352 (3.7%)	3.0%	1.02 (0.88-1.18)	0.79
MI	273 (2.9%)	2.6%	327 (3.4%)	3.3%	0.84 (0.71-0.98)	0.03
Stroke	178 (1.9%)	1.7%	219 (2.3%)	2.1%	0.82 (0.67-0.99)	0.04

Source: root/cdar/d513/d513bc00001/ar/csr/tlf/dev/program/s1102p001.sas (Table 11.2.1.2 CSR).

In subjects who were randomized to ticagrelor 60 mg BID (n=2492) or matching placebo (2532) in the FAS population following the protocol amendment, the Hazard Ratio (Table 23) was comparable to that of the FAS primary analysis (Table 15). The Kaplan-Meier (KM) estimate of the primary efficacy endpoint for subjects randomized to 60 mg was calculated at 24 months instead of 36 months due to the shorter exposure time to ticagrelor 60 mg. See discussion under "Dose/Dose Response" in this section.

Table 23: Primary Efficacy Results-Subjects Randomized to Ticagrelor 60 mg or Matching Placebo (FAS)

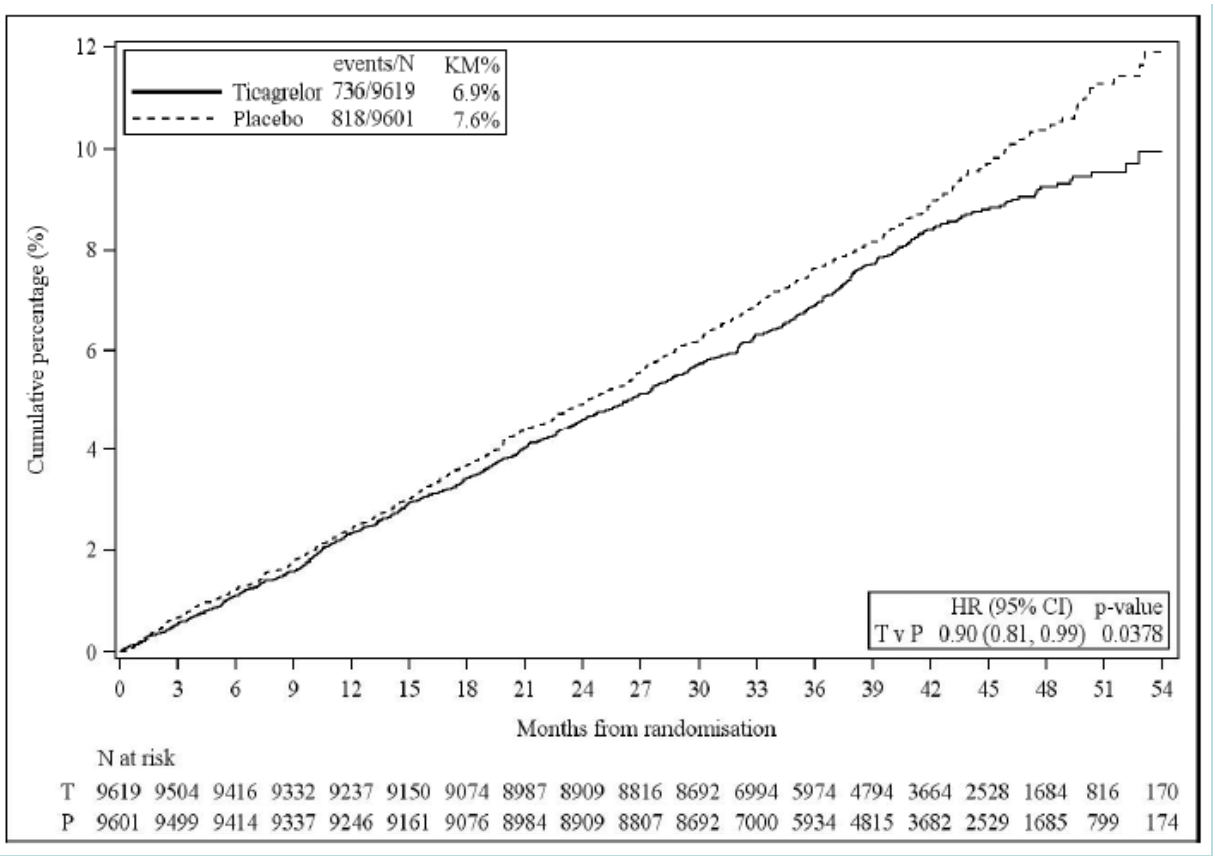
PEP	Ticagrelor 60 mg BID		Placebo 60 mg BID Image			
	N=2492		N=2532		α = 0.0496	
	Number of Pts with PEP		Number of Pts with PEP			
	Pt with Events (%)	KM% at 24 M	Pt with Events (%)	KM% at 24 M	HR (95%CI)	p-value
Composite	127 (5.1%)	3.5%	147 (5.8%)	4.2%	0.87 (0.69-1.11)	0.26
CV Death	58 (2.3%)	1.5%	47 (1.9%)	1.2%	1.25 (0.85-1.84)	
MI	50 (2.0%)	1.6%	61 (2.4%)	1.9%	0.83 (0.57-1.21)	
Stroke	30 (1.2%)	0.8%	50 (2.0%)	1.3%	0.61 (0.39-0.95)	

Source: root/cdar/d513/d513bc00001/ar/csr/tlf/dev/program/as036.sas (Table 11.2.1.3 CSR). *Note: The numbers of patients experiencing each component are first events and therefore do not add up to the number of events in the composite endpoint.*
[verified by the statistical reviewer]

A KM plot of the primary efficacy endpoint (Figure 4) showed durability of effect. This pattern was also evident in the subgroup of subjects randomized to ticagrelor 60 mg or matching placebo (Figure 5). In both KM plots, the curves began to noticeably separate at 12-15 months, suggesting the benefit to this population begins after taking ticagrelor for this period of time. In those subjects who had a PCI, the KM plot suggests a benefit beginning to take effect earlier:

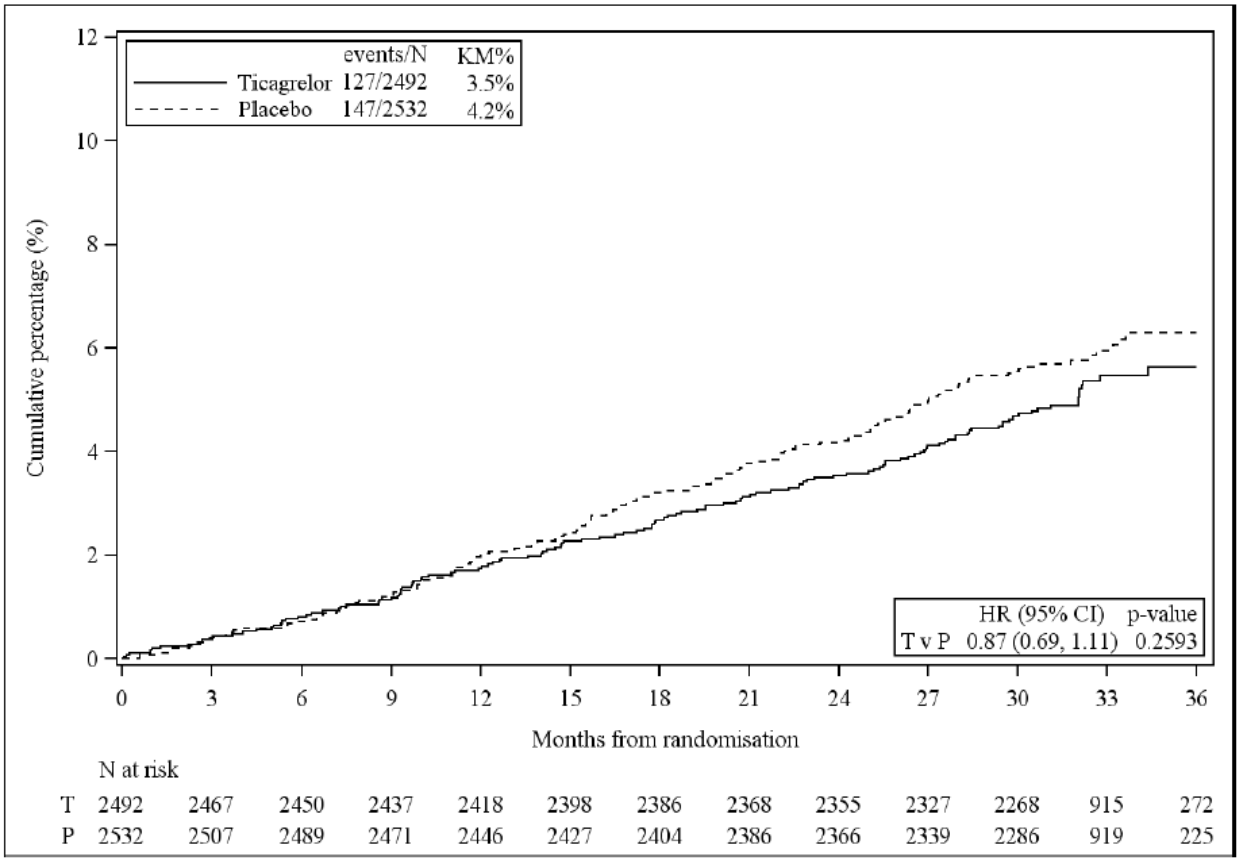
approximately 6-9 months (Figure 6).

Figure 4: Kaplan-Meier Plot of Primary Efficacy Variable-both doses (FAS)



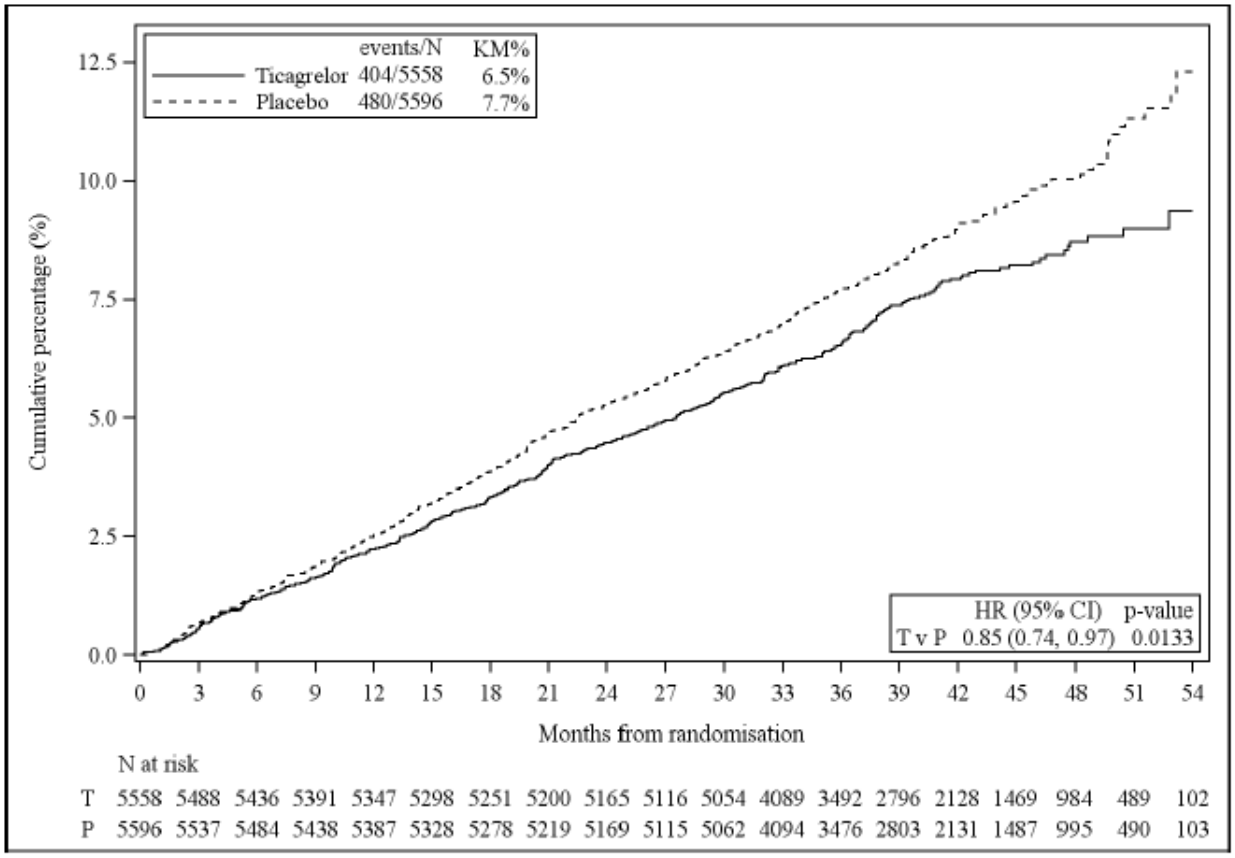
Source: root/cdar/d513/d513bc00001/ar/csr/tlf/dev/program/s1102p003.sas (Figure 11.2.1.1 CSR)

Figure 5: Kaplan-Meier Plot of Primary Efficacy Variable-subjects randomized to 60 mg (FAS)



Source: root/cdar/d513/d513bc00001/ar/csr/tlf/dev/program/s1102p003.sas (Figure 11.2.1.2 CSR)

Figure 6: Kaplan-Meier Plot of Primary Efficacy Variable-both doses (FAS) in Pts who had PCI



Source: root/cdar/d513/d513bc00001/ar/csr_adm/tlf/dev/program/s1102p003.sas

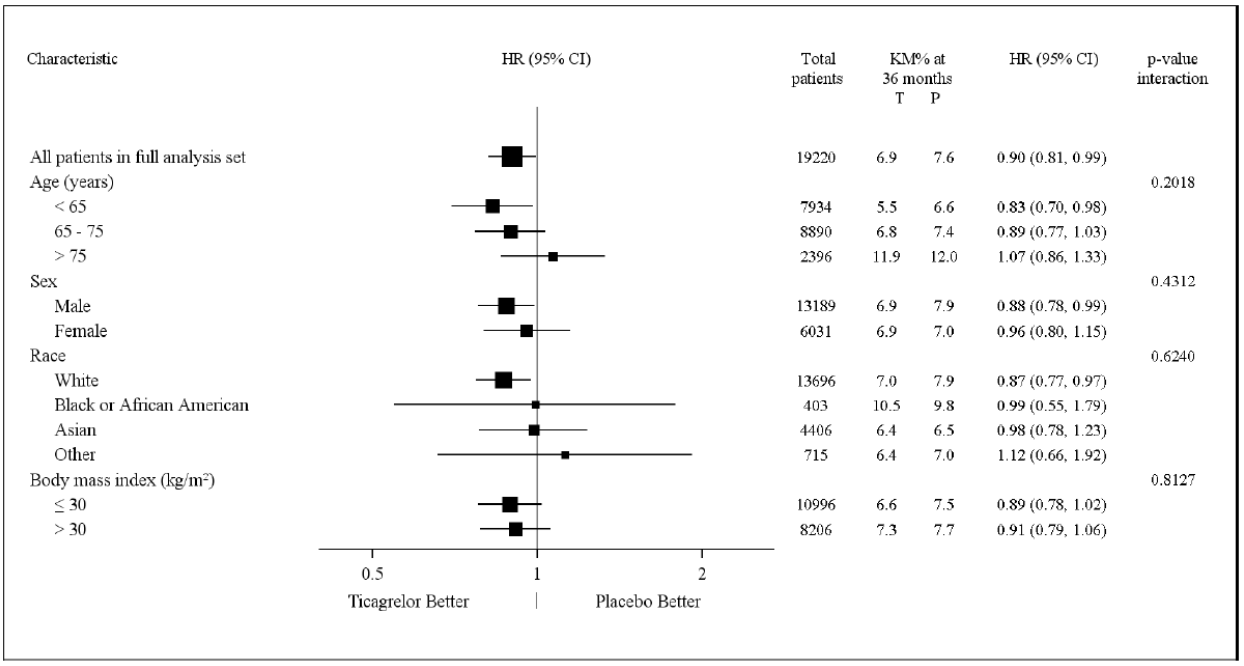
The treatment effect of ticagrelor versus placebo was consistent across pre-specified subgroups:

- Age, gender, race, body mass index (Figure 7).
- Geographic region, use of aspirin and aspirin dose at baseline, HbA1c at baseline, eGFR at baseline, and use of insulin at baseline (Figure 8).
- History of angina, presence of multivessel CAD (yes or no), history of PCI, type of stent placed (drug eluting, bare metal, PCI with no stent), time since the most recent PCI, and history of Coronary Artery Bypass Surgery (CABG) (Figure 9). There was an anomalous finding of marginal significance in favor of placebo over ticagrelor for 859 subjects who had a PCI without stent implantation (KM % at 36 months: 8.1% in the ticagrelor arm and 5.1% in the placebo arm, HR 1.47, 95%CI 0.87-2.48). There was also an anomalous finding of greater efficacy for ticagrelor over placebo in 1145 subjects who had a PCI less than 1 year prior to randomization (KM% at 36 months: 5.4% in the ticagrelor arm and

9.2% in the placebo arm, HR 0.54, 95%CI 0.36-0.83).

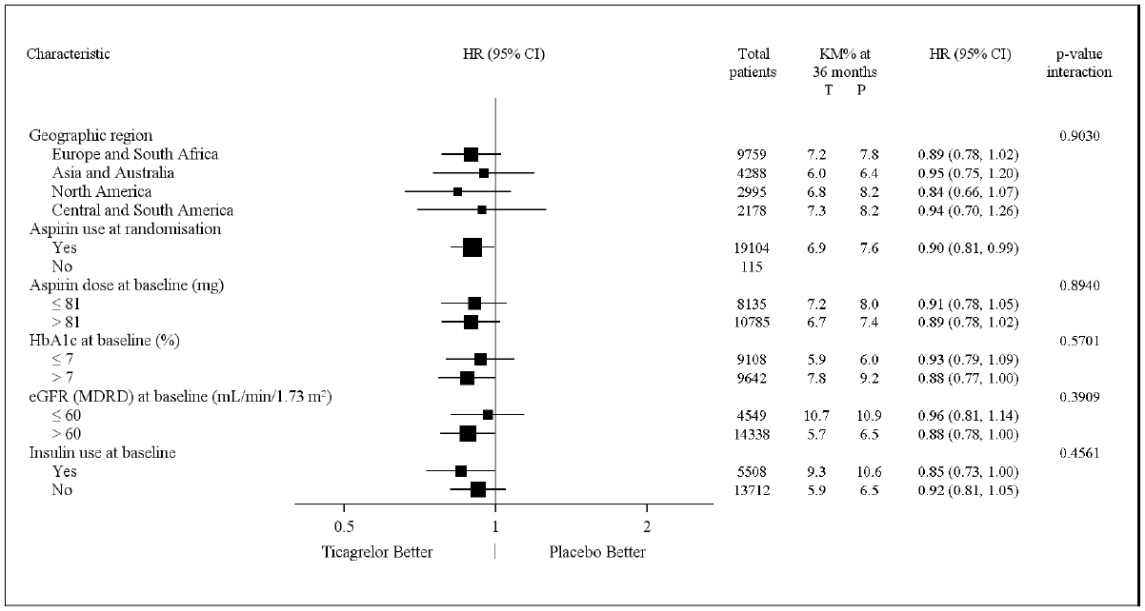
- Time since most recent CABG, history of coronary arterial revascularization (PCI or CABG), statin use at baseline, proton-pump inhibitor use at baseline, current smoking status, and duration of diabetes (Figure 10).
- History of diabetic complications at baseline, number of prior diabetic complications, history of PAD, history of poly-vascular disease and number of vascular beds (Figure 11).

Figure 7: Subgroup Analyses Baseline Characteristics: Age, Gender, Race, BMI (FAS)



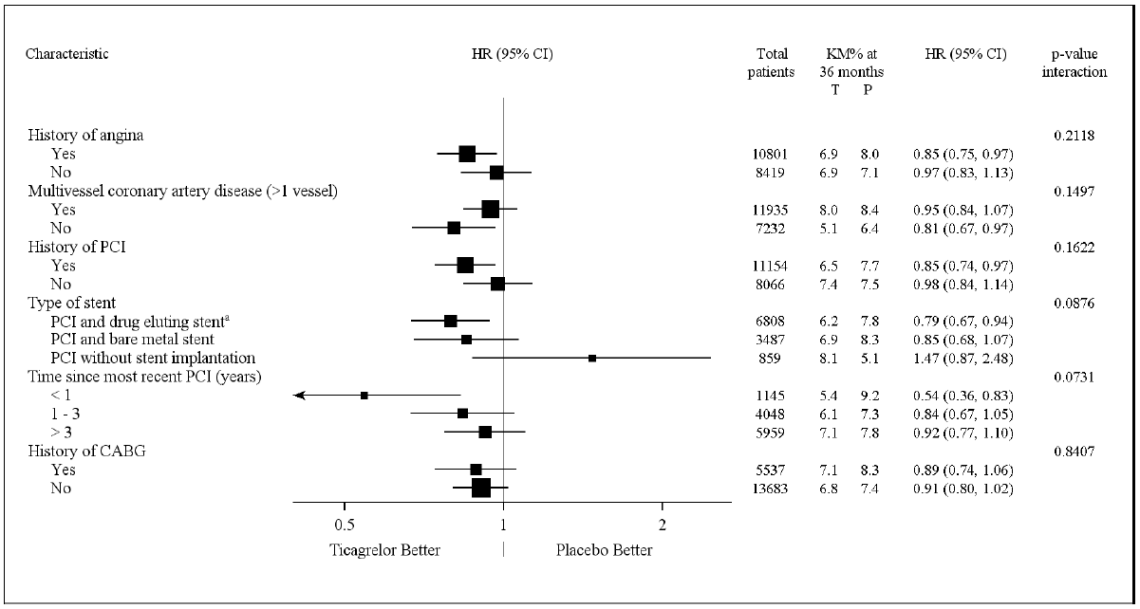
Source: root/cdar/d513/d513bc00001/ar/csr/tlf/dev/program/s1102p015.sas (Fig. 11.2.4.1 CSR) [verified by the statistical reviewer]

Figure 8: Subgroup Analyses Baseline Characteristics: Region, ASA, HbA1c, GFR, Insulin (FAS)



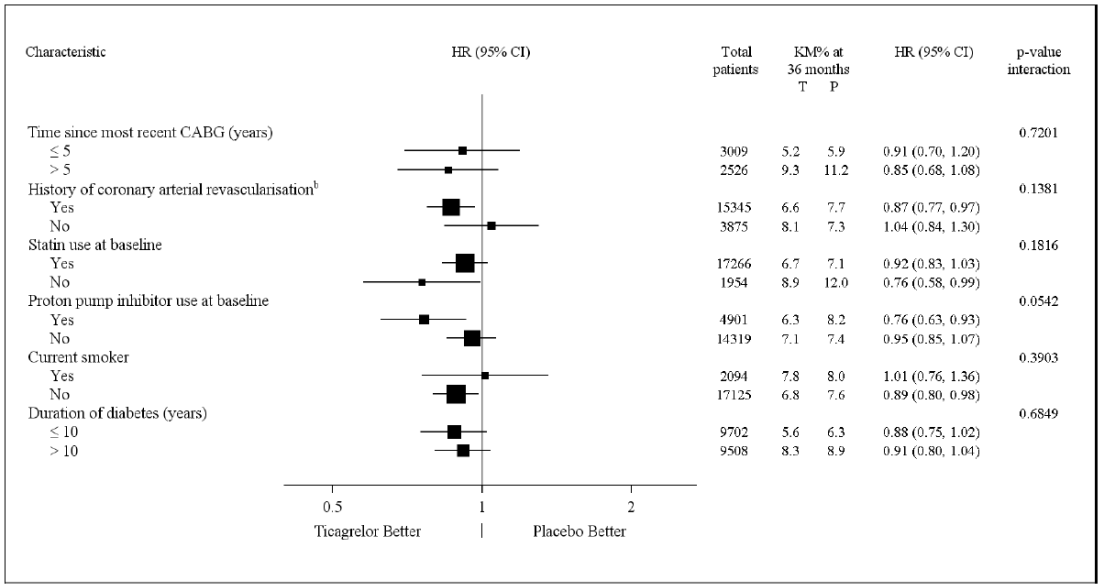
Source: root/cdar/d513/d513bc00001/ar/csr/tlf/dev/program/s1102p015.sas (Fig. 11.2.4.1 CSR)

Figure 9: Subgroup Analyses Baseline Characteristics: Angina, CAD, PCI, CABG (FAS)



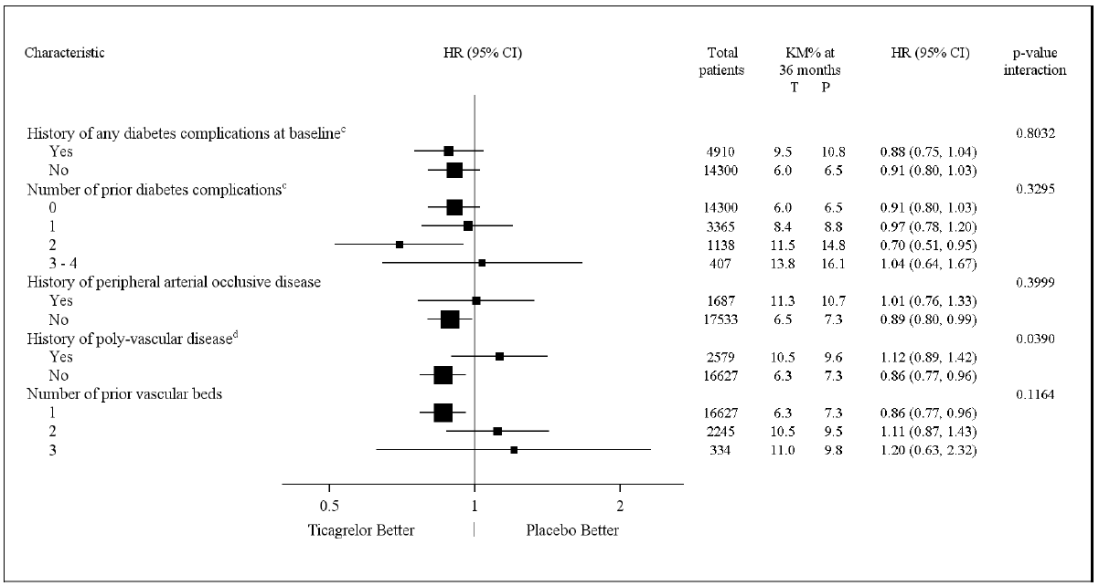
Source: root/cdar/d513/d513bc00001/ar/csr/tlf/dev/program/s1102p015.sas (Fig. 11.2.4.1 CSR) (*a: includes any subject with a drug eluting stent, or both a drug eluting stent and a bare metal stent*)

Figure 10: Subgroup Analyses Baseline Characteristics: Statin, PPI, Smoking, Diabetes (FAS)



Source: root/cdar/d513/d513bc00001/ar/csr/tlf/dev/program/s1102p015.sas (Fig. 11.2.4.1 CSR) (*b: defined as PCI ore CABG*)

Figure 11: Subgroup Analyses Baseline Characteristics: Diabetic Complication, Poly-Vasc (FAS)



Source: root/cdar/d513/d513bc00001/ar/csr/tlf/dev/program/s1102p015.sas (Fig. 11.2.4.1 CSR) (*c: history of retinopathy, autonomic neuropathy, peripheral neuropathy, and nephropathy*; *d: defined as arterial obstructive disease involving at least 2 vascular beds where a vascular bed is characterized by either as coronary, peripheral, or cerebral*)

Data Quality and Integrity

In a joint clinical, statistical and OSI meeting, a decision was made not to perform a routine or for-cause audit-see Office of Scientific Investigations (OSI), section 3.1.

Efficacy Results – Secondary and other relevant endpoints

A hierarchical analysis of the secondary efficacy endpoints: 1) CV death; 2) MI; 3) Ischemic stroke; and 4) All-Cause Death is shown in Table 24. There was no difference between ticagrelor and placebo in the incidence of CV death. Thus, the statistical hierarchical testing to control type-1 error was stopped.

Table 24: Secondary Endpoint Hierarchical Analysis (FAS)

Secondary EP	Ticagrelor		Placebo			
	N=9619		N=9601		α = 0.0496	
	Number of Pts with SEP		Number of Pts with SEP			
	Pt with Events (%)	KM% at 36 M	Pt with Events (%)	KM% at 36 M	HR (95%CI)	Nominal p-value
CV Death	364 (3.8%)	3.3%	357 (3.7%)	3.0%	1.02 (0.88-1.18)	0.79
MI	274 (2.8%)	2.6%	328 (3.4%)	3.3%	0.84 (0.71-0.98)	0.03
Ischemic Stroke	152 (1.6%)	1.5%	191 (2.0%)	1.8%	0.80 (0.64-0.99)	0.04
All-cause death*	579 (6.0%)	5.1%	592 (6.2%)	4.9%	0.98 (0.87-1.10)	0.68

Source: root/cdar/d513/d513bc00001/ar/csr/tlf/dev/program/s1102p002.sas (Table 11.2.2.1 CSR)
(**Note: all-cause death included deaths based on publicly available vital status in subjects who have withdrawn consent; the significance level was 0.0496 due to adjustment for an interim analysis*)
[verified by the statistical reviewer]

Dose/Dose Response

Sensitivity analyses of the primary efficacy endpoint were conducted to evaluate the consistency between the overall effect and the effect of the 60 mg dose (Table 25). These analyses included: *1)* the overall treatment effect using treatment as the only explanatory variable as previously reported for both 90 mg and 60 mg combined doses (Table 15); *2)* the subgroup of subjects who received only the 60 mg dose (i.e., randomized to 60 mg) using treatment effect as the only explanatory variable as previously reported (Table 23). An additional analysis included patients randomized to either ticagrelor 60 mg or 90 mg, the latter were event-free up to the day the dose was reduced to 60 mg. Onset date was either the randomization date for those randomized to 60 mg or the date when patients switched to 60 mg. All events after patients started on 60 mg were included in the analysis (even after patient

discontinued 60 mg), resulting a HR of 0.86 with 95% CI (0.76, 0.97).

The sensitivity analyses showed that the FAS population who received 60 mg, either upon initial randomization or by dose reduction after having been randomized to 90 mg had similar efficacy to that of the overall FAS population (*HR 0.90, 95%CI 0.81-0.99* .vs. *HR 0.86, 95%CI 0.76-0.97*). Subjects who received only the 60 mg dose using treatment as the only explanatory variable in the sensitivity analysis showed a similar hazard ratio.

Table 25: Sensitivity Analysis: consistency of effect (60 mg vs overall) (FAS)

FAS	Ticagrelor			Placebo				
	N	Pts w PEP	KM%*	N	Pts w PEP	KM%*	HR (95%CI)	p-value
T vs P[A]	9619	736 (7.7%)	4.6%	9601	818 (8.5%)	4.9%	0.90 (0.81-0.99)	0.038
T vs P 60 mg[B]	2492	127 (5.1%)	3.5%	2532	147 (5.8%)	4.2%	0.87 (0.69-1.11)	0.259

** KM timepoint is 24 months; HR=Hazard Ratio; Pts w PEP= patients experiencing a primary endpoint; T=ticagrelor; P=placebo*
A: PEP using treatment as the only explanatory (i.e., explanatory = "independent but not certain to be independent"- https://www.statisticshowto.datasciencecentral.com/explanatory-variable/*) variable.*
B: PEP using treatment as the only explanatory variable in only those subjects randomized to 60 mg or matching placebo.

Source: root/cdar/d513/d513bc00001/ar/csr/tlf/dev/program/s1102p018.sas (Table11.2.4.2 CSR)
[verified by the statistical reviewer]

On-treatment sensitivity analyses of the primary efficacy endpoint were conducted on the safety dataset to compare the effect of the 60 mg dose vs the 90 mg dose (Table 26). Treatment was the only explanatory variable used. These analyses included: *1)* overall treatment effect in the safety population; *2)* subgroup of subjects randomized to the 60 mg dose (events were included with onset date from randomization to 7 days after the last dose of study drug 60 mg); *3)* subgroup of subjects randomized to the 90 mg dose (events were included with onset date from randomization to 7 days after the last dose of study drug 90 mg); and *4)* subjects randomized to either 60 mg or 90 mg, the latter were event-free up to the day the dose was reduced to 60 mg.

These on-treatment sensitivity analyses showed the 60 mg dose to be comparable in efficacy to that seen in the safety dataset. Similarly, subjects randomized to 60 mg or to 90 mg whereby the latter were event free when the dose was reduced to 60 mg showed comparable efficacy to that seen in the safety dataset. The subset of subjects randomized to the 90 mg dose where collected events included those that occurred while on 90 mg and up to 7 days since the last dose of the 90 mg dose, showed no difference in efficacy compared to placebo at 24 months.

This is likely due to the short duration that most subjects were on 90 mg dose (the median on-treatment duration was 273 days). The treatment benefit was not shown until 12 to 15 months.

Table 26: Sensitivity Analysis: consistency of effect (60 mg vs 90 mg) (Safety Dataset)

Safety Set	Ticagrelor			Placebo				
	N	Pts w PEP	KM%*	N	Pts w PEP	KM%*	HR (95%CI)	p-value
All pts	9562	425 (4.4%)	3.8%	9531	580 (6.1%)	4.2%	0.83 (0.73-0.94)	0.003
Only 60 mg[a]	2482	70 (2.8%)	2.7%	2516	108 (4.3%)	3.4%	0.72 (0.53-0.97)	0.031
90 mg[b]	7080	116 (1.6%)	3.4%	7015	131 (1.9%)	3.8%	0.99 (0.77-1.27))	0.932
90 or 60 mg[c]	7917	309 (3.9%)	3.6%	8524	450 (5.3%)	4.3%	0.78 (0.68-0.90)	0.0009

** KM timepoint is 24 months; HR=Hazard Ratio; Pts w PEP= patients experiencing a primary endpoint;*
a: Includes only patients randomized to 60 mg or matching placebo. Includes events with onset date from randomization to 7 days after last dose of study drug 60 mg.
b: Includes only patients randomized to 90 mg or matching placebo. Includes events with onset date from randomization to 7 days after last dose of study drug 90 mg.
c: Includes patients randomized to study drug 60 mg or 90 mg who were event-free up to the day the dose was reduced to 60 mg. Time was counted when subjects started 60 mg dose.

Source: root/cdar/d513/d513bc00001/ar/csr/tlf/dev/program/s1102p018.sas (Table 11.2.4.3 CSR) [verified by the statistical reviewer]

The sensitivity analyses showed consistency of effect between the 60 mg dose and the overall effect.

6. Integrated Review of Effectiveness

6.1. Assessment of Efficacy Across Trials

This sNDA was based on a single clinical trial. Therefore, this section is not applicable.

6.2. Additional Efficacy Considerations

6.2.1. Considerations on Benefit in the Postmarket Setting

The post-marketing benefit is expected to be consistent with that observed in the THEMIS trial.

The dosing regimen of ticagrelor for the proposed indication emanating from the THEMIS trial is the same as that currently described in the label for the currently approved indications based on the PLATO and PEGASUS trials, except the loading dose.

The characteristics of the patient population in the THEMIS trial are similar to that previously

studied. As pointed out in section 2.2 of this review, the PLATO trial (N=18,624) included a total of 4662 subjects (25%) with diabetes mellitus. Similarly, the PEGASUS TIMI-54 trial (N= 14,112) included a total of 4565 subjects (32%) with diabetes mellitus. Also, 56% of the THEMIS population had a history of angina pectoris and a similar percentage had a PCI.

The distinguishing subject characteristic in the THEMIS trial compared to the previous trials is the lack of baseline MI and stroke, and no ACS upon presentation for enrollment. Thus, it is reasonable to infer that the THEMIS population represented a primary prevention segment, thus widening the spectrum of coronary artery disease under which ticagrelor is effective.

The African-American population was under-represented in THEMIS (2% of the FAS population), as well as in the antecedent trials. This is in contradistinction to the current initiatives from the FDA and academic organizations to provide adequate racial / ethnic representation in clinical trials.

6.3. Integrated Assessment of Effectiveness

The applicant met the evidentiary standard pursuant to §21 CFR 314.126 to support approval of ticagrelor for the primary prevention of treatment myocardial infarction and stroke in patients with established CAD.

The THEMIS trial of 19,220 subjects with diabetes mellitus, coronary artery disease and other risk factors (hypertension and dyslipidemia) but without a history of MI or stroke, served as the sole trial to support the proposed indication.

The study was well conducted in 42 countries at 1315 sites, with 51% of the FAS population enrolled in Europe, 22% from Asia, 12% from the USA, 4% from Canada, and 11% from Central / South America. The review team determined that no single site or group of sites could have impacted the overall study results. Furthermore, clinical guidelines were uniformly applied to the management of the FAS population, thereby attenuating regional differences in clinical practice that may have impacted interpretation of the trial outcome.

There was a paucity of protocol violations or conflict of interest amongst the investigators.

Baseline characteristics, baseline medications, and concomitant medications were evenly distributed between the two arms of the THEMIS trial.
The hazard ratio for the composite endpoint of CV death, MI, and stroke was statistically significant (HR 0.90, 95%CI 0.81-0.99). These results were based on the combination of 2 doses used in the study: 60 mg and 90 mg PO twice daily. The results showed durability of effect over a 36-month follow-up period. The results were consistent across pre-specified subgroups. The

overall results were not dissimilar those from the PLATO and PEGASUS-TIMI 54 trials for their respective indications.

The hazard ratio for the 60 mg dose was similar to the overall FAS population but did not meet statistical significance (HR 0.87, 95%CI 0.69-1.11) likely due to the relatively smaller sample size in this subgroup (n=2492 in the ticagrelor arm; and n=2532 in the placebo arm). A sensitivity analysis using treatment and a time covariate indicator (i.e., the duration of time spent on 60 mg PO twice daily) demonstrated consistency of effect between the 60 mg dose and the overall FAS population having received either 90 mg only, 90 mg then 60 mg at some timepoint, or 60 mg only.

The results were driven by MI and stroke, each showing statistically significant benefit. The MIs were mostly type 1, and the strokes were mostly ischemic. CV death did not contribute to efficacy.

See section 9 for proposed labeling.

7. Review of Safety

7.1. Safety Review Approach

The safety review was abbreviated and focused on bleeding risk that has already been established in the BRILINTA® label as a warning. The evaluation of bleeding was based on the TIMI, PLATO and BARC criteria (see Appendix 12.1 for criteria). Other adverse events of specific interest (e.g., dyspnea, renal impairment, bradyarrhythmia, gout) were reviewed because they occurred in higher frequency in previous trials.

7.2. Review of the Safety Database

7.2.1. Overall Exposure

In the THEMIS trial, 9562 subjects received ticagrelor and 9531 subjects received placebo (*note: compared to Table 8, there was 1 subject who was randomized to placebo who inadvertently received ticagrelor. Therefore, the numbers here and those from the table are off by 1)*. Of the subjects receiving ticagrelor, 7080 were instructed to reduce the dose to 60 mg and 2482 subjects were randomized directly to ticagrelor 60 mg BID.

The mean duration of ticagrelor (both doses) and corresponding matching placebos was 28.2 months and 32.3 months, respectively. The mean duration of ticagrelor 90 mg and

corresponding matching placebo was 8.6 months and 9.6 months, respectively. The mean duration of ticagrelor 60 mg and corresponding placebo was 26.2 and 28.0 months, respectively (Table 27, Table 28, and Table 29).

A total of 70.5% of the subjects on ticagrelor and 74.3% of the subjects on placebo received study drug without interruption. Of the 29.5% on ticagrelor and 25.7% on placebo who had an interruption of study drug, the majority had 1 interruption. The mean total number of days of drug interruption was 102.8 for ticagrelor and 88.7 for placebo (Table 30).

The difference in exposure between ticagrelor and placebo began within the first week of exposure and was maintained for the duration of the study (Table 31 and Figure 12). As the sample size decreased over time, the difference between ticagrelor and placebo in exposure was attenuated.

Table 27: Duration of Exposure to Ticagrelor-Both Doses (Safety Dataset)

Duration of Exposure (Months)	Ticagrelor (both doses)	Placebo
(Excluding Interruptions)	N=9562	N=9531
Mean (SD)	28.2 (16.7)	32.3 (14.7)
Median (1st, 3rd Quartile)	32.5 (12.0, 41.3)	35.4 (24.8, 42.9)
Minimum	0	0
Maximum	58	59

Source: root/cdar/d513/d513bc00001/ar/csr/tlf/dev/program/s1103p001.sas (Table11.3.1.1 CSR)

Table 28: Duration of Exposure to Ticagrelor-90 mg Dose (Safety Dataset)

Duration of Exposure (Months)	Ticagrelor (90 mg)	90 mg Matching Placebo
(Excluding Interruptions)	N=7078	N=7014
Mean (SD)	8.6 (6.2)	9.8 (6.1)
Median (1st, 3rd Quartile)	7.3 (3.1, 12.3)	9.1 (5.0, 14.2)
Minimum	0	0
Maximum	47	50

Source: root/cdar/d513/d513bc00001/ar/csr/tlf/dev/program/s1103p001.sas (Table11.3.1.1 CSR)

Table 29: Duration of Exposure to Ticagrelor-60 mg Dose (Safety Dataset)

Duration of Exposure (Months) (Excluding Interruptions)	Ticagrelor (60 mg) N=7953	60 mg Matching Placebo N=8562
Mean (SD)	26.2 (11.5)	28.0 (10.1)
Median (1st, 3rd Quartile)	31.6 (19.8, 35.0)	32.2 (23.3, 35.3)
Minimum	0	0
Maximum	40	46

Source: root/cdar/d513/d513bc00001/ar/csr/tlf/dev/program/s1103p001.sas (Table11.3.1.1 CSR)

Table 30: Treatment Interruptions (Safety Dataset)

Interruptions	Ticagrelor	Placebo
	N= 9562	N= 9531
Subjects without Interruption	6738 (70.5%)	7086 (74.3%)
Subjects with an interruption		
-any interruption	2824 (29.5%)	2445 (25.7%)
-1 interruption	1913 (20.0%)	1738 (18.2%)
-2 interruptions	604 (6.3%)	473 (5.0%)
-3 interruptions	189 (2.0%)	145 (1.5%)
->3 interruptions	118 (1.2%)	89 (0.9%)
Total days of interruption/pt		
n	2824	2445
Mean (SD)	102.8 (163.9)	88.7 (145.4)
Median (Min, Max)	28.0 (1, 1107)	23.0 (1, 1163)

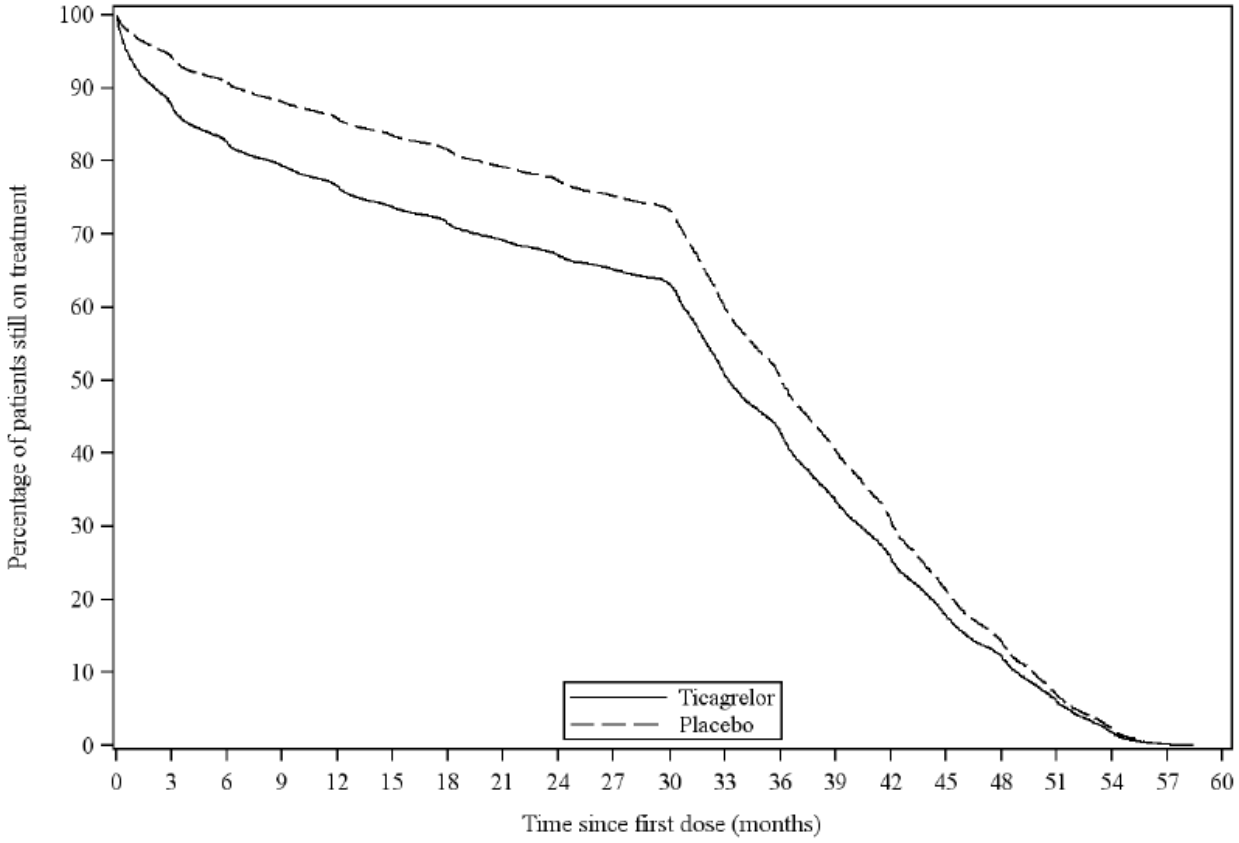
Source: root/cdar/d513/d513bc00001/ar/csr/tlf/dev/program/s1103p004.sas (Table11.3.1.3 CSR)

Table 31: Cumulative Exposure Over Time (Safety Dataset)

	Number (%) of Subjects	
Time on study treatment *	Ticagrelor	Placebo
	N=9562	N=9531
1 day	9562 (100%)	9531 (100%)
7 days	9348 (97.8%)	9437 (99.0%)
1 month	8912 (93.2%)	9269 (97.3%)
6 months	7906 (82.7%)	8659 (90.9%)
12 months	7322 (76.6%)	8182 (85.8%)
18 months	6837 (71.5%)	7779 (81.6%)
24 months	6421 (67.2%)	7373 (77.4%)
30 months	6035 (63.1%)	6983 (73.3%)
36 months	4107 (43.0%)	4797 (50.3%)
42 months	2486 (26.0%)	2968 (31.1%)
48 months	1175 (12.3%)	1363 (14.3%)
**Rows are cumulative, and subjects are included if they have taken treatment up to and including that day*		

Source: root/cdar/d513/d513bc00001/ar/csr/tlf/dev/program/s1103p002.sas (Table11.3.1.2 CSR)

Figure 12: Exposure Over Time (Safety Dataset)



Source: root/cdar/d513/d513bc00001/ar/csr/tlf/dev/program/s1103p003.sas (Figure 11.3.1.1 CSR)

7.3. Safety Results

7.3.1. Adverse Events

Adverse events of interest are displayed in Table 32. The incidence of any bleed was 2.7x greater in the ticagrelor arm compared to that in placebo arm. The incidence of dyspnea was 3.3x greater in the ticagrelor arm compared to that in the placebo arm. Other adverse events of interest (i.e., renal impairment, bradyarrhythmia, gout, and pneumonia) were balanced.

There were twice as many adverse events leading to discontinuation in the ticagrelor arm compared to the placebo arm, mostly due to dyspnea.

The incidence of death and of any serious adverse event were balanced between the two groups.
Serious adverse events by system organ class (Table 33) were evenly balanced between the two groups for each organ class.

Table 32: Adverse Events of Interest (Safety Dataset)

	Ticagrelor (N=9562)		Placebo (9531)	
AE	# pts (%) with event	Event Rate/100 y[a]	# pts (%) with event	Event Rate/100 y
Any Bleed[b]	1446 (15.1%)	6.2	595 (6.2%)	2.3
Any AESI	2562 (26.8%)	11.0	1302 (13.7%)	5.0
-dyspnea	2049 (21.4%)	8.8	700 (7.3%)	2.7
-renal imp	225 (2.4%)	1.0	220 (2.3%)	0.8
-brady-arr	137 (1.4%)	0.6	120 (1.3%)	0.5
-gout	190 (2.0%)	0.8	159 (1.7%)	0.6
-pneumonia	252 (2.6%)	1.1	263 (2.8%)	1.0
AE->Death	256 (2.7%)	1.1	309 (3.2%)	1.2
Any SAE	3049 (31.9%)	13.1	3210 (33.7%)	12.2
AE->discon	1987 (20.8%)	8.6	1167 (12.2%)	4.4
AESI = adverse event of specific interest; renal imp= renal impairment; brady-arr= bradyarrhythmia; AE->Death= AE leading to death; AE->discon=AE leading to study drug discontinuation				
a: number of subjects with AEs divided by the total duration of treatment across all subjects in a given arm, multiplied by 100; b: adverse events with a bleeding documented by the investigator on a bleeding event eCRF, excluding events adjudicated as not a bleeding event				

Source: root/cdar/d513/d513bc00001/ar/csr/tlf/dev/program/s1103p039.sas (Table11.3.3.1 CSR)

Table 33: Serious Adverse Events by System Organ Class (Safety Dataset)

	Number (%) of Subjects			Number (%) of Subjects	
	Ticagrelor	Placebo		Ticagrelor	Placebo
	N=9562	N=9531		N=9562	N=9531
Any SAE	3049 (31.9%)	3210 (33.7%)			
SOC			*SOC*		
Cardiac	1140 (11.9%)	1344 (14.1%)	*Hepatobiliary*	78 (0.8%)	100 (1.0%)
Infections	462 (4.8%)	489 (5.1%)	*Blood/Lymph*	82 (0.9%)	41 (0.4%)
Nervous Syst.	320 (3.3%)	410 (4.3%)	*Eye*	56 (0.6%)	61 (0.6%)
GI	355 (3.7%)	253 (2.7%)	*Reproductive*	57 (0.6%)	43 (0.5%)
Neoplasms	285 (3.0%)	296 (3.1%)	*Skin / Subcut.*	50 (0.5%)	48 (0.5%)
Injury/Poison	229 (2.4%)	212 (2.2%)	*Ear/labyrinth*	33 (0.3%)	20 (0.2%)
Vascular	185 (1.9%)	226 (2.4%)	*Investigations*	27 (0.3%)	21 (0.2%)
Metabolism	178 (1.9%)	213 (2.2%)	*Psychiatric*	23 (0.2%)	18 (0.2%)
Musculoskeletal	182 (1.9%)	199 (2.1%)	*Immune*	5 (0.1%)	11 (0.1%)
Renal	199 (2.1%)	169 (1.8%)	*Endocrine*	9 (0.1%)	6 (0.1%)
Respiratory	194 (2.0%)	172 (1.8%)	*Product Issues*	5 (0.1%)	6 (0.1%)
General	170 (1.8%)	175 (1.8%)	*Congenital*	3 (0.0%)	0 (0.0%)

Source: root/cdar/d513/d513bc00001/ar/csr/tlf/dev/program/s1103p051.sas (Table11.3.5.8 CSR)

The majority of any bleeding events were mostly subcutaneous, followed by gastrointestinal, epistaxis, and genitourinary (Table 34). Intracranial hemorrhages were balanced between the two groups (0.7% ticagrelor, 0.5% placebo).

There was a very low incidence of fatal bleeds: 17 subjects in the ticagrelor arm (0.2%) and 10 subject in the placebo arm (0.1%). Fatal bleeds by system organ class and preferred term (Table 35) were balanced between the two groups with the exception of *Injury/Poisoning/Procedural* class (7 cases in the ticagrelor arm and 2 cases in the placebo arm). The largest difference between the two groups in this class was subdural hematoma (3 ticagrelor, 0 placebo) and traumatic intracranial hemorrhage (2 ticagrelor cases, 0 placebo).

Data analysis of intracranial hemorrhage by neuroanatomy did not reveal any predilection (Table 36). Preferred terms distinguished an intracranial hemorrhage (1 ticagrelor vs 4 placebo) from a trauma-induced intracranial hemorrhage (11 ticagrelor cases, 7 placebo cases).

Table 34: Bleeding Events by Location (Safety Dataset)

Bleed Location[a]	Total # Bleeding Events		Number (%) of Pts with Bleeding Events	
	Ticagrelor	Placebo	Ticagrelor	Placebo
			N=9562	N=9531
Any Bleed[b]	1771	684	1446 (15.1%)	595 (6.2%)
Subcutaneous	587	114	519 (5.4%)	106 (1.1%)
GI	400	182	374 (3.9%)	169 (1.8%)
Epistaxis	358	127	287 (3.0%)	107 (1.1%)
GU	189	107	173 (1.8%)	96 (1.0%)
Intracranial	70	46	70 (0.7%)	46 (0.5%)
Intraocular	69	49	65 (0.7%)	45 (0.5%)
Other	55	29	54 (0.6%)	29 (0.3%)
Hemoptysis	29	19	26 (0.3%)	19 (0.2%)
PCI access site	3	4	3 (0.0%)	4 (0.0%)
Intra-articular	2	2	2 (0.0%)	2 (0.0%)
Pericardial	1	3	1 (0.0%)	3 (0.0%)
IM-compartment syndrome	2	1	2 (0.0%)	1 (0.0%)
Retroperitoneal	2	1	2 (0.0%)	1 (0.0%)
Intraspinal	0	0	0 (0.0%)	0 (0.0%)
IM= intramuscular				
a: location recorded on the eCRF form by the investigator; b: adverse events with a bleeding documented by the investigator on a bleeding event eCRF, excluding events adjudicated as not a bleeding event				

Source: root/cdar/d513/d513bc00001/ar/csr/tlf/dev/program/s1103p087.sas (Table11.3.2.24 CSR)

Table 35: Fatal Bleeds by System Organ Class and Preferred Term (Safety Dataset)

Fatal Bleeding	Ticagrelor (N=9562)		Placebo (N=9531)	
	# pts (%)	Rate (per 100 pt yrs)	# pts (%)	Rate (per 100 pt yrs)
Subjects with a fatal bleed	17 (0.2%)	0.07	10 (0.1%)	0.04
Nervous System	8 (0.1%)	0.03	6 (0.1%)	0.02
-Brain stem hemorrhage	2 (0.0%)	0.01	0 (0.0%)	0.00
-Cerebral hematoma	0 (0.0%)	0.00	1 (0.0%)	0.00
-Cerebral hemorrhage	2 (0.0%)	0.01	2 (0.0%)	0.01
-ICH	1 (0.0%)	0.00	1 (0.0%	0.00
-Hemorrhagic stroke	3 (0.0%)	0.01	2 (0.0%)	0.01
Cardiac	0 (0.0%)	0.00	1 (0.0%)	0.00
-Cardiac tamponade	0 (0.0%)	0.00	1 (0.0%)	0.00
GI	1 (0.0%)	0.00	0 (0.0%)	0.00
-GI hemorrhage	1 (0.0%)	0.00	0 (0.0%)	0.00
Hepatobiliary	0 (0.0%)	0.00	1 (0.0%)	0.00
-Cirrhosis alcoholic	0 (0.0%)	0.00	1 (0.0%)	0.00
General	1 (0.0%)	0.00	0 (0.0%)	0.00
-Device site hemorrhage	1 (0.0%)	0.00	0 (0.0%)	0.00
Injury/Poisoning/Procedural	7 (0.1%)	0.03	2 (0.0%)	0.01
-Post procedural hematoma	1 (0.0%)	0.00	0 (0.0%)	0.00
-Subdural hematoma	3 (0.0%)	0.01	0 (0.0%)	0.00
-Subdural hemorrhage	0 (0.0%)	0.00	2 (0.0%)	0.01
-Traumatic hemorrhage	1 (0.0%)	0.00	0 (0.0%)	0.00
-Traumatic ICH	2 (0.0%)	0.01	0 (0.0%)	0.00
ICH= intracranial hemorrhage; Event rate per 100 pt yrs: number of subjects with adverse events divided by the total duration of treatment across all patients in the given group, multiplied by 100				
Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than 1 category are counted once in each of those categories.				

Source: root/cdar/d513/d513bc00001/ar/csr/tlf/dev/program/s1103p023.sas (Table 11.3.2.19)

Table 36: Intracranial Hemorrhage Events by Anatomy and Preferred Term (Safety Dataset)

ICH	Ticagrelor			Placebo		
	N=9562			N=9531		
Characteristic						
	Pt with Events (%)	# Events	Rate per 100 pt yrs	Pt with events (%)	# Events	Rate per 100 pt yrs
Any ICH	70 (0.7%)	70	0.30	46 (0.5%)	46	0.18
Neoplasm	1 (0.0%)	1	0.00	0 (0.0%)	0	0.00
-Meningioma	1 (0.0%)	1	0.00	0 (0.0%)	0	0.00
CNS	23 (0.2%)	23	0.10	26 (0.3%)	26	0.10
-Basal ganglia	1 (0.0%)	1	0.00	0 (0.0%)	0	0.00
-Brain stem	2 (0.0%)	2	0.01	0 (0.0%)	0	0.00
-Cerebellar	0 (0.0%)	0	0.00	1 (0.0%)	1	0.00
-Cerebral	6 (0.1%)	6	0.03	7 (0.01)	7	0.02
-ICH	1 (0.0%)	1	0.00	4 (0.0%)	4	0.02
-Stroke Hem	10 (0.1%)	10	0.04	8 (0.1%)	8	0.03
-Stroke trans	0 (0.0%)	0	0.00	1 (0.0%)	1	0.00
-Putamen	0 (0.0%)	0	0.00	1 (0.0%)	1	0.00
-Subarach	2 (0.0%)	2	0.01	3 (0.0%)	3	0.01
-Thalamic	0 (0.0%)	0	0.00	1 (0.0%)	1	0.00
Injury/Proc	46 (0.5%)	46	0.20	20 (0.2%)	20	0.08
-Craniocerebr	2 (0.0%)	2	0.01	0 (0.0%)	0	0.00
-Epidural	0 (0.0%)	0	0.00	1 (0.0%)	1	0.00
-Extradural	0 (0.0%)	0	0.00	1 (0.0%)	1	0.00
-Head Injury	1 (0.0%)	1	0.00	0 (0.0%)	0	0.00
-Subdural	32 (0.3%)	32	0.10	11 (0.1%)	11	0.02
-Trauma-ICH	11 (0.1%)	11	0.05	7 (0.1%)	7	0.03
ICH= intracranial hemorrhage; Stroke Hem= hemorrhagic strok0.05e; Stroke trans= hemorrhagic transformation stroke; Subarach= subarachnoid hemorrhage; Injury/Proc= Injury/Procedures; Craniocerebr= craniocerebral; Trauma ICH= Traumatic intracranial hemorrhage						
Subjects with multiple events in the same category were counted only once in that category. Subjects with events in more than 1 category were counted once in each of those categories.						

Source: root/cdar/d513/d513bc00001/ar/csr/tlf/dev/program/s1103p023.sas (Table 11.3.2.21)

7.3.2. Bleeding Adverse Events by TIMI, PLATO and BARC Criteria

There were twice as many *TIMI major*, *TIMI major or minor*, and *TIMI major/minor or bleeds requiring medical attention* in the ticagrelor arm compared to the placebo arm (Table 37) and were mostly classified as spontaneous and traumatic (Table 38). TIMI bleeding classified as procedural were generally balanced between the two arms. This pattern was also evident when using PLATO criteria (Table 39 and Table 40) as well as BARC criteria (Table 41).

The pattern observed in TIMI bleeding between the two arms was consistent in all pre-specified subgroups with the exception of gender (see appendix 12.4). Women had a significantly higher risk of a TIMI major bleed (HR 5.00, 95% CI 2.67-9.35) than men (HR 1.95, 95% CI 1.50-2.54).

A sensitivity analysis was performed to ascertain the TIMI major bleeding effect of the 60 mg dose vs the 90 mg dose, each compared to respective placebo. TIMI major bleeding between the two arms was evaluated using: 1) treatment as the only explanatory variable; 2) treatment as the only explanatory variable in those subjects randomized to 60 mg or matching placebo (Table 42). An additional analysis on TIMI major bleeding included patients treated with either ticagrelor 60 mg or 90 mg, the latter were event-free up to the day the dose was reduced to 60 mg. Onset date was either the randomization date for those randomized to 60 mg or the date when patients switched to 60 mg. All events after patients started on 60 mg were included in the analysis (even after patient discontinued 60 mg), resulting in a HR of 2.02 with 95% CI (1.53, 2.67). There was a similar bleeding effect between the 60 mg dose and the overall effect of the combined doses.

Table 43 shows the results of a sensitivity analysis comparing the TIMI major bleeding effect of ticagrelor versus placebo that included: 1) subjects randomized only to 60 mg where included endpoint events occurred with onset from randomization to 7 days after the last dose of 60 mg; 2) subjects randomized to 90 mg where included endpoint events occurred with onset from randomization to 7 days after the last dose of 90 mg; and 3) subjects randomized to 60 mg or 90 mg who were event-free up to the day the dose was reduced to 60 mg. The results showed a higher hazard ratio for the 90 mg ticagrelor dose versus placebo compared to the 60 mg dose versus placebo.

The Kaplan-Meier curves for TIMI major bleeding in the safety dataset (Figure 13) show bleeding events accumulating at the onset of therapy. The ticagrelor and placebo curves continue to separate for the entire duration of data capture (4.5 years).

Table 37: TIMI Bleeding Events (Safety Dataset)

TIMI Bleeds	Ticagrelor		Placebo			
Safety Dataset	N=9562		N=9531			
TIMI Category	Pt with Events (%)	KM% at 36 M	Pt with Events (%)	KM% at 36 M	HR (95%CI)	p-value
Major	206 (2.2%)	2.7%	100 (1.0%)	1.2%	2.3 (1.8-2.9)	<.0001
Major or Minor	285 (3.0%)	3.6%	129 (1.4%)	1.6%	2.5 (2.0-3.1)	<.0001
Major, Minor, or needed Medical Attention	1072 (11.2%)	13.0%	485 (5.1%)	5.6%	2.5 (2.3-2.8)	<.0001

Source: root/cdar/d513/d513bc00001/ar/csr/tlf/dev/program/s1103p006.sas (Table11.3.2.1 CSR)

Table 38: TIMI Bleeding Events by Severity and Provocation (Safety Dataset)

TIMI Bleed Characteristics	Total # Bleeding Events		Number (%) of Pts with Bleeding Events	
	Ticagrelor	Placebo	Ticagrelor	Placebo
			N=9562	N=9531
TIMI Major Bleeding	209	102	206 (2.2%)	100 (1.0%)
-Spontaneous	145	68	143 (1.5%)	67 (0.7%)
-Procedural	13	17	13 (0.1%)	17 (0.2%)
-Traumatic	51	17	51 (0.5%)	17 (0.2%)
TIMI Major or Minor Bleeding	297	131	285 (3.0%)	129 (1.4%)
-Spontaneous	216	90	208 (2.2%)	89 (0.9%)
-Procedural	23	22	23 (0.2%)	22 (0.2%)
-Traumatic	58	19	58 (0.6%)	19 (0.2%)
TIMI Major, Minor or Requiring medical attention	1220	548	1072 (11.2%)	485 (5.1%)
-Spontaneous	978	435	876 (9.2%)	391 (4.1%)
-Procedural	77	51	76 (0.8%)	50 (0.5%)
-Traumatic	165	62	159 (1.7%)	58 (0.6%)
Subjects may be counted in more than one bleeding event category.				

Source: root/cdar/d513/d513bc00001/ar/csr/tlf/dev/program/s1103p028.sas (Table 11.3.2.13)

Table 39: PLATO Major Bleeding (Safety Dataset)

PLATO Bleeds	Ticagrelor		Placebo			
Safety Dataset	N=9562		N=9531			
PLATO Category	Pt with Events (%)	KM% at 36 M	Pt with Events (%)	KM% at 36 M	HR (95%CI)	p-value
Major	310 (3.2%)	4.0%	145 (1.5%)	1.7%	2.4 (2.0,2.9)	<.0001
Fatal/Life Threatening	206 (2.2%)	2.6%	99 (1.0%)	1.2%	2.3 (1.8, 3.0)	<.0001
Other Major Bleed	108 (1.1%)	1.4%	46 (0.5%)	0.6%	2.6 (1.9, 3.7)	<.0001
Subjects with multiple events in the same category were counted only once in that category. Subjects with events in more than 1 category were counted once in each of those categories.						

Source: root/cdar/d513/d513bc00001/ar/csr/tlf/dev/program/s1103p017.sas (Table 11.3.2.6)

Table 40: PLATO Bleeding Events by Severity and Provocation (Safety Dataset)

PLATO Bleed Characteristics	Total # Bleeding Events		Number (%) of Pts with Bleeding Events	
	Ticagrelor	Placebo	Ticagrelor	Placebo
			N=9562	N=9531
PLATO Major Bleeding	324	147	310 (3.2%)	145 (1.5%)
-Fatal/Life threatening	211	101	206 (2.2%)	99 (1.0%)
-Other PLATO Major Bleeding	113	46	108 (1.1%)	46 (0.5%)
-Spontaneous	241	103	231 (2.4%)	102 (1.1%)
-Procedural	25	24	25 (0.3%)	24 (0.3%)
-Traumatic	58	20	58 (0.6%)	20 (0.2%)
PLATO Major or Minor Bleeding	1020	457	912 (9.5%)	410 (4.3%)
-Spontaneous	804	358	728 (7.6%)	326 (3.4%)
-Procedural	68	47	67 (0.7%)	46 (0.5%)
-Traumatic	148	52	144 (1.5%)	50 (0.5%)
Subjects may be counted in more than one bleeding event category.				

Source: root/cdar/d513/d513bc00001/ar/csr/tlf/dev/program/s1103p030.sas (Table 11.3.2.15)

Table 41: BARC Bleeding Events by Severity and Provocation (Safety Dataset)

BARC Bleed Characteristics	Total # Bleeding Events		Number (%) of Pts with Bleeding Events	
	Ticagrelor	Placebo	Ticagrelor	Placebo
			N=9562	N=9531
BARC Type 5 Bleeding	17	10	17 (0.2%)	10 (0.1%)
-Type 5a, probable fatal	0	2	0 (0.0%)	2 (0.0%)
-Type 5b, definite fatal	17	8	17 (0.2%)	8 (0.1%)
-Spontaneous	11	6	11 (0.1%)	6 (0.1%)
-Procedural	1	3	1 (0.0%)	3 (0.0%)
-Traumatic	5	1	5 (0.1%)	1 (0.0%)
BARC Type 5 or 4 Bleeding	17	11	17 (0.2%)	11 (0.1%)
-Spontaneous	11	6	11 (0.1%)	6 (0.1%)
-Procedural	1	4	1 (0.0%)	4 (0.0%)
-Traumatic	5	1	5 (0.1%)	1 (0.0%)
BARC Type 5, 4 or 3 Bleeding	355	167	341 (3.6%)	163 (1.7%)
-Spontaneous	258	117	248 (2.6%)	115 (1.2%)
-Procedural	37	28	37 (0.4%)	28 (0.3%)
-Traumatic	60	22	60 (0.6%)	22 (0.2%)
Subjects may be counted in more than one bleeding event category.				

Source: root/cdar/d513/d513bc00001/ar/csr/tlf/dev/program/s1103p032.sas (Table 11.3.2.17)

Table 42: Sensitivity Analysis: Effect of 60 mg vs Overall Dosing on TIMI Major Bleeds

	Ticagrelor			Placebo			Safety Dataset	
	N	Pts w TIMI Major Bleed	KM%*	N	Pts w TIMI Major Bleed	KM%*	HR (95%CI)	p-value
T vs P[A]	9562	206 (2.2%)	2.0%	9531	100 (1.0%)	0.9%	2.32 (1.82-2.94)	<0.0001
T vs P 60 mg[B]	2482	33 (1.3%)	1.3%	2516	21 (0.8%)	0.7%	1.74 (1.00-3.00)	0.0482

** KM timepoint is 24 months; HR=Hazard Ratio; Pts w PEP= patients experiencing a primary endpoint; T=ticagrelor; P=placebo*
A:TIMI Major bleeding using treatment as the only explanatory (i.e., explanatory = "independent but not certain to be independent"- https://www.statisticshowto.datasciencecentral.com/explanatory-variable/*) variable.*
B: TIMI Major bleeding using treatment as the only explanatory variable in only those subjects randomized to 60 mg or matching placebo.

Source: root/cdar/d513/d513bc00001/ar/csr/tlf/dev/program/s1103p009.sas (Table 11.3.2.2)

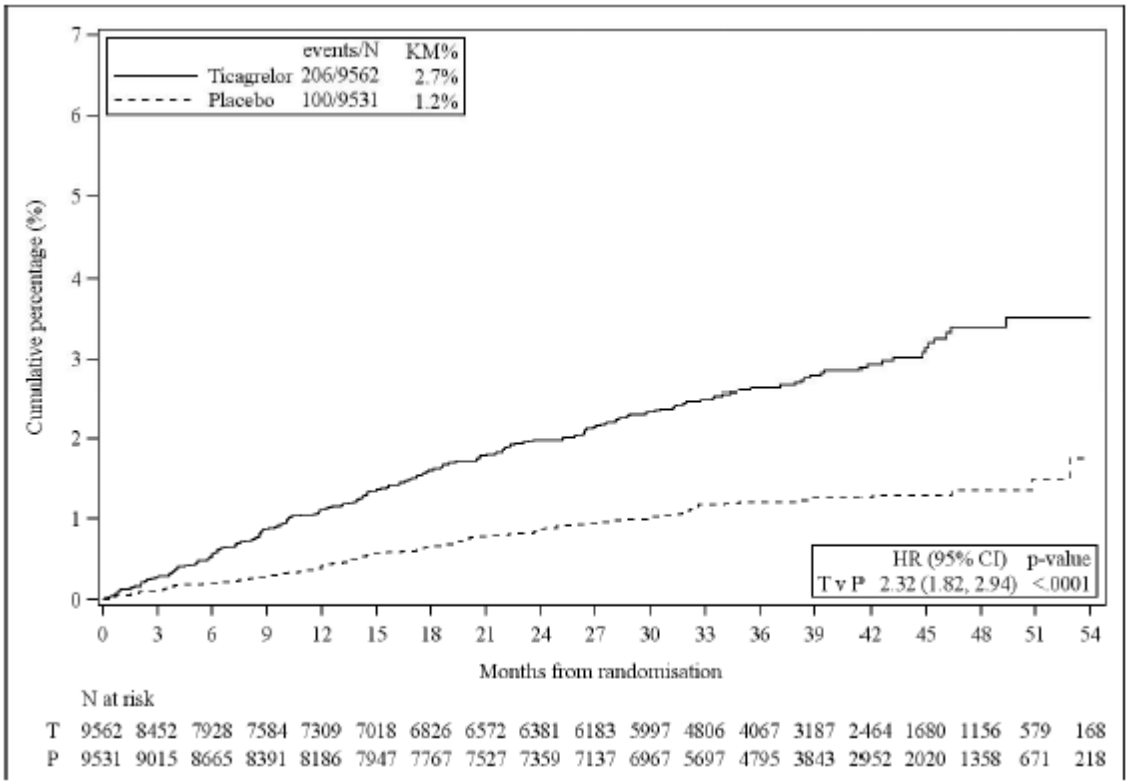
Table 43: Sensitivity Analysis: Effect of 60 mg vs 90 mg Dosing on TIMI Major Bleeds

Safety Set	Ticagrelor			Placebo				
	N	Pts w TIMI Major bleed	KM%*	N	Pts w TIMI Major bleed	KM%*	HR (95%CI)	p-value
Only 60 mg[a]	2482	33 (1.3%)	1.3%	2516	21 (0.8%)	0.7%	1.74 (1.00-3.00)	0.048
Only 90 mg[b]	7080	66 (0.9%)	2.7%	7015	23 (0.3%)	0.7%	3.21 (2.00-5.16))	<0.0001
90 or 60 mg[c]	7933	140 (1.8%)	1.6%	8551	78 (0.9%)	0.8%	2.05 (1.55-2.70)	<0.0001

** KM timepoint is 24 months; HR=Hazard Ratio; Pts w PEP= patients experiencing a primary endpoint;*
a: Includes only subjects randomized to 60 mg or matching placebo. Includes events with onset date from randomization to 7 days after last dose of study drug 60 mg.
b: Includes only subjects randomized to 90 mg or matching placebo. Includes events with onset date from randomization to 7 days after last dose of study drug 90 mg.
c: Includes subjects randomized to study drug 60 mg or 90 mg who were event-free up to the day the dose was reduced to 60 mg.

Source: root/cdar/d513/d513bc00001/ar/csr/tlf/dev/program/s1103p010.sas (Table 11.3.2.3)

Figure 13: Kaplan-Meier plot of TIMI major bleeding- on treatment (safety dataset)



Source: root/cdar/d513/d513bc00001/ar/csr/tlf/dev/program/s1103p005.sas (Figure 11.3.2.1)

7.4. Integrated Assessment of Safety

The number of subjects exposed to study drug without interruption (6738 of 9562: 71%), and the mean duration of exposure (28 months), were sufficient to evaluate key safety issues.

The data showed no safety signal for serious adverse events by any system organ class.

There were no differences between ticagrelor (combined 90 mg BID and 60 mg BID doses) and placebo for adverse events of specific interest except for dyspnea and bleeds.

Dyspnea occurred in 2049 of 9562 subjects (21%) in the ticagrelor arm vs 700 of 9531 subjects (7%) in the placebo arm over a mean 28-month period of exposure. In the PEGASUS-TIMI 54 trial, the 3-year event rates of dyspnea were 19% (1205 of 6988 subjects) in the ticagrelor 90 mg BID group, 16% (987 of 6958 subjects) in the ticagrelor 60 mg BID group, and 6% (383 of 6996 subjects) in the placebo group. The dyspnea event rates observed in the THEMIS trial were comparable to that observed in PEGASUS-TIMI 54.

The bleeding risk of ticagrelor compared to placebo was expected based on the mechanism of action and was consistent with the bleeding risk described in the previous trial PEGASUS-TIMI 54 (Table 44).

Table 44: Comparative Major Bleeding between PLATO, PEGASUS-TIMI 54, and THEMIS

Bleeding	PLATO		PEGASUS-TIMI 54			THEMIS			
	Ticagrelor	Clopidogrel	Ticagrelor	Ticagrelor	Placebo	Ticagrelor	Ticagrelor	Ticagrelor	Placebo
	90 mg	75 mg	90 mg	60 mg	---	90/60 mg	90 mg	60 mg	---
N	9235	9186	6988	6958	6996	9562	7080	2482	9531
PLATO Major n (%)	961 (12%)	929 (11%)				310 (3%)			145(2%)
TIMI Major n (%)	657 (8%)	638 (8%)	127 (3%)	115 (2%)	54 (1%)	206 (2%)	66 (1%)	33 (1%)	100(1%)

Source: Reviewer compilation of data from PLATO (Wallentin, 2009) and PEGASUS (Bonaca, 2015) and THEMIS NDA (Table 43) Note: percentages are rounded to the nearest integer.

In PLATO (Wallentin, 2009), major bleeding by PLATO criteria occurred in 961 of 9235 subjects (11.6%) in the ticagrelor 90 mg BID arm vs 929 of 9186 subjects (11.2%) in the clopidogrel 75 mg QD arm. Major bleeding by TIMI criteria occurred in 657 of 9235 subjects (7.9%) in the ticagrelor arm vs 638 of 9186 subjects (7.7%) in the clopidogrel arm.

In PEGASUS-TIMI 54 (Bonaca, 2015), TIMI major bleeding occurred in 127 of 6988 subjects (2.6%) in the ticagrelor 90 mg BID arm, 115 of 6958 subjects (2.3%) in the ticagrelor 60 mg BID and 54 of 6996 subjects (1.1%) in the placebo arm. Hazard Ratios (95% CI, p-value) were 2.7 (2.0-3.7, p<0.001) for ticagrelor 90 mg BID vs placebo, and 2.3 (1.7-3.2, p<0.001) for ticagrelor 60 mg BID vs placebo.

In the THEMIS trial, PLATO major bleeding occurred in 310 of 9562 subjects (3.2%) in the ticagrelor arm (combined 60 mg and 90 mg BID doses) vs 145 of 9531 subjects (1.5%) in the placebo arm. TIMI major bleeding occurred 206 of 9562 subjects (2.2%) in the ticagrelor arm (combined 60 mg and 90 mg BID doses) vs 100 of 9531 subjects (1.0%) in the placebo arm (*HR 2.3, 95% CI 1.8-2.9, p< 0.0001*). Based on the sensitivity analyses (Table 43), TIMI major bleeding occurred in 66 of 7080 subjects (1%) taking only 90 mg BID (*HR 3.2, 95% CI 2.0-5.2, p<0.0001*), and in 33 of 2482 subjects (1%) taking only 60 mg BID (*HR 1.7, 95% CI 1.0-3.0, p=0.048*).

In summary, the risk of ticagrelor in the patient population studied in the THEMIS trial was similar to the risk in other populations (i.e., subjects with a history of MI or stroke) previously studied and approved.

8. Advisory Committee Meeting and Other External Consultations

There is no plan for an advisory committee meeting or other external consultations.

9. Labeling Recommendations

9.1. Prescription Drug Labeling

The current indication and usage language in the label states: "*BRILINTA is a P2Y12 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. "*

The following modification to the current language is suggested:

"BRILINTA is a $P2Y_{12}$ platelet inhibitor indicated:

- *to reduce the rate of cardiovascular (CV) death, myocardial infarction (MI), and stroke in patients with acute coronary syndrome (ACS) or a history of 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.

- *to reduce the risk of a first myocardial infarction or stroke in patients diagnosed with coronary artery disease at high risk for such events. While use is not limited to this setting, the benefit of ticagrelor was established in a population also diagnosed with type 2 diabetes mellitus."*

(b) (4)

The inclusion criteria requiring concomitant T2DM was considered to be a risk-enrichment strategy to enhance the risk of cardiac events. However, the efficacy of ticagrelor was not considered contingent upon the presence of diabetes mellitus or any other risk factor.

Under section 1 of the label (indications and usage), a subsection 1.2 should describe the population studied in which benefit was established: concomitant coronary artery disease and T2DM in addition to other risk factors. This section should specify that in patients with low cardiovascular risk, the benefit-risk may be unfavorable due to the risk of hemorrhage.

The bleeding risk already retains a warning but highlighting the differentially worsened risk of a TIMI major bleed in women compared to men may be warranted.

A new section (14.2) of the label should be inserted to describe the results of the THEMIS trial.

9.2. Nonprescription Drug Labeling

Not applicable.

10. Risk Evaluation and Mitigation Strategies (REMS)

There is no need to institute a risk evaluation and mitigation strategy.

11. Postmarketing Requirements and Commitments

There are no postmarketing requirements or commitments.

12. Appendices

12.1. Bleeding Criteria

Taken from Mehran, R, et al (2011)

TIMI Bleeding Criteria

- Non-CABG related bleeding
  - Major:
    - 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 $\geq$ 5 g/dL.
    - Fatal bleeding (bleeding that directly results in death within 7 days).
  - Minor:
    - Clinically overt (including imaging), resulting in hemoglobin drop of 3 to < 5 g/dL.
  - Requiring Medical Attention:
    - Any overt sign of hemorrhage that meets one of the following criteria and does not meet criteria for a major or minor bleeding event as described above.
    - Requiring intervention (medical practitioner-guided medical or surgical treatment to stop or treat bleeding, including temporarily or permanently discontinuing or changing the dose of a medication or study drug).
    - Leading to or prolonging hospitalization.
    - Prompting evaluation (leading to an unscheduled visit to a healthcare professional and diagnostic testing, either laboratory or imaging).

    - Minimal:
        - Any overt bleeding event that does not meet the criteria above.
- Bleeding in the setting of CABG:
    - Fatal bleeding (bleeding that directly results in death).
    - Perioperative intracranial bleeding.
    - Reoperation after closure of the sternotomy incision for the purpose of controlling bleeding.
    - Transfusion of ≥ 5 PRBCs or whole blood within a 48-hour period; cell saver transfusion will not be counted in calculations of blood products.
    - Chest tube output > 2 L within a 24-hour period.

PLATO Bleeding Criteria

- Major (life-threatening):
    - Fatal.
    - Intracranial.
    - Intrapericardial with cardiac tamponade.
    - Resulting in hypovolemic shock or severe hypotension that requires pressors or surgery.
    - Clinically overt or apparent bleeding associated with decrease in hemoglobin > 5 g/dL.
    - Requiring transfusion of ≥ 4 U whole blood or PRBCs.
- Other Major:
    - Significantly disabling (e.g., intraocular with permanent vision loss).
    - Associated drop in hemoglobin of 3 to 5 g/dL
    - Requiring transfusion of 2 to 3 U whole blood or PRBCs
- Any Major
    - Any one of the above criteria.
- Minor:
    - Requiring medical intervention to stop or treat bleeding (e.g., epistaxis requiring visit to medical facility for packing).
- Minimal:
    - All others (e.g., bruising, bleeding gums, oozing from injection sites) not requiring intervention or treatment.

Bleeding Academic Research Consortium (BARC) Criteria

- Type 0:
    - No bleeding
- Type 1:

    - Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional.
- Type 2:
    - Any overt, actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation.
- Type 3:
    - Type 3a:
        - Overt bleeding plus hemoglobin drop of 3 to < 5 g/dL (provided hemoglobin drop is related to bleed).
        - Any transfusion with overt bleeding.
    - Type 3b:
        - Overt bleeding plus hemoglobin drop ≥ 5 g/dL (provided hemoglobin drop is related to bleed).
        - Cardiac tamponade.
        - Bleeding requiring surgical intervention for control (excluding dental / nasal / skin / hemorrhoid).
        - Bleeding requiring intravenous vasoactive agents.
    - Type 3c:
        - Intracranial hemorrhage (does include microbleeds or hemorrhagic transformation, does not include intraspinal).
        - Subcategories confirmed by autopsy or imaging or lumbar puncture.
        - Intraocular bleed compromising vision.
- Type 4 (CABG-related bleeding):
    - Perioperative intracranial bleeding within 48 hours.
    - Reoperation after closure of sternotomy for the purpose of controlling bleeding.
    - Transfusion of ≥ 5 U whole blood or packed red blood cells within a 48-hour period.
    - Chest tube output ≥ 2L within a 24-hour period.
- Type 5 (fatal bleeding):
    - Type 5a:
        - Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious.
    - Type 5b:

- Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation.

12.2. References

Angiolillo, D, et al., 2008, Prasugrel: a novel platelet ADP $P2Y_{12}$ receptor antagonist. A review on its mechanism of action and clinical development, Expert Opinion on Pharmacotherapy, 9 (16): 2893-2900 (https://doi.org/10.1517/14656566.9.16.2893).

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12.3. Financial Disclosure

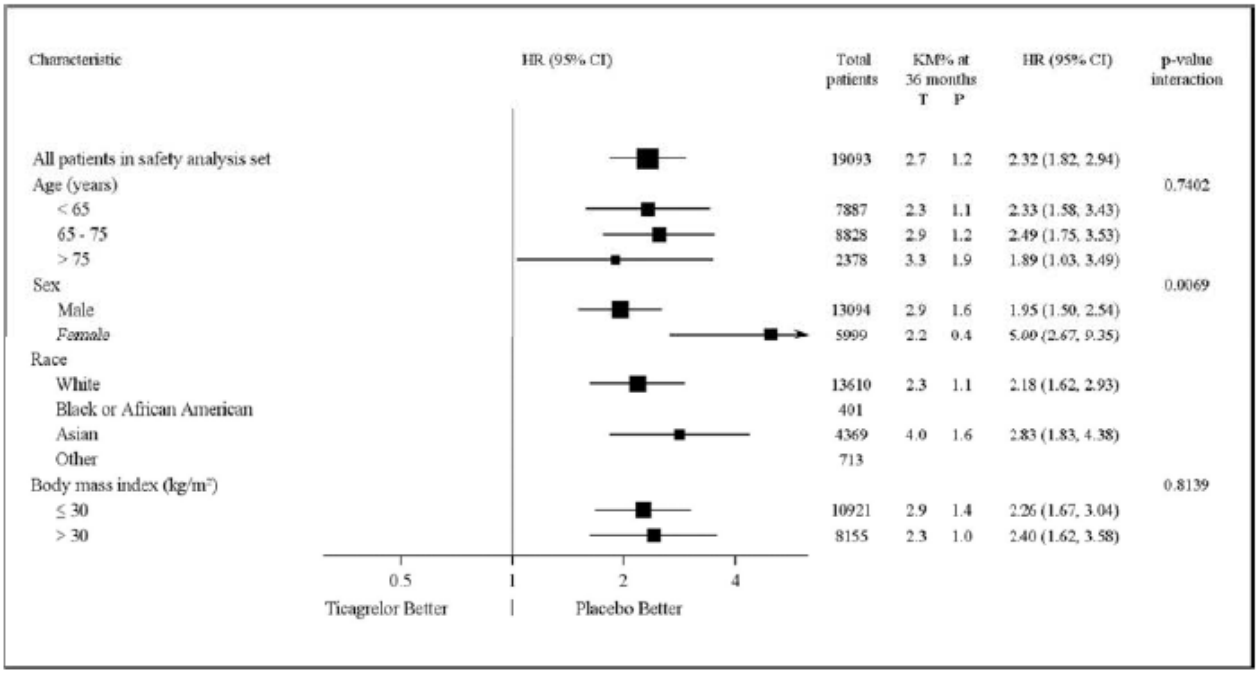
There were no issues that emerged from the financial disclosures (see Table 6 and associated discussion under Study Design).

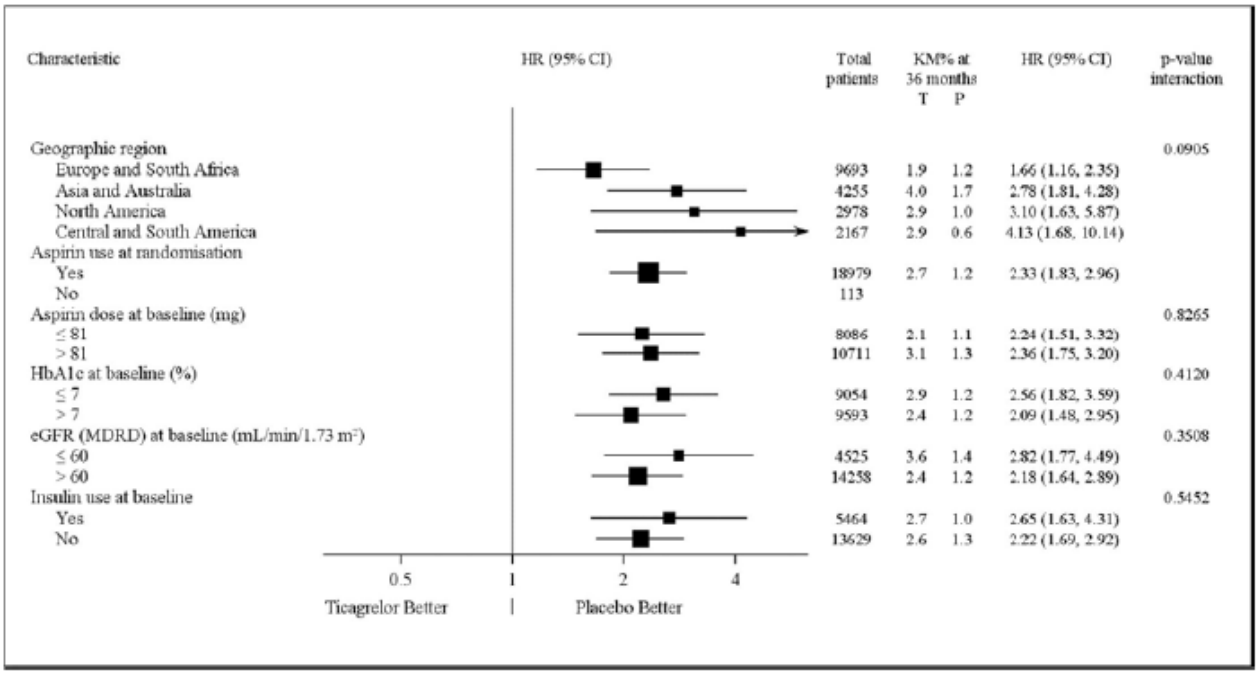
Covered Clinical Study (Name and/or Number): Themis Trial (D513BC00001)

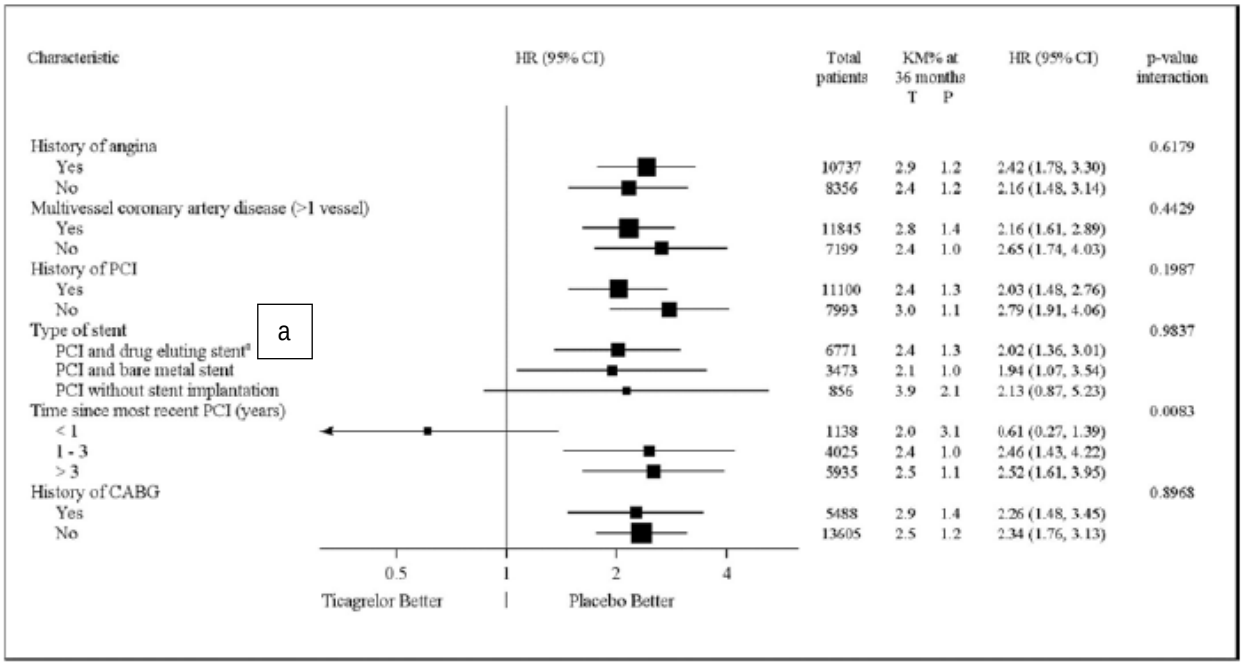
Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 6248		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 18		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 1 Significant payments of other sorts: 16 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 3		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 31		

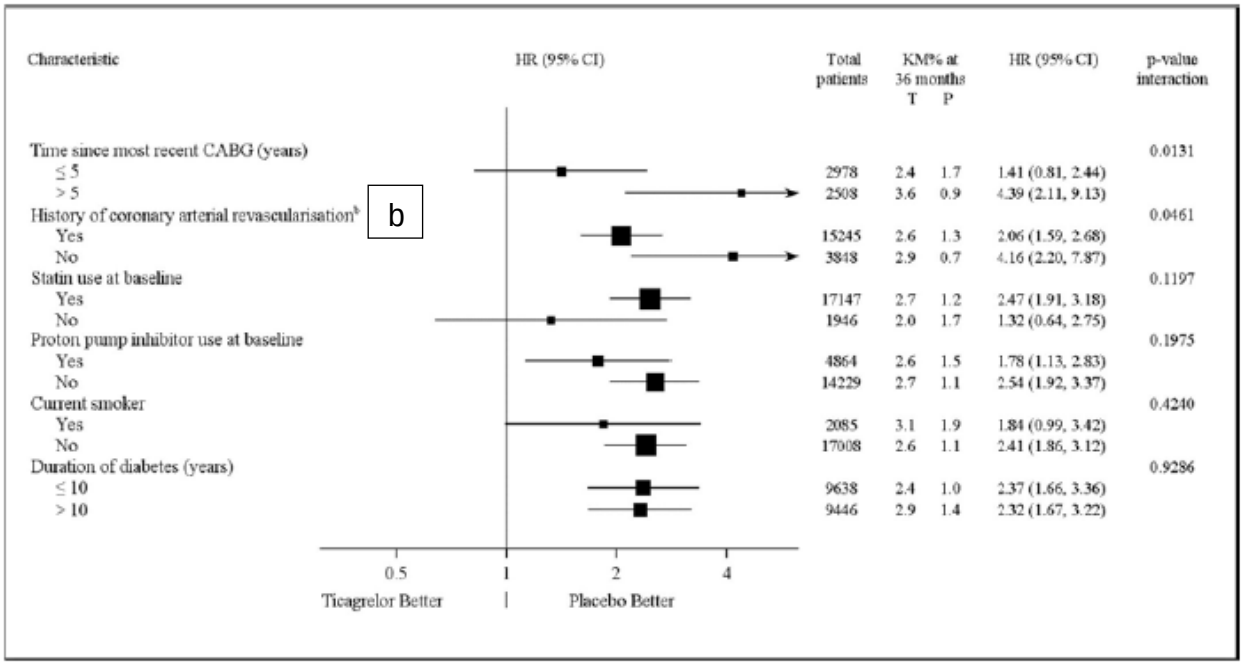
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

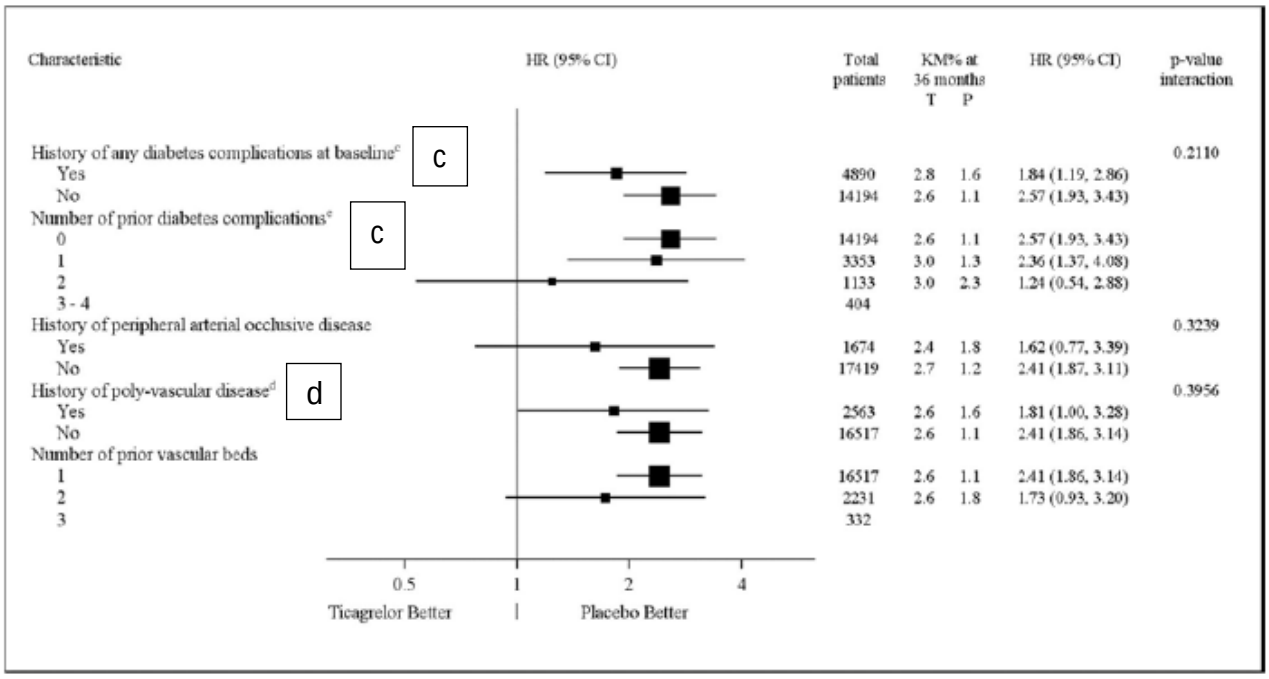
12.4. TIMI Major Bleeding Events-Subgroup Analysis






Characteristic
HR (95% CI)
Total patients
KM% at 36 months T P
HR (95% CI)
p-value interaction
History of angina 0.6179
Yes 10737 2.9 1.2 2.42 (1.78, 3.30)
No 8356 2.4 1.2 2.16 (1.48, 3.14)
Multivessel coronary artery disease (>1 vessel) 0.4429
Yes 11845 2.8 1.4 2.16 (1.61, 2.89)
No 7199 2.4 1.0 2.65 (1.74, 4.03)
History of PCI 0.1987
Yes 11100 2.4 1.3 2.03 (1.48, 2.76)
No 7993 3.0 1.1 2.79 (1.91, 4.06)
Type of stent 0.9837
PCI and drug eluting stent[a] 6771 2.4 1.3 2.02 (1.36, 3.01)
PCI and bare metal stent 3473 2.1 1.0 1.94 (1.07, 3.54)
PCI without stent implantation 856 3.9 2.1 2.13 (0.87, 5.23)
Time since most recent PCI (years) 0.0083
< 1 1138 2.0 3.1 0.61 (0.27, 1.39)
1 - 3 4025 2.4 1.0 2.46 (1.43, 4.22)
> 3 5935 2.5 1.1 2.52 (1.61, 3.95)
History of CABG 0.8968
Yes 5488 2.9 1.4 2.26 (1.48, 3.45)
No 13605 2.5 1.2 2.34 (1.76, 3.13)
a
0.5
1
2
4
Ticagrelor Better
Placebo Better


Characteristic
HR (95% CI)
Total patients
KM% at 36 months T P
HR (95% CI)
p-value interaction
Time since most recent CABG (years) 0.0131
≤ 5 2978 2.4 1.7 1.41 (0.81, 2.44)
> 5 2508 3.6 0.9 4.39 (2.11, 9.13)
History of coronary arterial revascularisation[b] 0.0461
Yes 15245 2.6 1.3 2.06 (1.59, 2.68)
No 3848 2.9 0.7 4.16 (2.20, 7.87)
Statin use at baseline 0.1197
Yes 17147 2.7 1.2 2.47 (1.91, 3.18)
No 1946 2.0 1.7 1.32 (0.64, 2.75)
Proton pump inhibitor use at baseline 0.1975
Yes 4864 2.6 1.5 1.78 (1.13, 2.83)
No 14229 2.7 1.1 2.54 (1.92, 3.37)
Current smoker 0.4240
Yes 2085 3.1 1.9 1.84 (0.99, 3.42)
No 17008 2.6 1.1 2.41 (1.86, 3.12)
Duration of diabetes (years) 0.9286
≤ 10 9638 2.4 1.0 2.37 (1.66, 3.36)
> 10 9446 2.9 1.4 2.32 (1.67, 3.22)
b
0.5
1
2
4
Ticagrelor Better
Placebo Better



Source: root/cdar/d513/d513bc00001/ar/csr/tlf/dev/program/s1103p011.sas (Figure 11.3.2.3CSR) *Note:*
a: Includes any patient with drug eluting stent, or both drug eluting stent and bare metal stent.
b: Defined as PCI or CABG.
c: History of any complications: retinopathy, neuropathy (autonomic or peripheral), and nephropathy.
d: Defined as arterial obstructive disease involving at least 2 vascular beds where vascular bed involvement is characterized by either 1) CAD, OCI or CABG; 2) PAD; 3) Carotid artery stenosis or cerebral revascularization

12.5. Study Governance

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12.6. ASCVD Risk Assessment

Analyses were conducted by Lars Johannesen, PhD and Christine Garnett, PharmD

Summary of Findings

- This exploratory analysis did not conclusively identify a high risk group of subjects who would have a more favorable benefit-risk as compared to the overall study population and no labeling recommendations are made based on this exploratory analysis.
- Because ticagrelor was found to have marginal benefit-risk in the THEMIS study population, we explored whether a high risk sub-group would show a more favorable benefit-risk profile. For this assessment, we used the ASCVD risk score, recognizing that the score is developed in a different patient population, to quantify risk at baseline because the predictors in the ASCVD risk score (e.g., increased BP, age, smoking) are expected to reflect risk in the THEMIS population.
- Subjects who were high risk for an ASCVD event had higher event rates for the primary efficacy outcome (CV death, MI, stroke) compared to patients with lower ASCVD risk scores; however, these high risk subjects did not show a consistent treatment benefit with ticagrelor. This finding could be attributed to:
    - The observed event rate and baseline ASCVD risk score were in general agreement but did not perfectly match — the observed event rates in THEMIS were higher for the low/intermediate risk subjects (22 vs. 18 events per 1000 py) and were lower for the high risk subjects (34 vs. 41 events per 1000 py). This mismatch could be due to the enrolled subjects in this study had established CAD, whereas the ASCVD risk score was developed in a patient population without established CAD. Additionally, it is also worth noting that the predicted ASCVD risk reflects 10 year risk, whereas the THEMIS study only had ~3 year follow-up. However, as the ASCVD risk score correlated with predicted absolute risk at 3 years using the multivariable cox proportional hazard model, it seems reasonable to consider the ASCVD risk score as a metric for identifying subjects at higher risk.
    - The high risk group is confounded by elderly subjects (>70 years) who did not appear to have a robust benefit from taking ticagrelor when a multivariable Cox regression model was applied to the data. When subjects >70 years were removed from the analysis, the treatment benefit (as expressed as Hazard Ratio) for high risk subjects was similar to the HR for the intermediate/low risk subjects. Given the exploratory nature of this analysis, no recommendations in this subgroup are warranted.
- There was no reduction in the composite outcome of CV death, MI, stroke, fatal bleeds and ICH with ticagrelor treatment in any of the subgroups.

- The sponsor's analysis showing a favorable benefit-risk for high risk subjects is not convincing because most subjects are predicted to have an individual risk of < 5 events / 100 patient years and in this range, the net benefit per the sponsor's analysis tends to be negative.

Background

The purpose of this review is to investigate whether there is a favorable benefit-risk for subjects with high risk for an atherosclerotic cardiovascular disease (ASCVD) events.

Furthermore, we assessed the benefit-risk of ticagrelor use in subjects >70 years because low-dose aspirin (75-100 mg orally daily) is not recommended for the primary prevention of ASCVD among adults >70 years of age.[1]

Application of ASCVD Risk Calculator

The ASCVD risk score[2] was computed using baseline demographic, laboratory and medical history data for each subject in THEMIS. The covariates included in the risk score are age, sex, race (white, black, other), systolic blood pressure, total cholesterol, HDL cholesterol, current smoker (yes/no), treated hypertension (yes/no) and current diabetes (yes/no). Covariates not collected in THEMIS (e.g., total and HDL cholesterol) were imputed from the NHANES database stratified for sex and age.[3] The ASCVD risk score was categorized as high risk (≥20% 10-year risk), intermediate risk (7.5% to 19.9% 10-year risk), or low risk (<7.5% 10-year risk).[1]

In THEMIS, 70% of the subjects were high risk, 26% were intermediate risk and 5% were low risk. It should be recognized that the ASCVD risk score was developed in a different patient population and that the risk categories based on this risk score therefore might have a different interpretation in the THEMIS population. Nevertheless, the increasing ASCVD score is still expected to correspond to a greater risk in the THEMIS population and we therefore used the proposed ASCVD risk categories in this exploratory analysis. For the exploratory efficacy and safety subgroup analyses, the intermediate and low risk subjects were pooled.

Analysis Datasets

The demographic table, efficacy sub-group analyses and net clinical benefit analyses are based on the FAS population which is defined as all subjects who were randomized to study treatment irrespective of their protocol adherence and continued participation in the study. There are 19,220 subjects in the FAS population.

All bleeding events are based on the safety population which is defined as all subjects who received at least 1 dose of randomized ticagrelor or placebo. There were 127 subjects who did not receive treatment; therefore, the safety population consists of 19,093 subjects.

Demographic and Baseline Characteristics

Subjects that are high risk for ASCVD are predominately males (79%), older (43% were > 70 years), and with type 2 diabetes for >10 years (52%), systolic BP >130 mmHg (73%) and with history of

cardiovascular diseases (Table A-54). Within each risk group, the covariates were balanced between placebo and ticagrelor treatment groups (data not shown).

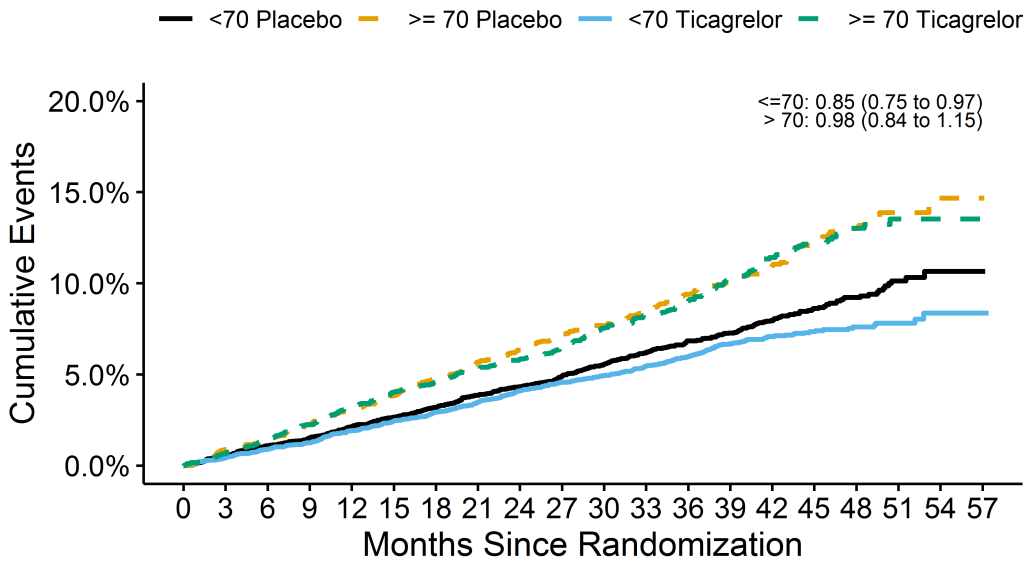
Efficacy Analysis by Subgroups

Age Subgroup

Among treatment groups, 30% of subjects were >70 years [2,930 (30.5%) in placebo; 2,914 (30.3%) in ticagrelor].

A KM plot of the primary efficacy variable (composite of CV death/MI/stroke) is provided in Figure A-14 for age subgroup analysis. The absolute event rate was higher in subjects > 70 years and ticagrelor did not show a treatment benefit as evidenced by overlapping curves for both placebo and ticagrelor treatments. Accounting for other covariates also failed to identify a robust treatment benefit in elderly subjects (Table A-46). The covariates included in the multivariable model were identified by backward elimination as proposed by the sponsor, but with an added interaction between age and treatment (Appendix A in eCTD 0588), which was marginally insignificant (interaction p value = 0.068). The event rate was 34 per 1000 p-y for both treatment groups (Table A-45).

Figure A-14. Kaplan-Meier plot of primary efficacy variable (composite of CV death/MI/stroke) by age group (FAS population, N=19,220)



Source: Reviewer's analysis.

Table A-45. Analysis of primary efficacy variable (composite of CV death/MI/stroke) by age subgroup (FAS population, N=19,220)

Subgroup	Subjects with Events n (%)		Event Rate (per 1000 PY)		HR (95% CI)	Interaction p-value
	Ticagrelor	Placebo	Ticagrelor	Placebo		
≤70 y (N=13,376)	435 (6.5%)	509 (7.6%)	21	24	0.85 (0.75, 0.97)	0.17
>70 y (N=5,844)	301 (10.3%)	309 (10.5%)	34	34	0.98 (0.84, 1.15)	

Source: Reviewer's analysis. Event rate is computed as the number subjects with events/patient years.

Table A-46. Multivariable Cox Regression Model for primary efficacy variable (composite of CV death/MI/stroke)

Variable	HR	Lower 95%	Upper 95%	p-value
TRT Ticagrelor	0.84	0.73	0.96	0.008
AGE > 70 y	1.29	1.11	1.50	<0.001
AGE > 70 y:TRT interaction	*1.22*	*0.99*	*1.50*	*0.068*
eGFR > 60 mL/min/1.73 m2	0.73	0.65	0.82	<0.001
CHF	1.34	1.18	1.52	<0.001
CKD	1.18	1.00	1.38	0.045
COPD	1.42	1.19	1.70	<0.001
Diabetic Complications	1.19	1.05	1.34	0.005
Diabetes Duration > 10 y	1.13	1.01	1.27	0.035
HBA1C >7%	1.27	1.13	1.42	<0.001
Hypertension	1.45	1.13	1.85	0.003
Insulin Use	1.30	1.16	1.47	<0.001
LDL >1.8 mmol/l	1.17	1.04	1.31	0.009
MI history	1.76	1.14	2.71	0.01
Multivessel disease	1.30	1.16	1.45	<0.001
PAD	1.22	1.04	1.43	0.015
Systolic BP >130 mmHg	1.14	1.01	1.27	0.028
SEX (Male)	1.16	1.03	1.30	0.013
SMOKER	1.23	1.04	1.45	0.014
STATIN USE	0.73	0.63	0.85	<0.001
TIA History	1.53	1.12	2.08	0.007
Triglycerides >1.7 mmol/l	1.09	0.98	1.21	0.11

Source: Reviewer's analysis.

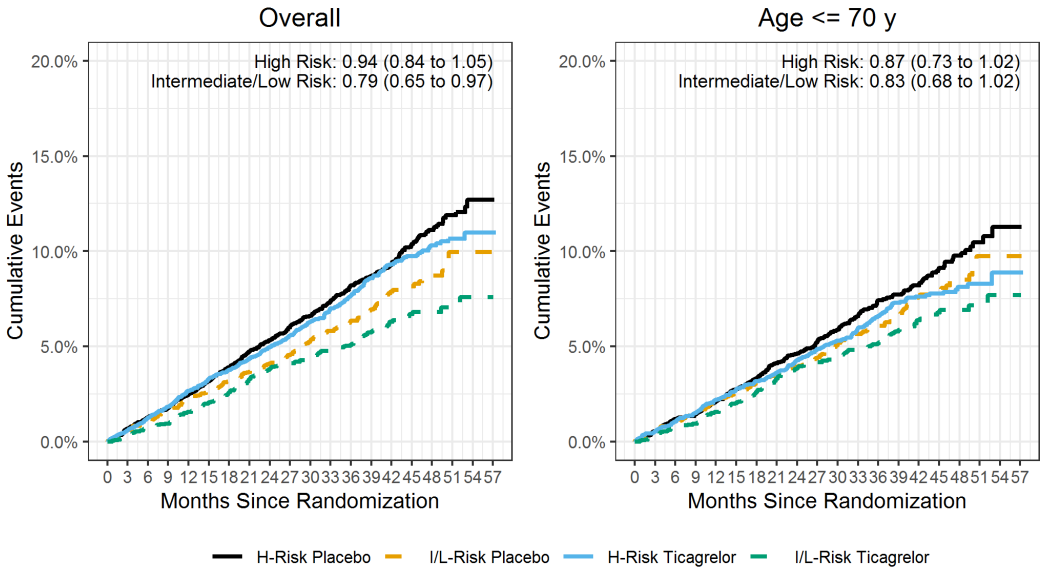
ASCVD Risk Subgroup Analysis

A KM plot of the primary efficacy variable (composite of CV death/MI/stroke) is provided in Figure A-15, showing constant event rates and increased separation of the curves over time for only the intermediate/low risk group. The event rate was higher in the high risk group and ticagrelor did not show a treatment benefit for most of study.

The lower treatment response in the high risk group appears to be driven by those subjects with the highest risk score (Figure 3). While, the observed event rate in the placebo group and the ASCVD risk score were in general agreement, the observed event rates were higher in the low/intermediate group and lower in the high ASCVD risk groups, respectively. Two possible explanations include that the ASCVD risk score was developed in a different patient population and that the ASCVD risk score reflects 10 year risk and THEMIS included ~3 year follow-up. However, as the predicted absolute risk for primary events correlated with the ASCVD risk score predicted at baseline, it seems reasonable to use the ASCVD risk score as a metric reflecting risk. The analysis of the primary efficacy endpoint is summarized in Table 3 by risk subgroups.

Because 98% of subjects >70 years are in the high risk subgroup (Table A-54), a KM plot of the primary efficacy variable stratified by ASCVD risk group is also presented for only subjects ≤70 years in Figure A-15. There was no difference in treatment effect in high risk vs. intermediate/low risk in subjects ≤70 years (Table A-48).

Figure A-15. Kaplan-Meier plot of primary efficacy variable (composite of CV death/MI/stroke) by ASCVD risk subgroup (FAS population, N=19,220)



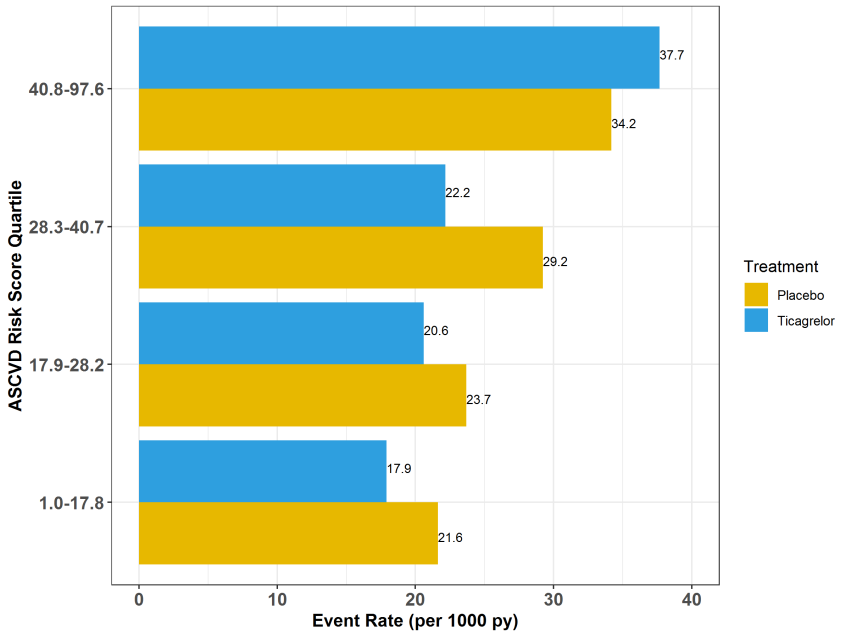
Source: Reviewer's analysis.

Table A-47. Analysis of primary efficacy variable (composite of CV death/MI/stroke) by ASCVD risk subgroup (FAS population, N=19,220)

Subgroup	Subjects with Events n (%)		Event Rate (per 1000 PY)		HR (95% CI)	Interaction p-value
	Ticagrelor	Placebo	Ticagrelor	Placebo		
High (n = 13,384)	568 (8.5%)	607 (9.1%)	27.2	29.0	0.94 (0.84, 1.05)	0.16
Intermediate/Low (n = 5,831)	168 (5.8%)	211 (7.2%)	18.2	22.9	0.79 (0.65, 0.97)	

Source: Reviewer's analysis. Event rate is computed as the number subjects with events/patient years.

Figure A-16. Bar plot of event rates of the primary efficacy variable by ASCVD risk score quartile (FAS population, N=19,220)



Source: Reviewer's analysis.

Table A-48. Analysis of primary efficacy variable (composite of CV death/MI/stroke) by ASCVD risk subgroup in subjects ≤ 70 years (FAS population)

Subgroup (N=13,376)	Subjects with Events n (%)		Event Rate (per 1000 PY)		HR (95% CI)	Interaction p-value
	Ticagrelor	Placebo	Ticagrelor	Placebo		
High (n=7,653)	268 (7.0%)	308 (8.1%)	22	26	0.87 (0.74, 1.0)	0.75
Intermediate/Low (n=5,719)	167 (5.9%)	201 (7.0%)	18	22	0.83 (0.68, 1.0)	

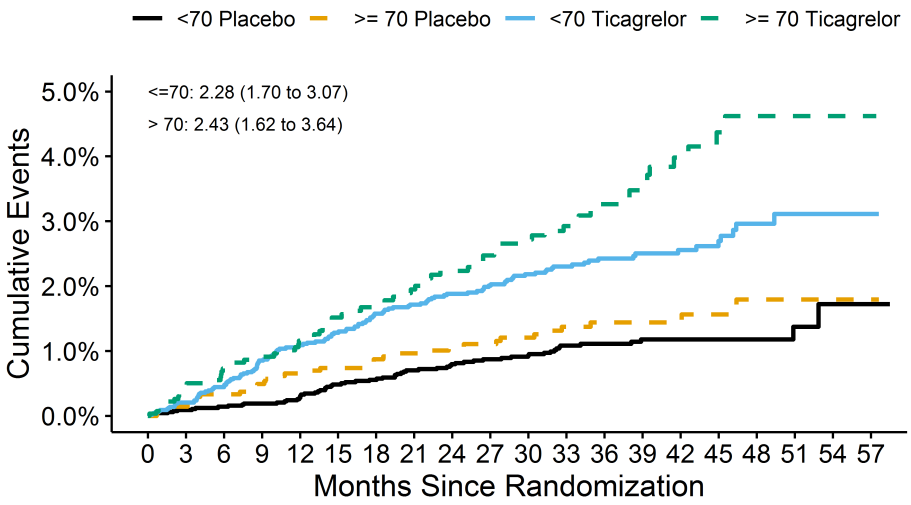
Source: Reviewer's analysis. Event rate is computed as the number subjects with events/patient years.

Safety Analysis by Subgroup

TIMI Major Bleeds

Age and Sex Subgroups: A KM plot of TIMI major bleeds is provided in Figure A-17 for age subgroup analysis. In both age groups, subjects taking ticagrelor had increased bleeding events compared to placebo group (Table A49).

Figure A-17. Kaplan-Meier plot of TIMI major bleeds by age group (safety population)



Source: Reviewer's analysis.

Table A49. Analysis of TIMI major bleeds by age subgroup (safety population, N=19,093)

Subgroup	Subjects with Events n (%)		Event Rate (per 1000 PY)		HR (95% CI)	Interaction p-value
	Ticagrelor	Placebo	Ticagrelor	Placebo		
≤70 y (n=13,301)	135 (2.0%)	65 (1.0%)	8	4	2.3 (1.7 3.1)	0.804

Subgroup	Subjects with Events n (%)		Event Rate (per 1000 PY)		HR (95% CI)	Interaction p-value
	Ticagrelor	Placebo	Ticagrelor	Placebo		
>70 y (n=5,792)	71 (2.5%)	35 (1.2%)	12	5	2.4(1.6, 3.7)	

Source: Reviewer's analysis. Event rate is computed as the number subjects with events/patient years.

A KM plot of TIMI major bleeds in females and males is provided in Figure A-18. In both groups, subjects taking ticagrelor had increased bleeding events compared to placebo group. Although the relative risk of bleeding was higher in females (interaction p-value: 0.007), the event rates were lower. (Table A-50).

Figure A-18. Kaplan-Meier plot of TIMI major bleeds by sex (safety population)

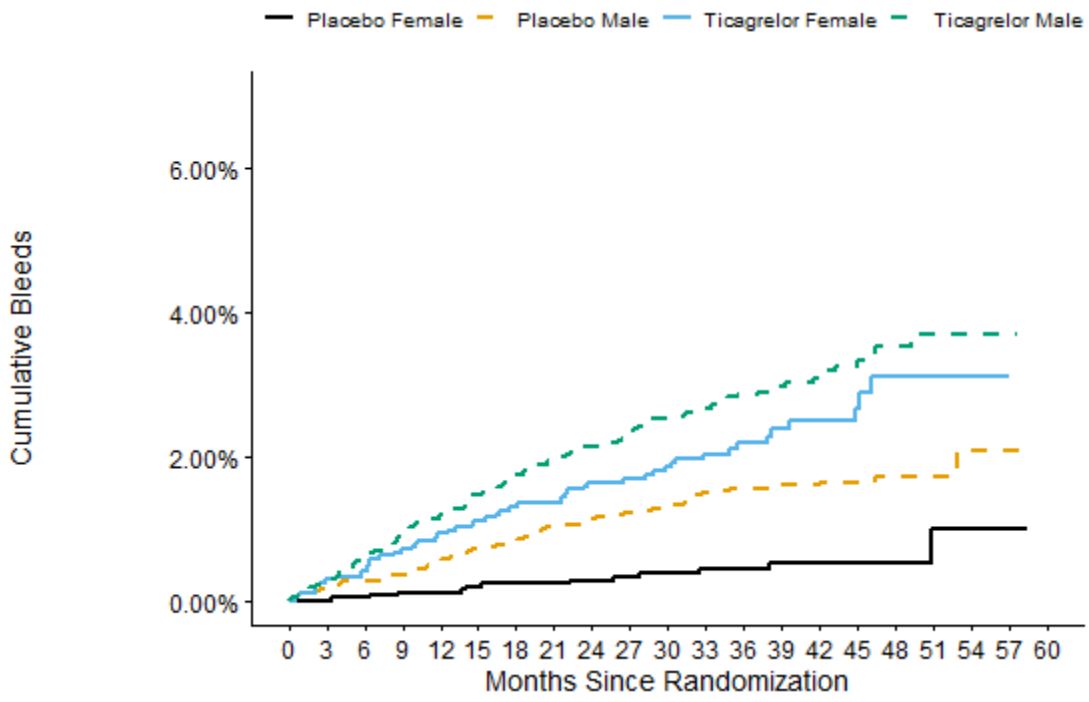


Table A-50. Analysis of TIMI major bleeds by sex subgroup (safety population, N=19,093)

Subgroup	Subjects with Events n (%)		Event Rate (per 1000 PY)		HR (95% CI)	Interaction p-value
	Ticagrelor	Placebo	Ticagrelor	Placebo		
Female	53 (1.7%)	12 (0.4%)	7.6	1.5	5.0 (2.7,9.3)	0.007
Male	153 (2.3%)	88 (1.3%)	9.6	4.9	2.0 (1.5, 2.5)	

Source: Reviewer's analysis. Event rate is computed as the number subjects with events/patient years.

ASCVD Subgroup*:* A KM plot of TIMI major bleeds is provided in Figure A-19 by ASCVD risk subgroup. In both risk groups, subjects taking ticagrelor had increased bleeding events compared to placebo group. The absolute event rate for bleeding appears higher in the high risk subjects.

Figure A-19. Kaplan-Meier plot of primary safety variable (TIMI major bleeds) by risk subgroup and subjects <70 years (safety population)

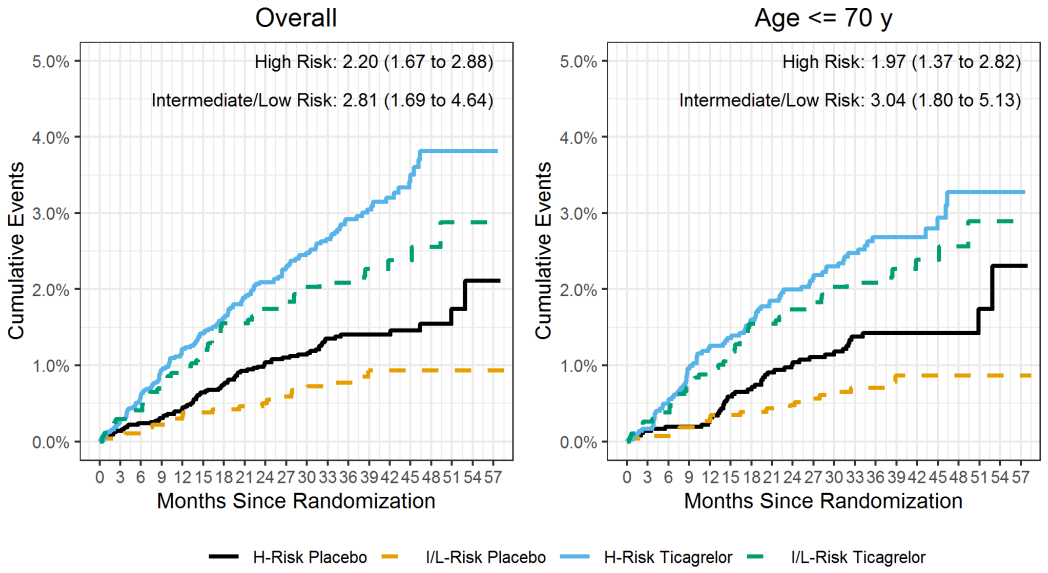


Table A-51. Analysis of TIMI major bleed by ASCVD risk subgroup (safety population, N=19,093)

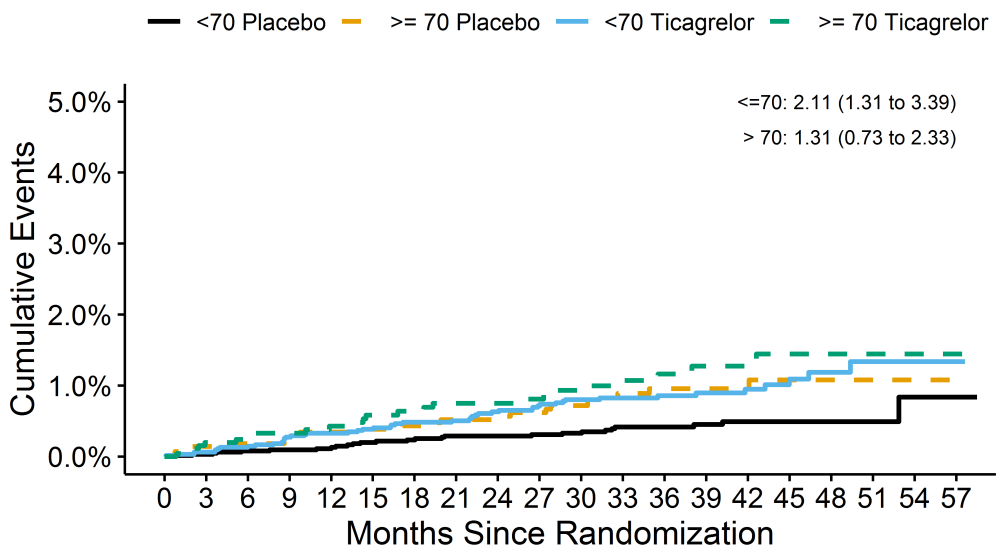
Subgroup	Subjects with Events n (%)		Event Rate (per 1000 PY)		HR (95% CI)	Interaction p-value
	Ticagrelor	Placebo	Ticagrelor	Placebo		
High (n = 13,289)	152 (2.3%)	79 (1.2%)	9.9	4.5	2.20 (1.67, 2.88)	0.4
Intermediate/Low (n = 5,799)	54 (1.9%)	21 (0.7%)	7.3	2.6	2.81 (1.69, 4.64)	

Source: Reviewer's analysis. Event rate is computed as the number subjects with events/patient years.

Fatal Bleeds and Non-Fatal ICH

Age Subgroup: A KM plot of fatal bleed/ICH is provided in Figure A-20 for age subgroup analysis. In both age groups, subjects taking ticagrelor had increased bleeding events compared to placebo group (Figure A-21).

Figure A-20. Kaplan-Meier plot of composite of fatal bleeds and non-fatal ICH by age group (safety population, N=19,093)



Source: Reviewer's analysis.

Table A-52. Analysis of fatal bleeds/ICH by age subgroup (safety population, N=19,093)

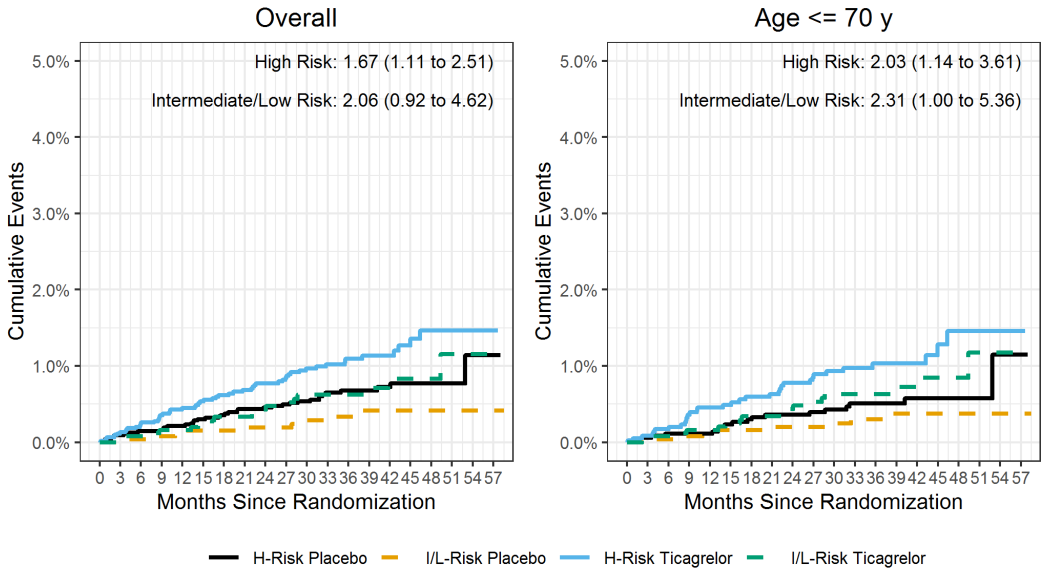
Subgroup	Subjects with Events n (%)		Event Rate (per 1000 PY)		HR (95% CI)	Interaction p-value
	Ticagrelor	Placebo	Ticagrelor	Placebo		
≤70 y (n=13,301)	50 (0.7%)	26 (0.4%)	3.0	1.4	2.1 (1.3, 3.4)	0.21
>70 y (n=5,792)	24 (0.8%)	22 (0.8%)	3.9	3.0	1.3 (0.7, 2.3)	

Source: Reviewer's analysis. Event rate is computed as the number subjects with events/patient years.

ASCVD Subgroup

A KM plot of a composite of fatal bleeds and non-fatal ICH is provided in Figure A-19 by ASCVD risk subgroup. In both risk groups, subjects taking ticagrelor had increased bleeding events compared to placebo group.

Figure A-21. Kaplan-Meier plot of a composite of fatal bleeds and nonfatal ICH by risk subgroup and subjects <70 years (safety population, N=19,093)



Source: Reviewer's analysis.

Table A-53. Analysis of fatal bleeds/ICH by ASCVD risk subgroup (safety population, N=19,093)

ASCVD Risk Subgroup	Subjects with Events n (%)		Event Rate (per 1000 PY)		HR (95% CI)	Interaction p-value
	Ticagrelor	Placebo	Ticagrelor	Placebo		
High (n = 13,289)	57 (0.9%)	39 (0.6%)	3.7	2.2	1.7 (1.1, 2.5)	0.65
Intermediate/Low (n = 5,799)	17 (0.6%)	9 (0.3%)	2.3	1.1	2.1 (0.9, 4.6)	

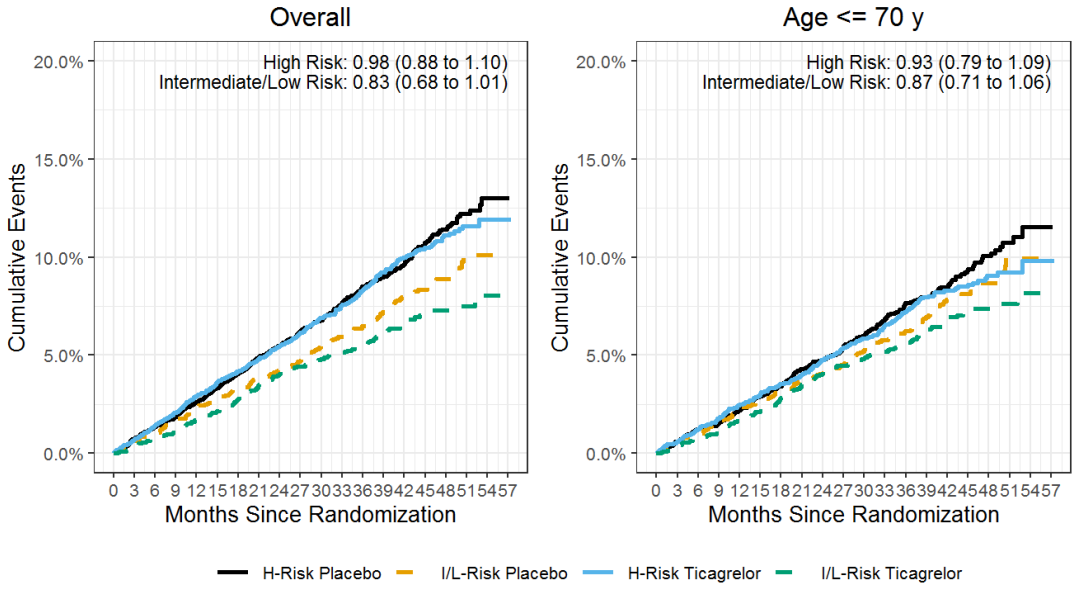
Source: Reviewer's analysis. Event rate is computed as the number subjects with events/patient years.

Benefit-Risk Assessment

Irreversible Harm (benefit-risk endpoint)

Irreversible harm was defined for the full analysis population as a composite of CV death/MI/stroke/fatal bleed/nonfatal ICH. Kaplan-Meier plots are provided in Figure A-22. There were numerically fewer subjects with irreversible harm events in the ticagrelor group compared with placebo for both intermediate/low risk group and in the high risk group with subjects <70 years.

Figure A-22. Kaplan-Meier plot of exploratory variable net clinical harm (composite of CV death/stroke/MI/fatal bleeds/non-fatal ICH) by risk subgroup and subjects <70 years



Source: Reviewer's analysis.

Sponsor's model-based method

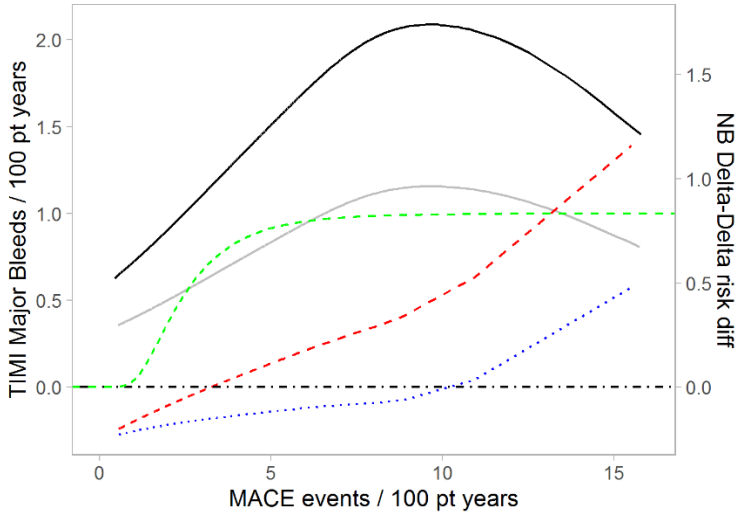
The sponsor submitted a net-benefit analysis in eCTD 0588 following an approach similar to a published FDA analysis for ticagrelor based on PEGASUS.[4] This analysis was conducted to support the following labeling text in sections 1.2 (Limitation of use): "(b) (4)

The analysis conducted by the sponsor consists of two steps. In the first step, a multivariate cox proportional hazard model for primary efficacy events is used to predict individual risk at one year (bolded terms in Appendix A in eCTD 0588 describe the covariates included). The individual risk is then incorporated into a cox proportional hazard model for TIMI major bleeding together with treatment in the second step to predict individual risk at 1 year. Lastly, the predicted TIMI major bleed is plotted

against risk for primary efficacy events with superimposed net benefit (predicted reduction in primary events – predicted increase in TIMI major bleed) either with equal weighing or with reduction in primary events weighed 1.5 times higher. The results of this analysis are shown in Figure A-23.

From the analysis described above, the sponsor concludes that a higher benefit is seen at the higher end of the risk spectrum. The reviewer disagrees with this conclusion, as most subjects are predicted to have an individual risk of < 5 events / 100 patient years (see cumulative distribution in green). In this range, the net benefit per the sponsor's analysis tends to be negative, except towards the higher end when absolute risk reduction is weighed higher. Additionally, it is unclear how this approach could be practically implemented.

Figure A-23: Sponsor's net-benefit analysis (black: Ticagrelor TIMI major bleeding; gray: Placebo TIMI major bleeding; Blue: Net benefit – equal weighing; Red: Net benefit – 1.5 higher weighing for reduction; green cumulative distribution of individual risk for primary events)



Source: Reviewer's reproduction of sponsor's analysis

References

1. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2019.
2. Goff DC, Jr., Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2014;129(25 Suppl 2):S49-73.
3. Kit BK, Carroll MD, Lacher DA, Sorlie PD, DeJesus JM, Ogden C. Trends in serum lipids among US youths aged 6 to 19 years, 1988-2010. *JAMA.* 2012;308(6):591-600.

4. McDowell TY, Blank M, Lawrence J, Stockbridge N. Food and Drug Administration Analysis of Ticagrelor: Using Data From an Enriched Trial to Evaluate Benefit-Risk Difference in an Unstudied Population. *Circulation.* 2016;134(19):1500-1502.

Demographic and Baseline Characteristics

Table A-54. Demographic and Baseline Characteristics

		High Risk (n = 13384)	Intermediate/Low Risk (n = 5831)
Sex	F	2845 (21.3%)	3185 (54.6%)
	M	10539 (78.7%)	2646 (45.4%)
Race	Asian	2891 (21.6%)	1515 (26.0%)
	Black	301 (2.2%)	102 (1.7%)
	Other	477 (3.6%)	237 (4.1%)
	White	9715 (72.6%)	3977 (68.2%)
Age Group	<=70	7653 (57.2%)	5719 (98.1%)
	>70	5731 (42.8%)	112 (1.9%)
BMI Group	<= 30	7926 (59.2%)	3068 (52.6%)
	> 30	5446 (40.7%)	2760 (47.3%)
	missing	12 (0.1%)	3 (0.1%)
ASA Dose	<= 81	5781 (43.2%)	2352 (40.3%)
	> 81	7393 (55.2%)	3389 (58.1%)
	Missing	125 (0.9%)	60 (1.0%)
	No Aspirin	85 (0.6%)	30 (0.5%)
Insulin Use	N	9602 (71.7%)	4107 (70.4%)
	Y	3782 (28.3%)	1724 (29.6%)
PCI History	N	5499 (41.1%)	2563 (44.0%)
	Y	7885 (58.9%)	3268 (56.0%)
Multivessel Disease	N	4773 (35.7%)	2458 (42.2%)
	Y	8574 (64.1%)	3357 (57.6%)
	missing	37 (0.3%)	16 (0.3%)
CAD History	N	22 (0.2%)	6 (0.1%)

		High Risk (n = 13384)	Intermediate/Low Risk (n = 5831)
	Y	13362 (99.8%)	5825 (99.9%)
Statin Use	N	1351 (10.1%)	603 (10.3%)
	Y	12033 (89.9%)	5228 (89.7%)
Smoker	N	11583 (86.5%)	5537 (95.0%)
	Y	1800 (13.4%)	294 (5.0%)
	missing	1 (0.0%)	
Duration of Diabetes (y)	<= 10	6379 (47.7%)	3320 (56.9%)
	> 10	6997 (52.3%)	2509 (43.0%)
	missing	8 (0.1%)	2 (0.0%)
HBA1C	<= 7	6587 (49.2%)	2521 (43.2%)
	> 7	6445 (48.2%)	3193 (54.8%)
	missing	352 (2.6%)	117 (2.0%)
Diabetic Complications	N	9929 (74.2%)	4366 (74.9%)
	Y	3447 (25.8%)	1463 (25.1%)
	missing	8 (0.1%)	2 (0.0%)
eGFR	<= 60	3514 (26.3%)	1034 (17.7%)
	> 60	9626 (71.9%)	4709 (80.8%)
	missing	244 (1.8%)	88 (1.5%)
PAD History	N	12090 (90.3%)	5440 (93.3%)
	Y	1294 (9.7%)	391 (6.7%)
Coronary Artery Revascularization	N	2367 (17.7%)	1507 (25.8%)
	Y	11017 (82.3%)	4324 (74.2%)
CABG History	N	9223 (68.9%)	4459 (76.5%)
	Y	4161 (31.1%)	1372 (23.5%)
CHF History	N	11422 (85.3%)	4649 (79.7%)
	Y	1962 (14.7%)	1181 (20.3%)
	missing		1 (0.0%)
Carotid Artery Stenosis	N	12442 (93.0%)	5546 (95.1%)
	Y	942 (7.0%)	284 (4.9%)

		High Risk (n = 13384)	Intermediate/Low Risk (n = 5831)
	missing		1 (0.0%)
CKD History	N	11988 (89.6%)	5473 (93.9%)
	Y	1396 (10.4%)	357 (6.1%)
	missing		1 (0.0%)
COPD History	N	12485 (93.3%)	5562 (95.4%)
	Y	899 (6.7%)	268 (4.6%)
	missing		1 (0.0%)
Dyslipidemia	N	1637 (12.2%)	829 (14.2%)
	Y	11747 (87.8%)	5001 (85.8%)
	missing		1 (0.0%)
Family History of CVD	N	9464 (70.7%)	4040 (69.3%)
	Y	3920 (29.3%)	1790 (30.7%)
	missing		1 (0.0%)
Hypertension	N	867 (6.5%)	576 (9.9%)
	Y	12517 (93.5%)	5254 (90.1%)
	missing		1 (0.0%)
Ischemic Stroke History	N	13361 (99.8%)	5821 (99.8%)
	Y	23 (0.2%)	9 (0.2%)
	missing		1 (0.0%)
MI History	N	13269 (99.1%)	5792 (99.3%)
	Y	115 (0.9%)	38 (0.7%)
	missing		1 (0.0%)
TIA History	N	13153 (98.3%)	5757 (98.7%)
	Y	231 (1.7%)	73 (1.3%)
	missing		1 (0.0%)
LDL >1.8 mmol/l	N	4541 (33.9%)	1626 (27.9%)
	Y	8421 (62.9%)	4025 (69.0%)
	missing	422 (3.2%)	180 (3.1%)
Triglycerides	N	7312 (54.6%)	2878 (49.4%)

		High Risk (n = 13384)	Intermediate/Low Risk (n = 5831)
>1.7 mmol/l	Y	5813 (43.4%)	2858 (49.0%)
	missing	259 (1.9%)	95 (1.6%)
Systolic BP >130 mmHg	N	3584 (26.8%)	2775 (47.6%)
	Y	9800 (73.2%)	3056 (52.4%)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

FORTUNATO F SENATORE
04/19/2020 02:40:00 PM

JIALU ZHANG
04/19/2020 03:49:02 PM

CHRISTINE E GARNETT
04/20/2020 07:57:12 AM

KAREN A HICKS
04/20/2020 09:10:52 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022433Orig1s028

OTHER REVIEW(S)

DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Regulatory Project Manager Review

sNDA:	22433/S-028
Drug:	Brilinta (ticagrelor) tablets
Class:	$P2Y_{12}$ inhibitor
Applicant:	Astra Zeneca
Supplement description:	This supplement provides for changes to labeling based on the results of study #D513BC00001, titled "Effect of **T**icagrelor on **H**ealth outcomes in diab**E**tes **M**ellitus patients **I**ntervention **S**tudy (THEMIS)".
Proposed Indication:	BRILINTA is indicated to reduce (b) (4) myocardial infarction, and stroke in patients with coronary artery disease and type 2 diabetes mellitus (b) (4) .
Approved Indication:	BRILINTA is indicated to reduce the risk of a first MI or stroke in patients with coronary artery disease (CAD) at high risk for such events. While use is not limited to this setting, the efficacy of BRILINTA was established in a population with type 2 diabetes mellitus (T2DM).
Date of Submission:	30 July 2019
Approval date:	28 May 2020
PDUFA date:	30 May 2020

- **REVIEW TEAM**
  - Office of New Drugs, Office of Cardiology, Hematology, Endocrinology and Nephrology
    - Division of Cardiology and Nephrology
      - Norman Stockbridge, MD, PhD – Division Director
      - Mary Ross Southworth, PharmD – Deputy Director for Safety
      - Michael Monteleone, MS, RAC – Associate Director for Labeling
      - Karen Hicks, MD – Cross Disciplinary Team Leader (CDTL)
      - Fred Senatore, MD, PhD – Clinical Reviewer
      - Christine Garnett, PharmD – Clinical Reviewer
      - Bridget Kane, MS – Sr. Regulatory Health Project Manager
  - Office of Biometrics, Division of Biometrics II
    - Jialu Zhang, PhD – Team Leader/Reviewer

❖ BACKGROUND

BRILINTA (ticagrelor), manufactured by Astra Zeneca (AZ), is an oral, reversible blocker of the platelet $P2Y_{12}$ receptor, an action which blocks ADP-mediated platelet activation and aggregation. BRILINTA was first approved under NDA 22433 on 20 July 2011 and is currently indicated (based on the results of PLATO and PEGASUS) to reduce the rate of cardiovascular (CV) death, myocardial infarction (MI), and stroke in patients with acute coronary syndrome (ACS) or a history of 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.

Under IND 119344, AZ developed ticagrelor for the reduction in rate of thrombotic events (CV death, MI or stroke) in patients with coronary artery disease (CAD) and Type 2 Diabetes Mellitus (T2DM) without a history of MI or stroke. To support the indication, the sponsor conducted a phase 3b trial, # D513BC00001, titled "Effect of **T**icagrelor on **H**ealth outcomes in diabetes **M**ellitus patients **I**ntervention **S**tudy (THEMIS)". THEMIS was an event-driven, randomized, double blind, placebo controlled, parallel group, global, multi-center study that evaluated the effect of ticagrelor twice-daily vs. placebo for prevention of major CV events in patients with T2DM at high risk for CAD. The primary endpoint for THEMIS was time to first occurrence of any event from the composite of CV death, MI, or stroke (ischemic, hemorrhagic or unknown etiology).

The sponsor randomized 19,271 subjects to accrue 1554 primary events. The last subject was enrolled on 24 May 2016; the trial was completed in January 2019 and the database was locked in February 2019. A pre-sNDA meeting was scheduled for 14 November 2018; the Division's preliminary responses, sent 8 November 2018, were sufficient for the applicant so the meeting was cancelled.

The applicant presented the Topline results to the Division on 9 April 2019 (minutes dated 28 April 2019) and subsequently submitted the supplemental application on 30 July 2019. The application was filed on 28 September 2019. Three years of exclusivity were requested.

At the mid-cycle meeting, the ongoing data analysis showed a numerically narrow benefit-risk margin based on the primary endpoint and major bleeding. This narrow margin was potentially reversible based on investigator and patient preferences. The apparent fragility of the clinical benefit-risk evaluation precipitated consultation with the Decision Support and Analysis Team (Office of Planning and Strategic Analysis, Office of Strategic Programs) to provide a more in-depth benefit/risk analysis. The Division also issued a Discipline Review letter on 24 February 2020 notifying the applicant of its concern.

The Division engaged the applicant in further discussion of the benefit/risk assessment during a teleconference on 16 March 2020.

No other concerns were raised during the review.

❖ REGULATORY TIMELINE

- sNDA Stamp Date: 12 June 2019
- Site Selection Meeting 4 September 2019
- Filing Meeting: 16 September 2019
- Filing Date: 28 September 2019
- 74-day Letter: 12 October 2019
- Mid-cycle Meeting: 6 January 2020
- Team Meeting: 13 February 2020

- PeRC Review: 18 February 2020
- T-con with Applicant: 16 March 2020
- Team Meeting: 18 March 2020
- Labeling Meeting #1 18 March 2020
- Labeling Meeting #2 25 March 2020
- Labeling Meeting #3 13 April 2020
- PDUFA Date: 30 May 2020

❖ ADMINISTRATIVE ITEMS

User Fee
Per PDUFA VI, there was no user fee associated with this efficacy supplement.

Facilities
N/A

Site Inspections
The review team determined site inspections were not needed.

Pediatric Review Committee (PeRC)
The Division and the PeRC agreed with the Applicant's request for full waiver of pediatric studies because necessary studies are impossible or highly impracticable.

Advisory Committee
N/A

Review Status
The application was considered a Standard review.

❖ LABELING REVIEW

Labeling negotiations began on 30 March 2020 and concluded on 20 May 2020. Attached is a tracked changes version of the label that includes all changes made to Package Insert during this review cycle.

The following is a summary of the changes made to labeling during this review cycle:

In addition to the content changes outlined below, multiple minor editorial and formatting revisions were made throughout the label. Tables depicting number of events were changes from Events/100 patient years to Events/1000 patient years (Table 4, 7 – these tables are aligned with tables in new section 14.2).

Package Insert

1 INDICATIONS AND USAGE

- New section headings and Section 1.2 (new indication): 'Coronary Artery Disease but No prior Stroke or Myocardial Infarction' (CAD/No prior stroke or MI) added.

2 DOSING AND ADMINISTRATION

- New section headings added
- Section 2.2 – dosing directions for new indication CAD/No prior stroke or MI

4 WARNINGS AND PRECAUTIONS

- Section 5.3 Dyspnea – Percentage of patients broken down by study (PLATO, PEGASUS, THEMIS)

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience – Updated total # of patients in safety database
  - Figure 3 – Time to first TIMI Major bleeding (THEMIS) added
  - Table 6 – Bleeding Events (THEMIS) added
  - Bradycardia section – **Removed** the following sentence: (b) (4) [redacted]

8 USE IN SPECIFIC POPULATIONS

- Section 8.5 Geriatric Use – Updated to include THEMIS study
- Section 8.7 Renal Impairment – Updated to include THEMIS study

14 CLINICAL STUDIES

- 14.1 Acute Coronary Syndromes and Secondary Prevention after Myocardial Infarction
  - Table 9 – Streamlined/revised for consistency with THEMIS tables
- Section '14.2 Coronary Artery Disease but no Prior Stroke or Myocardial Infarction' added
  - 'THEMIS' section added to describe study results that support new indication (Section 1.2)

Medication Guide

Section 'What is BRILINTA?'

- Added new use 'decrease your risk of a first heart attack or stroke in people who have a condition where the blood flow to the heart is decreased (coronary artery disease or CAD) who are at high risk for having a heart attack or stroke'
- Revised wording for other uses for clarity

Section 'Before taking BRILINTA, tell your doctor about all of your medical conditions if you:'

- Added 'medicine used to control pain' and 'an antibiotic medication'
- **Removed** rifampin (b) (4) [redacted]

❖ **DISCIPLINE REVIEWS**

Below are the conclusions reached by the application primary reviewers. Please refer to DARRTS for the completed reviews.

Clinical/Statistics Review (20 April 2020 – Senatore, Garnett, Zhang)
Recommended Action: Approval

The reviewers concluded that per 21 CFR 314.126, the applicant conducted an adequate and well controlled trial and that this trial provided substantial evidence of effectiveness to support approval of ticagrelor for the following indication: *to reduce the risk of a first MI or stroke in patients with coronary artery disease (CAD) at high risk for such events. While use is not limited to this setting, the efficacy of BRILINTA was established in a population with type 2 diabetes mellitus (T2DM)*.

The reviewers agreed that the aggregate benefit of preventing MI and stroke to be greater than the increased risk of a TIMI major bleed (mostly falls in hemoglobin > 5 g/dL). Observed risks such as dyspnea and bleeding are consistent with the established warning in the approved ticagrelor label.

CDTL Memo (01 May 2020 – Hicks)
Recommended Action: Approval
The CDTL agreed with the team's recommendation for approval but believed the indicated use should specify the population and setting in which the study was conducted – for patients with type 2 diabetes mellitus and coronary artery disease.

Division Memo (17 May 2020 – Stockbridge)
Recommended Action: Approval

Dr. Stockbridge conveyed his agreement with the review team's recommendation for approval.

❖ CONSULT REVIEWS

The following is a list of consult reviews obtained during this review. Refer to DARRTS for complete reviews.

- DMEPA (labeling) – Jones/Tu, 20 December 2019
- Decision Support (benefit/risk) – Lackey, 30 March 2020
- OPDP (labeling) – Patel, 27 April 2020
- Patient Labeling – Walker/Patel/Griffiths – 28 April 2020

❖ CONCLUSION

After taking into consideration all primary and consult reviews, the Division issued an approval letter for NDA 22433/S-028 on 28 May 2020. This approval letter was signed by Norman Stockbridge, MD, PhD – Division Director.

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

PATIENT LABELING REVIEW

Date:	April 27, 2020
To:	Bridget Kane **Division of Cardiovascular and Renal Products (DCaRP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Morgan Walker, PharmD, MBA, CPH Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Zarna Patel, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	BRILINTA (ticagrelor)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 22433
Supplement Number:	S-028
Applicant:	AstraZeneca

1 INTRODUCTION

On August 2, 2019, AstraZeneca submitted for the Agency's review a supplement to their New Drug Application (NDA) 22433/S-028 for BRILINTA (ticagrelor) tablets. This supplement proposes a new indication, " BRILINTA is indicated to reduce (b) (4) myocardial infarction, and stroke in patients with coronary artery disease (CAD) and type 2 diabetes mellitus (T2DM) (b) (4)

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Cardiovascular and Renal Products (DCaRP) on September 19, 2019 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for BRILINTA (ticagrelor) tablets.

2 MATERIAL REVIEWED

- Draft BRILINTA (ticagrelor) tablets MG received on August 2, 2019, and received by DMPP and OPDP on April 21, 2020.
- Draft BRILINTA (ticagrelor) tablets Prescribing Information (PI) received on August 2, 2019, and received by DMPP and OPDP on April 21, 2020.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

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

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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LASHAWN M GRIFFITHS
04/28/2020 08:25:01 AM

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

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

Memorandum

Date: April 27, 2020

To: Bridget Kane, Regulatory Project Manager
Division of Cardiology and Nephrology (DCN) [Formerly Division of Cardiovascular and Renal Products, DCRP]

Michael Monteleone, Associate Director for Labeling, (DCN)

From: Zarna Patel, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: James Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for BRILINTA (ticagrelor) tablets, for oral use

NDA/BLA: 022433/Supplement 28

In response to DCN consult request dated September 19, 2019, OPDP has reviewed the proposed product labeling (PI) and the Medication Guide for BRILINTA (ticagrelor) tablets, for oral use (Brilinta). This supplement (S28) pertains to the indication for coronary artery disease.

PI and Medication Guide: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DCN (Bridget Kane) on April 21, 2020, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide will be sent under separate cover.

Thank you for your consult. If you have any questions, please contact Zarna Patel at (301) 796-3822 or zarna.patel@fda.hhs.gov.

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U.S. FOOD & DRUG ADMINISTRATION

Center for Drug Evaluation and Research

Decision Support and Analysis Memorandum

Date:	March 30, 2020
Reviewer(s):	Leila Lackey, MHS, DEnv, Decision Support and Analysis Team, OPSA Graham Thompson, BS, Decision Support and Analysis Team, OPSA
Team Leader:	Sara Eggers, PhD, Decision Support and Analysis Team, OPSA
Drug Name:	Brilinta (ticagrelor)
NDA/BLA #:	NDA 022433, Supplement 28
Indication:	Reduce the rate of myocardial infarction and stroke in patients with coronary artery disease and type 2 diabetes mellitus.
Applicant:	Astrazenica

Summary

The Division of Cardiovascular and Renal Products requested decision support for the ticagrelor supplemental new drug application (sNDA) for primary prevention of cardiovascular events. The request was motivated by a challenging benefit-risk assessment for this product and indication. This request was initiated under a program in the Office of Planning and Strategic Analysis to provide real-time, by-request decision support for regulatory review teams. The program is described in the Appendix.

This memo describes the additional analysis DSAT performed to inform the review team's benefit-risk assessment. Specifically, DSAT performed a multiple criteria decision analysis (MCDA), incorporating quantitative judgements from members of the review team about the relative importance of outcomes. This case highlights the heterogeneity of preference between individuals and the sensitivity of aggregated utility to even small, insignificant imbalances in fatal outcomes.

Introduction

As the first anti-platelet agent (if approved) intended for primary prevention of cardiovascular outcomes, FDA anticipated the need to carefully consider the benefit-risk profile of ticagrelor for the target patient population. To begin, the review team calculated the number needed to treat (NNT) to prevent one cardiovascular outcome (NNT-benefit) and the NNT to cause one major bleeding event (NNT-harm) — the primary efficacy and safety endpoints in the THEMIS trial. This analysis showed NNT-benefit exceeded NNT-harm. In other words, fewer patients need to be treated to cause one major bleeding event than must be treated to prevent one cardiovascular event, a potentially unfavorable benefit-risk tradeoff.

Recognizing the limitations of the NNT approach — principally that the relative importance of the events is not considered — DCRP requested decision support from DSAT. To inform the benefit-risk assessment for ticagrelor, DSAT applied MCDA, which is a method to quantify the aggregate performance of different alternatives, across multiple benefits and risks, that explicitly incorporates the relative importance of the outcomes. MCDA produces an overall

score for the different options (placebo and ticagrelor) that can range between 0 and 1, with higher values being preferred (Figure 1). In this case, the overall score of ticagrelor is based on the observed performance of ticagrelor and placebo in the THEMIS trial; relative importance of the different outcomes was elicited from the review team by DSAT.

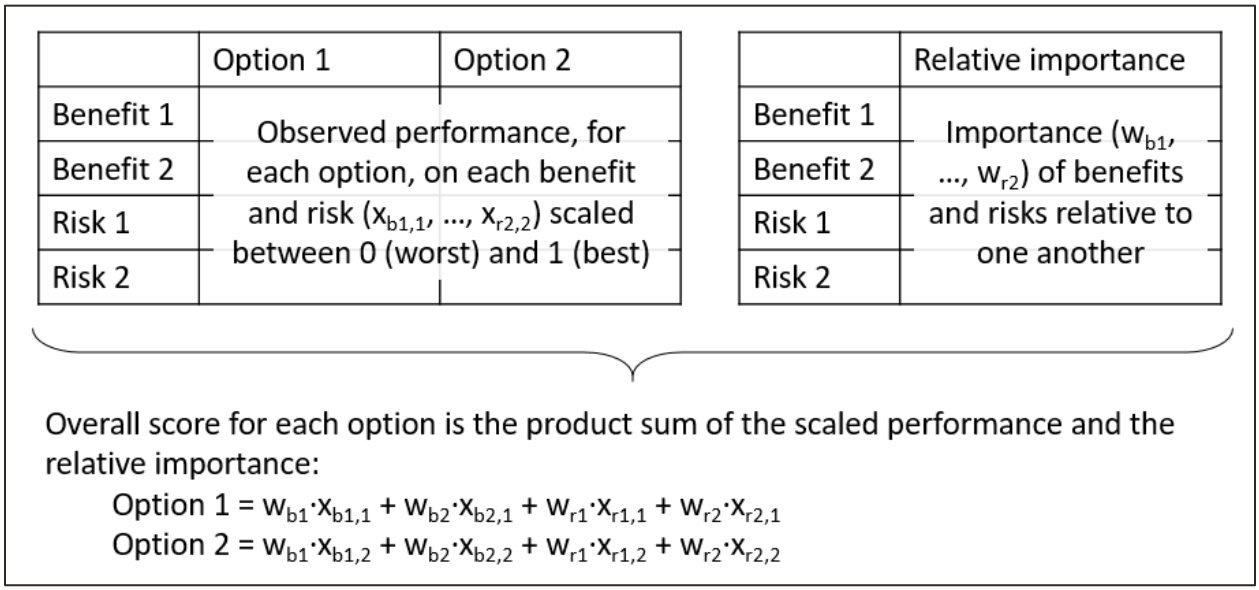


Figure 1. MCDA weighted aggregation of performance.

DSAT conducted the analysis following the recommendations from the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) MCDA Emerging Good Practices Task Force.[1,2] The Applicant utilized the Pharmaceutical Research and Manufacturers of America (PhRMA) Benefit Risk Action Team (BRAT) Framework[3] to inform their benefit-risk assessment, documented in section 2.5.6 of the sNDA. We briefly review their approach at the end of this memo.

Decision Problem

The decision under consideration was approval of ticagrelor for primary prevention of cardiovascular death, heart attack, and stroke in patients at increased risk, specifically patients with coronary artery disease and type 2 diabetes. (b) (4) The official authorized to take action, the Signatory Authority, was Dr. Stockbridge, who took into consideration the recommendations of the entire review team, and strove to build a consensus, while reserving authority to take the final action. DSAT confirmed the decision problem and approach with Dr. Stockbridge and the review team prior to starting the process. DSAT and the review team recognized this would be the first application of MCDA with quantification of preferences by a CDER review team for a regulatory decision on a drug application. The analysis contained in this memo reflect the views of the review team, informing their recommendation for Dr. Stockbridge.

A primary element of decision support is clarifying the decision context — the regulatory background, the severity of the condition, and the degree of unmet medical need — that influence FDA's tolerance for risk and uncertainty, acceptable benefit-risk tradeoffs, and the ultimate regulatory decision. The clinical review documents, including the Benefit-Risk

Framework, provides a complete account of the regulatory history, analysis of condition, and current treatment options. Salient points are summarized below as context for this memo.

Relevant Regulatory Background

Tiacagrelor was approved in 2011 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). It is also labeled as being superior to clopidogrel and for prevention of stent thrombosis. Like all anti-platelet agents, ticagrelor has a boxed warning for bleeding risk.

Analysis of Condition

Heart disease is the leading cause of death in the United States. Coronary artery disease (CAD) is the most common type of heart disease. Heart disease is often "silent" — causing few, if any, symptoms until a clinical event occurs. Risk factors for heart disease include high blood pressure and cholesterol, smoking and alcohol use, overweight and obesity, unhealthy diet and physical inactivity, and diabetes. Prevention of clinical events can be divided between primary (prevention of the first clinical event) and secondary (prevention of subsequent clinical events). While the first clinical event is often less severe than subsequent events, mortality can still occur and having one event increases the risk of subsequent events. Patients with CAD and type 2 diabetes, but without history of an MI, have similar risk of a clinical event as patients with ACS or a history of MI.

Current Treatment Options

Preventing clinical events, both fatal and non-fatal, is the primary goal of treatment. Low dose aspirin is frequently recommended but is not without risks and adherence is generally poor. Several medications for glycemic control in type 2 diabetes have also been shown to reduce the risk of cardiovascular events. No anti-platelet agents are currently approved for primary prevention, although some are used off-label.

Identifying the Key Benefits and Risks of Ticagrelor

The first step of the MCDA approach is to identify the specific outcomes (potential benefits and harms from the drug) that have the most bearing on the regulatory decision. Anti-platelet agents for prevention of cardiovascular outcomes have well-established key* benefits and risks: prevention of cardiovascular death, myocardial infarction (MI), and ischemic stroke as the benefit; increase in bleeding events, including fatal bleeds and intracranial hemorrhages, as the risks. For this analysis, the review team focused on type-1 (spontaneous) MI, as these accounted for more than 80% of all MIs and, as they occur without warning and outside the hospital, are the most clinically concerning. For bleeding events, the review team focused on TIMI major bleeds, the primary safety event for this trial. Ticagrelor also has a well-established side effect of dyspnea, but the review team considered this to be a tolerability concern and so did not include it in the MCDA. Table 1 shows the number of first events by 12 and 36 months in the THEMIS trial.

* Key benefits are favorable effects generally assessed by primary and other clinically important endpoints across the studies in a development program; key risks are unfavorable effects that are important from a clinical and/or public health perspective in terms of their frequency and/or severity and/or seriousness. See FDA Guidance M4E(R2): The CTD – Efficacy Guidance for Industry. December 2017. https://www.fda.gov/media/93569/download.

Table 1. Counts of first events by 12 and 36 months in the full analysis set (benefits) and safety analysis set (risks).

Outcome	Between 0 and 12 months first events/number treated (95% CI per 10,000 patients)		Between 0 and 36 months first events/number treated (95% CI per 10,000 patients)	
	Placebo	**Ticagrelor**	**Placebo**	**Ticagrelor**
Key benefit: Primary composite endpoint (full analysis set)				
Cardiovascular death	82/9601 (67-107)	94/9619 (78-117)	279/9601 (257-324)	306/9619 (283-353)
Type-1 myocardial infarction	98/9601 (82-122)	102/9619 (86-127)	299/9601 (277-346)	236/9619 (214-276)
Ischemic stroke	66/9601 (52-85)	40/9619 (29-54)	164/9601 (145-197)	132/9619 (114-160)
Key risk: TIMI major bleed (safety analysis set)				
TIMI fatal bleed	3/9531 (0-7)	9/9562 (3-16)	8/9531 (3-14)	17/9562 (9-26)
TIMI intracranial hemorrhage	17/9531 (9-26)	28/9562 (18-40)	42/9531 (31-57)	62/9562 (49-81)
Other TIMI major bleed	17/9531 (9-26)	53/9562 (41-70)	44/9531 (33-60)	109/9562 (93-135)

Source: statistical reviewer's analysis

The outcomes listed in Table 1 are nonredundant, nonoverlapping, and preference independent ("how much one cares about the performance on a criterion should not depend on the performance of other criteria").[2] Outcomes were also complete from the regulator's perspective, meaning that they encompassed the entire set of clinical outcomes that the review team considered relevant to this decision. The review team did not include some of the other adverse events of ticagrelor, such as dyspnea and moderate or minor bleeding events, because they were felt to carry less overall clinical importance at the population level. The team recognized individual patients may view these outcomes as important but felt these risks could be described in labeling to support decision-making by individual patients based on what they felt was important.

There was also discussion about whether cardiovascular death should be included in the set of effects. The primary reason not to include was that there was no difference between the treatment arms (there was a small, insignificant imbalance in favor of placebo). Arguments for including were it was a pre-specified component of the composite benefit endpoint, it is a fatal outcome and therefore would have significant relative importance, and it is critical for completeness of the benefits and risks. The choice of whether to include or exclude cardiovascular death from the set of decision factors was an issue discussed throughout the decision analysis. Our analysis considered both choices, discussed further in the results.

The FDA review team considered two timepoints, 12 months and 36 months, because of the expected time course of benefit in a primary prevention population. The review team considers the benefit-risk balance at the 36-month timepoint as the most relevant assessment for the regulatory decision. The review team also felt it important to consider that under a primary prevention indication, the patient must take ticagrelor for several years in order to meaningfully reduce the patient's risk of experiencing a cardiovascular event. However, the risk of a bleeding event increases immediately and remains elevated. Therefore, the review team wanted to investigate the benefit-risk balance at an earlier timepoint.

Eliciting Importance Weights of Benefits & Risks

In order aggregate the benefits and risks into a single measure, MCDA requires quantification of two judgements: the importance of incremental changes within an outcome (termed scores) and the importance of outcomes relative to one another (termed weights).

DSAT initially utilized a swing weighting approach to elicit scores and weights for the benefits and risks from the review team and other stakeholders. Swing weighting is a commonly-recommended technique for eliciting weights from a small group of stakeholders.[2] However, individual follow-up with a subset of the review team suggested the swing weighting responses were likely unreliable. Therefore, DSAT shifted to a greatly simplified elicitation task. Both approaches are described below.

For the initial swing weighting, DSAT conducted a two-hour elicitation session with four representatives from the FDA review team for ticagrelor and nine additional subject-matter experts from DCRP. The session began with a brief introduction to MCDA and swing weighting, as well as discussion of the decision context and decision problem.

DSAT began the elicitation by discussing the scores for changes within the feasible ranges of the benefits & risks. Feasible ranges are shown in Table 2 and were defined based on the observed 95% confidence intervals of the benefits and risks in the THEMIS trail. Several options are available for quantitatively scoring the importance of incremental changes within an outcome. Elicitation participants agreed to use a linear scoring function (Figure 2), consistent with a "population" interpretation of the benefits and risks (in other words: changes within the feasible range represent additional people who will experience the outcome; therefore, each change is equally important).

Table 2. Feasible ranges of benefits and risks used for the swing weighing elicitation (events per 10,000 patients).

	Between 0 and 12 months		Between 0 and 36 months	
Outcome	**Best**	**Worst**	**Best**	**Worst**
Key benefit: Primary composite endpoint (full analysis set)				
Cardiovascular death	65	120	255	355
Type-1 myocardial infarction	80	130	210	350
Ischemic stroke	25	90	110	200
Key risk: TIMI major bleed (safety analysis set)				
TIMI fatal bleed	0	20	0	30
TIMI intracranial hemorrhage	5	45	30	85
Other TIMI major bleed	5	75	30	140

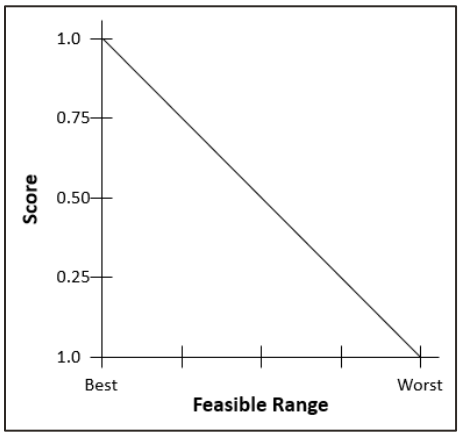


Figure 2. Linear scoring function where the lower end of the feasible range is the "best" (score = 1) and the upper end is the "worst" (score = 0).

After establishing the linear scoring functions, DSAT elicited individual responses from the thirteen participants for the relative importance of the swings from worst to best from the perspective of an FDA regulator. Reponses were elicited for the 12 and 36-month timepoint for two sets of benefit and risk outcomes — one without cardiovascular death (5-item) and one with cardiovascular death (6-item). Responses for the 5-item set were elicited first and the 36-month timepoint was emphasized as the key decision-point for the clinical trial. Some of the elicitation participants also provided responses from the imagined perspective of a patient. Individual responses were collected and presented to the group to facilitate discussion of potential reasons for differences in responses. Participants were given the option to revise responses after this discussion.

One limitation identified during the elicitation was the lack of severity information for the clinical events (in particular, MI and stroke). For example, the Modified Rankin Score (mRS) is widely used in clinical trials to assess disability before and after a stroke. Larger increases in mRS before/after a stroke, and higher final scores, indicate a more debilitating event. In the THEMIS trial, mRS missing data rates were approximately 60% at baseline, 45% during hospitalization for the stroke, and 70-75% 90 days after hospitalization. Elicitation participants struggled with quantifying the relative importance of the nonfatal events without this type of information for the clinical trial events. Some chose to assess the importance by focusing on the worst-case outcome. Others focused on the more "typical" outcome.

After the elicitation session, DSAT met one-on-one with two participants who were also members of the FDA review team (here referred to as reviewer A and reviewer B) to validate their responses. To prepare for the validation, DSAT used the participant's responses during the elicitation session to calculate the per-event importance and individual-event tradeoffs relative to the outcome with the greatest per-event importance (Table 3). We also ranked the outcomes based on the calculated per-event importance, with the highest importance ranked first. We utilized the responses to the 5-item set of outcomes at 36-months for this exercise, which excluded cardiovascular death as an outcome. As the elicitation participants agreed to a linear scoring function, results should be transferrable to other timepoints and outcome sets. Table 3 provides these calculations.

Table 3. Calculations (shaded columns) based on swing weighting response to support one-on-one validations.

Outcome	Swing width per 10,000 patients[a]	Swing weighting response	Calculated per-event importance[b]	Calculated Rank	Calculated event tradeoffs[c]
Reviewer A					
Type-1 myocardial infarction	140	50	0.36	4	9.3
Ischemic stroke	90	100	1.11	3	3.0
TIMI fatal bleed	30	100	3.33	1	1.0
TIMI intracranial hemorrhage	55	100	1.82	2	1.8
Other TIMI major bleed	110	30	0.27	5	12.2
Reviewer B					
Type-1 myocardial infarction	140	90	0.64	4	5.2
Ischemic stroke	90	90	1.00	2	3.3
TIMI fatal bleed	30	100	3.33	1	1.00
TIMI intracranial hemorrhage	55	40	0.73	3	4.6
Other TIMI major bleed	110	10	0.09	5	36.7

[a] Swing width per 10,000 patients treated = 10,000 x (worst – best); worst and best from Table 2

[b] Per-event importance = respondent's swing weight / swing width per 10,000 patients treated

[c] Event tradeoffs = maximum[per-event importance for all outcomes] / per-event importance

To start the one-on-one validation, DSAT presented just the calculated rank, without other calculations or the overall result, and asked if the ranking seemed to correctly reflect their perspective on the events. Reviewer A responded with a revised ranking (most to least important): ischemic stroke, tie between TIMI fatal bleed and TIMI intracranial hemorrhage, type-1 myocardial infarction, and TIMI major bleed. The high rank of ischemic stroke was based on the possibility of devastating disability following the event. Reviewer B responded that the calculated ranking seemed correct.

As mentioned, our final MCDA analysis included cardiovascular death as an outcome. Therefore, we next asked the reviewer where they would place cardiovascular death within the relative ranking. Reviewer A placed it as a tie with fatal bleeds, moving intracranial hemorrhage down. Reviewer B ranked it after fatal bleeds, based on the "do no harm" principle — a fatal bleed occurs due to the mechanism of action of the drug while a cardiovascular death suggests the drug didn't work well enough. Table 4 has the final ranking for the two reviewers.

Table 4. Revised importance rankings.

Reviewer A	Reviewer B
1. Ischemic stroke	1. TIMI fatal bleed
2. TIMI fatal bleed (tie)	2. Cardiovascular death
2. Cardiovascular death (tie)	3. Ischemic stroke
4. TIMI intracranial hemorrhage	4. TIMI intracranial hemorrhage
5. Type-1 myocardial infarction	5. Type-1 myocardial infarction
6. Other TIMI major bleeds	6. Other TIMI major bleed

After discussing the ranking, DSAT presented the calculated individual-event tradeoffs (Table 3) to the reviewer and asked for their impressions, as well as how cardiovascular death would tradeoff against their most important outcome. Reviewer A felt the calculated tradeoffs for ischemic stroke and intracranial hemorrhage under-valued the importance of these events and that the calculated tradeoff for other TIMI major bleeds over-valued this event. In contrast, reviewer B felt the calculated tradeoffs for type-1 myocardial infarction, ischemic stroke, and TIMI intracranial hemorrhage over-estimated the importance of these events. Both reviewers felt that cardiovascular death was equal to TIMI fatal bleed in importance. Final tradeoffs are in Table 5. For both reviewers we made all tradeoffs relative to cardiovascular death.

Table 5. Tradeoffs against cardiovascular death for reviewer A and reviewer B.

Reviewer A	Reviewer B
1 cardiovascular death is equal in importance to:	1 cardiovascular death is equal in importance to:
10 type-1 myocardial infarctions	13 type-1 myocardial infarctions
1 ischemic stroke	10 ischemic strokes
1 TIMI fatal bleeds	1 TIMI fatal bleeds
2 TIMI intracranial hemorrhages	12 TIMI intracranial hemorrhages
50 other TIMI major bleeds	40 other TIMI major bleeds

Due to the substantial changes for reviewer A and B during the one-on-one elicitation, DSAT determined that the responses from the group elicitation were likely not reliable. All methods for eliciting privately-held judgements and tradeoffs have limitations, but it became clear that the cognitive burden of swing weighting limited its usefulness in this case. Both reviewer A and B felt that the simple tradeoff question was substantially easier to respond to and felt comfortable with the stated numeric tradeoffs. Using the final tradeoffs (Table 5), DSAT calculated final swing weights (Table 6).

Table 6. Final swing weights (shaded column) for reviewer A and B for 12 and 36-months.

Outcome	Tradeoff against cardiovascular death[a]	Between 0 and 12 months		Between 0 and 36 months	
		Swing width per 10,000 patients[b]	Swing weight[c]	Swing width per 10,000 patients[b]	Swing weight[c]
Reviewer A					
Cardiovascular death	1	55	85	100	100[d]
Type-1 myocardial infarction	10	50	8	140	7
Ischemic stroke	1	65	100[d]	90	12
TIMI fatal bleed	1	20	31	30	36
TIMI intracranial hemorrhage	2	40	31	55	6
Other TIMI major bleed	50	70	2	110	3
Reviewer B					
Cardiovascular death	1	55	100[d]	100	100[d]
Type-1 myocardial infarction	13	50	14	140	14
Ischemic stroke	10	65	90	90	9
TIMI fatal bleed	1	20	30	30	30
TIMI intracranial hemorrhage	12	40	28	55	5
Other TIMI major bleed	40	70	2	110	3

[a] From Table 5

[b] Swing width per 10,000 patients treated = 10,000 x (worst – best); worst and best from Table 2

[c] Swing weight = (100 x swing width of outcome) / (swing width of most important outcome x tradeoff against the most important outcome)

[d] Most important outcome determined from the stated tradeoff against cardiovascular death and the swing width at that timepoint; manually assigned a swing weight of 100

MCDA Results and Uncertainty

As described above (Figure 1), MCDA integrates, for each option, ticagrelor and placebo,: a) the demonstrated effect on each outcome (Table 1), and b) the relative important weights of each outcome (Table 6). The result is an overall utility score between 0 and 1 for each option, with higher values being preferred. As the overall score is a weighted sum of performance on the individual benefits and risks, we can also examine differences between ticagrelor and placebo for the individual benefits and risks.

The overall utility score defined above considered the observed results of the THEMIS trial for each benefit and risk outcome. In addition, we conducted repeated random simulations to explore the impact of statistical uncertainty on conclusions. Each iteration, we randomly sampled event counts from probability distributions based on the observed data from the THEMIS trial (specifically, Bayesian inference using a flat uniform prior). In a given iteration, the option (placebo or ticagrelor) with higher utility is designated the "preferred" alternative. The result is the percent of iterations where each alternative is preferred.

The MCDA results found differences in utility between the two reviewers (Table 7). For the 0-36 month timeframe, Reviewer A had very close utility scores, 0.54 for placebo and 0.51 for ticagrelor; what may be considered indifference (no clear preference) between the two. Reviewer B, however, placed higher utility on placebo over ticagrelor at 36 months, 0.62 versus 0.42. These results were similar between the 12 and 36-month timepoint. In a primary prevention population, the patient must take ticagrelor for several years in order to experience the expected benefit. However, the risk of a bleeding event increases immediately and remains elevated. Therefore, the review team had initially assumed that the aggregate benefit-risk may not be favorable if assessed after only 12 months of treatment. Unexpectedly, the results of the

MCDA suggest the aggregate benefit-risk conclusion at 12-months may be similar to the conclusion at 36-months.

Table 7. MCDA results for ticagrelor versus placebo.

		Reviewer A		Reviewer B	
		Placebo	Ticagrelor	Placebo	Ticagrelor
Between 0 and 12 months					
Overall Utility (unitless, [0, 1])		0.54	0.55	0.66	0.46
Utility by Outcome	*Cardiovascular death*	0.21	0.13	0.38	0.25
	Type-1 myocardial infarction	0.02	0.02	0.02	0.02
	Ischemic stroke	0.13	0.29	0.02	0.06
	TIMI fatal bleed	0.10	0.06	0.19	0.12
	TIMI intracranial hemorrhage	0.08	0.05	0.03	0.01
	Other TIMI major bleed	0.01	0.00	0.02	0.01
Percent of simulations where preferred		46%	54%	89%	11%
Between 0 and 36 months					
Overall Utility (unitless, [0, 1])		0.54	0.51	0.62	0.42
Utility by Outcome	*Cardiovascular death*	0.24	0.14	0.41	0.23
	Type-1 myocardial infarction	0.02	0.04	0.02	0.05
	Ischemic stroke	0.11	0.24	0.02	0.04
	TIMI fatal bleed	0.08	0.05	0.14	0.08
	TIMI intracranial hemorrhage	0.08	0.04	0.02	0.01
	Other TIMI major bleed	0.01	0.00	0.02	0.00
Percent of simulations where preferred		61%	39%	90%	10%

Also shown in Table 7 are the results of the MCDA simulations, which tested the robustness of the conclusions to the statistical uncertainty in the clinical trial results. These simulations were consistent with the overall utility scores. Incorporating the tradeoffs from reviewer A yielded almost a "coin-flip" number of simulations where ticagrelor was preferred — 54% of simulations at 12-months, and 39% at 36-months, preferred ticagrelor. In contrast, incorporating the tradeoffs from reviewer B yielded fewer simulations where ticagrelor was preferred — 11% of simulations at 12-months, and 10% at 36-months, preferred ticagrelor.

Next, we considered the contribution of each benefit and risk to the overall utility of each option in order to explore how the overall assessment depends on views on individual components. Figure 3 shows the difference in utility between ticagrelor and placebo broken down across the six key benefits and risks. Positive values (bars going to the right) indicate ticagrelor has an advantage over placebo for the given benefit or risk and negative values (bars going to the left) indicate placebo has an advantage over ticagrelor. The length of the bar indicates the magnitude of the utility-weighted difference; longer bars mean a greater difference between placebo and ticagrelor. This figure highlights two major conclusions. First, the differences between the reviewers is driven primarily by the greater relative importance reviewer A placed on ischemic stroke compared to reviewer B. This highlights the heterogeneity in how individuals think about the key benefits and risks and increases the importance of adequately describing the different outcomes in labeling, in order to support benefit-risk decision-making by patients and providers.

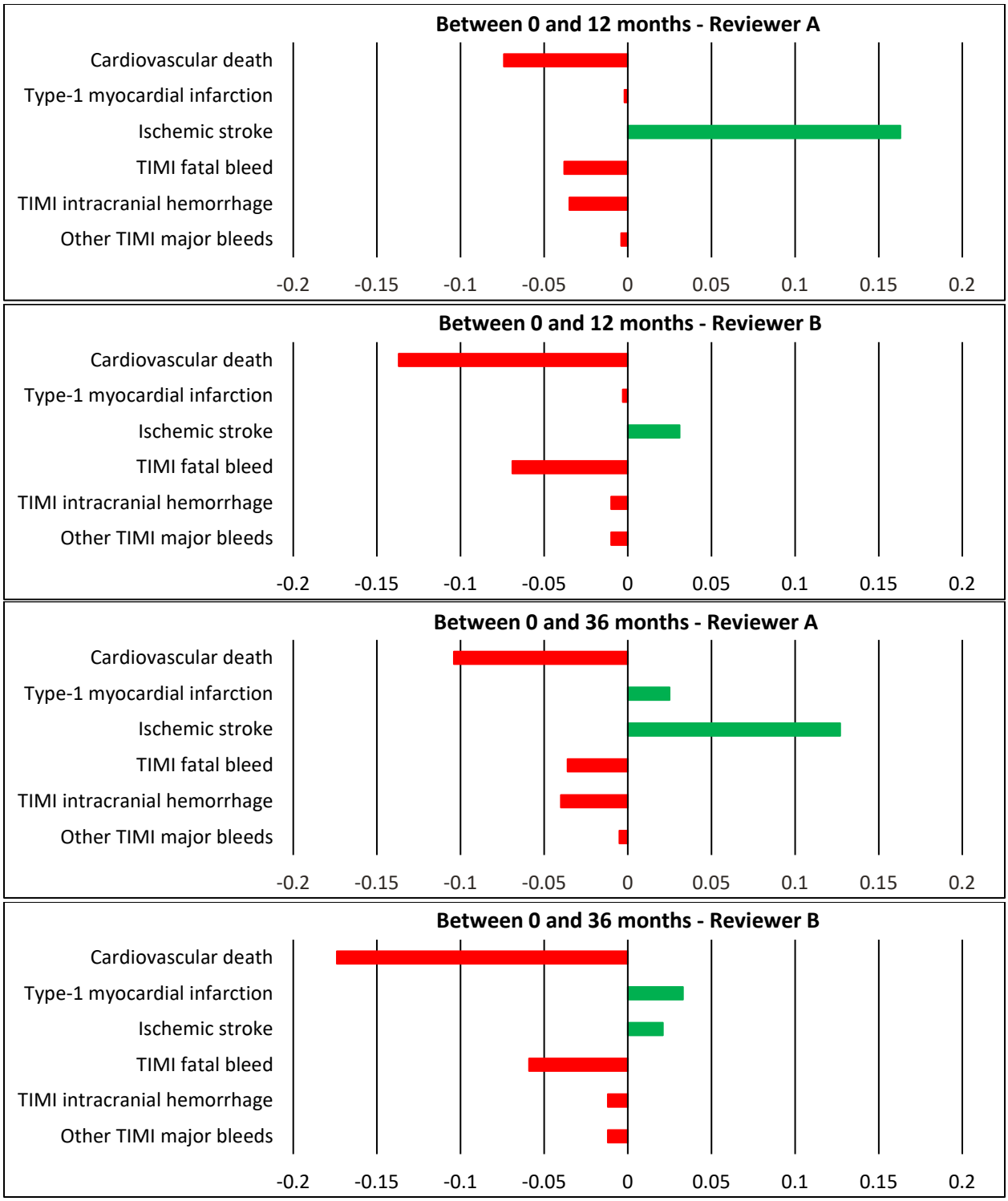


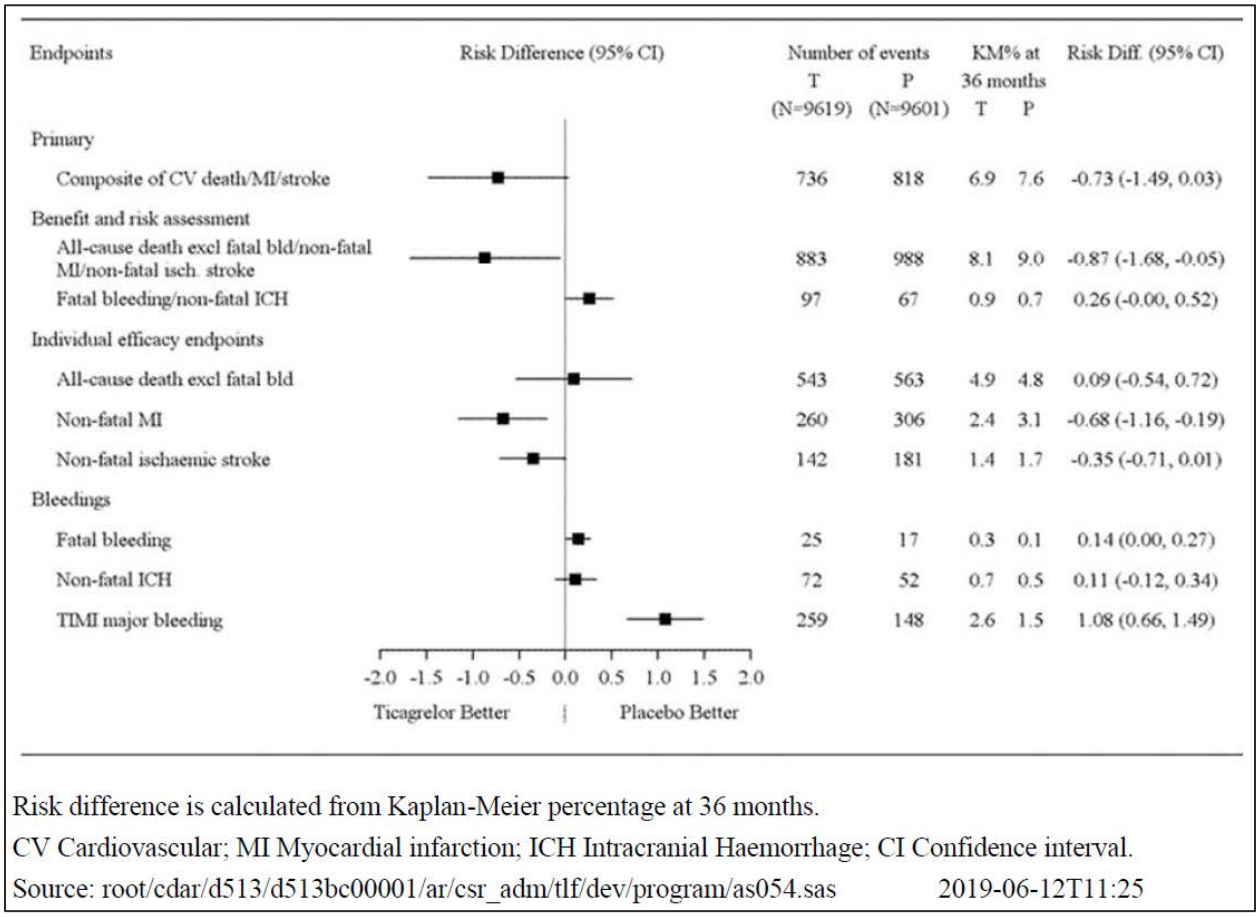
Figure 3. Difference in utility by outcome, ticagrelor minus placebo, by reviewer, at 12 and 36-months. Positive values (green) favor ticagrelor and negative (red) favor placebo.

Second, cardiovascular death counted significantly against ticagrelor for both reviewers. This was driven by the importance both reviewers placed on avoiding fatal outcomes and by the small, statistically insignificant, numerical imbalance in the THEMIS trial in cardiovascular

death at 36 months in favor of placebo. In the judgement of the clinical reviewers for ticagrelor, based in part on what is known about the mechanism of action of anti-platelet agents and ticagrelor and on the positive effect of ticagrelor on cardiovascular death in other trials for other indications, the true effect of ticagrelor on CV death is more likely to be neutral (or possibly even positive) than negative. Although this is speculative, if this is true the overall utility for ticagrelor would increase. For reviewer A, the overall utility of ticagrelor would exceed the utility of placebo. For reviewer B, the utility of ticagrelor would approximately equal the utility of placebo.

Applicant's Benefit-Risk Assessment

As mentioned above, section 2.5.6 of the sNDA contains the Applicant's benefit-risk assessment, which follows the PhRMA BRAT Framework.[3] Similar to MCDA, the first steps in the BRAT Framework are to clarify the decision (the product, the proposed indication and target population, the severity of the condition, availability of alternatives, etc.), identify the key benefits and risks, and assess performance. However, the BRAT Framework does not require specification of the relative importance of the different outcomes and the Applicant did not include them in the sNDA. Instead, the Applicant utilized forest plots (Figure 4) to qualitatively assess the benefit-risk balance of ticagrelor.



Risk difference is calculated from Kaplan-Meier percentage at 36 months.
CV Cardiovascular; MI Myocardial infarction; ICH Intracranial Haemorrhage; CI Confidence interval.
Source: root/cdar/d513/d513bc00001/ar/csr_adm/tlf/dev/program/as054.sas 2019-06-12T11:25

Figure 4. Forest plot of estimated risk difference including all-cause death (full analysis set). Reproduced from section 2.5.6 of the sNDA.

The benefits and risks considered by the Applicant are similar to those considered by the FDA review team in the MCDA but there are a few important differences. First, the Applicant

considers a number of composite endpoints — composite of CV death/MI/stroke, all-cause death excl fatal bld/non-fatal MI/non-fatal isch stroke, and fatal bleeding/non-fatal ICH. The FDA review team did not consider any composite endpoints because of the difficulty of assessing tradeoffs for composites when the components have significantly different severities (such as both fatal and non-fatal outcomes). The individual efficacy endpoints and bleeding outcomes are similar to the key benefits and risks considered by the FDA review team, although there may be some minor differences

Second, by including the composites, the Applicant has thereby introduced triple-counting of clinical outcomes. While the definitions are clearly stated through the labels, and correct interpretation can be explained in accompanying text, it does require careful review by the reader in order to avoid misinterpretation. For example, the top two rows on the forest plot in Figure 4 are virtually identical composites (the difference being CV death versus all-cause death excluding fatal bleeds) and the effect of ticagrelor on the individual components is also included on rows 4-6 (for the individual efficacy endpoints). As a result, the effect of ticagrelor on these clinical outcomes is effectively triple-counted. Visually, this also places four points on the "Ticagrelor Better" side of the forest plot. If the Applicant had considered only one composite, or only the individual components of the composite, there would only be one or two points on the "Ticagrelor Better" side. Bleeding outcomes are triple-counted between the composite on line 3 and the components on lines 7-9 (fatal bleeds and non-fatal ICHs are included in the definition of TIMI major bleeds).

Third, the Applicant used the full analysis set for all measures. In contrast, the FDA statistical reviewer used the full analysis set for key benefits and the safety analysis set for key risks. These dilemmas — whether to use the intent-to-treat population or the safety population for analysis of risks and whether different populations can be used for a combined benefit-risk assessment — have no clear consensus on best practices. The ISPOR MCDA task force does not provide specific recommendations. The use of different populations in FDA's analysis reflects the conventions that the intent-to-treat population (based on randomization) is generally the appropriate one for assessing efficacy and that the safety population (which received at least one dose of the drug) is the appropriate one for assessing safety.

(b) (4)

The Applicant's overall benefit-risk conclusion was that the benefit-risk of ticagrelor is not favorable in the entire populatio (b) (4) . DSAT notes that the Applicant's approach to benefit-risk assessment does not include explicit

qualitative or quantitative statements about tradeoffs between benefit and risk outcomes. It appears the Applicant assumed all events were of equal importance, but this is not explicitly stated. Therefore, DSAT cannot comment on the specific reasons for the differences between the Applicant's benefit-risk conclusion and the FDA review team's interpretation of the MCDA results.

FDA MCDA Conclusions

DSAT supported application of MCDA to inform DCRP's benefit-risk assessment of ticagrelor for primary prevention of cardiovascular events. The analysis considered the components of the primary efficacy and safety endpoints as the key benefits and risks (Table 1) and assessed performance after 12 and 36 months of treatment. Swing weighting was explored for eliciting tradeoffs from the review team and other stakeholders but, ultimately, a simplified elicitation task was employed (Table 5). Participating members of the review team felt the final tradeoffs were a reasonable estimate of the relative importance of the key benefits and risks. Weights were combined with the performance of ticagrelor and placebo in the THEMIS trial to assess the overall utility of ticagrelor to patients. The Applicant for ticagrelor presented a benefit-risk assessment for ticagrelor in section 2.5.6 of the sNDA. This assessment considered similar key benefits and risks but did not quantify tradeoffs or overall utility.

Given the clinical assumptions about cardiovascular death, the results of our MCDA suggest that the benefit-risk of ticagrelor is likely neither clearly favorable nor clearly unfavorable to the target patient population as a whole. In cases where there is no clear direction on favorability, DSAT's recommendation is that the analysis should be viewed as an indication that the decision is a close call and relies heavily on the review team's and the signatory's judgement in light of the therapeutic context and the identified uncertainties regarding benefit and risks.

In the case of ticagrelor, the assessment of favorability is also highly dependent on individual judgement about the importance of the benefit and risk outcomes. Findings from this additional benefit-risk analysis are consistent with the review team's recommendation to approve ticagrelor in order to make it available to patients who might find the benefit-risk profile acceptable. The benefit-risk is sensitive to individual views on the relative importance of the benefits and risks and to what is assumed about the effect on cardiovascular death. For people who view the relative importance of health outcomes similar to reviewer A, the benefit-risk profile of ticagrelor for primary prevention of cardiovascular events is neutral or positive, depending on what is believed about the effect on cardiovascular death. For people who view the relative importance of health outcome similar to reviewer B, the benefit-risk balance may be negative or neutral. A limitation of this approach is that it cannot capture individuals who view the relative importance of health outcomes differently from reviewer A or Reviewer B. Detailed description in labeling of the clinical outcomes avoided and caused will support benefit-risk decision-making by patients and providers by allowing them to align treatment decisions with their judgement and individual patient characteristics.

Appendix: Decision Support Service

CDER is currently exploring ways in which decision analysis approaches can further aid drug regulatory decision-making. As part of this effort, CDER's Office of Program and Strategic Analysis is piloting a decision support service to assess how such approaches may be effectively and efficiently applied to support particularly challenging premarket or postmarket review decisions. This service offers a dedicated support team and a suite of resources that can be tailored to the review team's specific needs.

A decision support service may inform CDER's most challenging regulatory decisions by a) helping to add structure to the process where necessary and b) providing new, tailored methods to inform assessments of benefits, risks and benefits versus risks. The decision support team can help the review team to:

- Clearly characterize the decision problem, public health goals, regulatory options, and key uncertainties.
- Focus discussion and deliberations on decision-relevant issues.
- Clarify areas of agreement and constructively address differing perspectives.
- Systematically assess key uncertainties and their implications on the decision; identify information needed to reduce uncertainty.
- Identify when quantitative benefit-risk or decision analysis tools may be useful and help review teams apply these tools to fit their needs.
- Communicate key issues to a broader audience, internal or external.

Decision support cases typically begin with a request from a member of the product review Division (primary reviewer, CDTL, or Division Director). DSAT meets with the requestor to get background on the application and the decision problem as the requestor understands it. Based on this initial meeting, review of available materials, and interactions with other members of the review team, DSAT will propose qualitative and quantitative analyses. Most consults involve development of value trees, benefit-risk outcomes tables, and use of the Benefit-Risk Framework. The analysis is designed to be tailored to the decision problem, available data, timeframe, and needs of the review team. The focus is on supporting the review team's decision-making, not on producing a set deliverable. Analyses and interpretation may be conducted by DSAT or by members of the review team, depending on capacity, capabilities, and interest.

References

1. Thokala P, Devlin N, Marsh K, et al. Multiple Criteria Decision Analysis for Health Care Decision Making--An Introduction: Report 1 of the ISPOR MCDA Emerging Good Practices Task Force. *Value Health.* 2016;19(1):1-13.

2. Marsh K, M IJ, Thokala P, et al. Multiple Criteria Decision Analysis for Health Care Decision Making--Emerging Good Practices: Report 2 of the ISPOR MCDA Emerging Good Practices Task Force. *Value Health.* 2016;19(2):125-137.

3. Coplan PM, Noel RA, Levitan BS, Ferguson J, Mussen F. Development of a framework for enhancing the transparency, reproducibility and communication of the benefit-risk balance of medicines. *Clin Pharmacol Ther.* 2011;89(2):312-315.

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LABEL AND LABELING REVIEW
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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:	December 20, 2019
Requesting Office or Division:	Division of Cardiovascular and Renal Products (DCRP)
Application Type and Number:	NDA 022433/S-028
Product Name, Dosage Form, and Strength:	Brilinta (ticagrelor) tablets, 60 mg and 90 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	AstraZeneca Pharmaceuticals LP
FDA Received Date:	November 7, 2019
OSE RCM #:	2019-1635
DMEPA Safety Evaluator:	Grace P. Jones, PharmD, BCPS
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS

1 REASON FOR REVIEW

AstraZeneca Pharmaceuticals LP (AstraZeneca) submitted an efficacy supplement for Brilinta, proposing to add the following indication, to reduce (b) (4) myocardial infarction, and stroke in patients with coronary artery disease (CAD) and type 2 diabetes mellitus (T2DM) (b) (4)

DCRP requested that we review the proposed changes to the Brilinta Prescribing Information (PI) for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

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

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

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the proposed changes to the Brilinta PI, Section 2 Dosage and Administration. We note that in Section 2.1 Dosing, AstraZeneca proposes to delete "After one year", which changes the dosing instructions such that patients managed for acute coronary syndrome (ACS) no longer continue Brilinta therapy beyond 12 months. We learned via internal email communication with the DCRP that Brilinta therapy for 12 months in patients with ACS is reasonable.

Additionally, we note that in Section 2.1 Dosing, AstraZeneca proposes to relocate the statement, *"Do not administer BRILINTA with another oral P2Y12 platelet inhibitor."* to Section 2.3 Administration, and proposes to edit and relocate the statement "(b) (4) *BRILINTA with a daily maintenance dose of aspirin 75-100 mg…should take one tablet (their next dose) at its*

scheduled time." to Section 2.3 Administration. We find these changes acceptable from a medication error perspective.

4 CONCLUSION & RECOMMENDATIONS

Our review of the proposed Brilinta PI did not identify any areas of vulnerability from a medication error perspective. We have no recommendations at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Brilinta received on November 7, 2019 from AstraZeneca Pharmaceuticals LP.

Table 2. Relevant Product Information for Brilinta	
Initial Approval Date	July 20, 2011
Active Ingredient	ticagrelor
Indication	Acute Coronary Syndrome (ACS) or a History of Myocardial Infarction (MI) 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)]*. <u>Proposed</u>: (b) (4) BRILINTA is indicated to reduce (b) (4) myocardial infarction, and stroke in patients with coronary artery disease (CAD) and type 2 diabetes mellitus (T2DM) (b) (4) *[see Clinical Studies (14.2)]*.
Route of Administration	oral
Dosage Form	tablets
Strength	60 mg and 90 mg
Dose and Frequency	Acute Coronary Syndrome (ACS) or a History of Myocardial Infarction (MI) 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. In patients with a history of MI administer 60 mg twice daily. <u>Proposed:</u> (b) (4) Administer 60 mg twice daily. For all patients with ACS *[see Dosage and Administration (2.1)]*.

How Supplied	90 mg is supplied as a round, biconvex, yellow, film-coated tablet with a “90” above “T” on one side: • Bottles of 60 • 100 count Hospital Unit Dose 60 mg is supplied as a round, biconvex, pink, film-coated tablet with a “60” above “T” on one side: • Bottles of 60
Storage	Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F)

APPENDIX B. PREVIOUS DMEPA REVIEWS

On December 5, 2019, we searched for previous DMEPA reviews relevant to this current review using the term, Brilinta. Our search identified 6 previous reviews[a,b,c,d,e,f,g], and we considered our previous recommendations to see if they are applicable for this current review.

[a] Stewart, J. Label and Labeling Review for Brilinta (NDA 022433/S-019). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 MAY 27. RCM No.: 2016-549.

[b] Gao, T. Label and Labeling Review for Brilinta (NDA 022433/S-015). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 JUN 16. RCM No.: 2015-663.

[c] Stewart, J. Label and Labeling Memorandum for Brilinta (NDA022433). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 JAN 30. OSE RCM No.: 2013-2291.

[d] Stewart, J. Label and Labeling Review for Brilinta (NDA022433). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 JAN 17. OSE RCM No.: 2013-2291.

[e] Siahpoushan, M. Label and Labeling Review for Brilinta (NDA022433). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2011 JUL 13. OSE RCM No.: 2013-2291.

[f] Toombs, L. Label and Labeling Review for Brilinta (NDA022433). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2011 MAY 10. OSE RCM No.: 2013-2291.

[g] Toombs, L. Label and Labeling Review for Brilinta (NDA022433). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2010 JUL 30. OSE RCM No.: 2009-2288.

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,[h] along with postmarket medication error data, we reviewed the following Brilinta labels and labeling submitted by AstraZeneca Pharmaceuticals LP.

- Prescribing Information (Image not shown) received on November 7, 2019, available from \\cdsesub1\evsprod\nda022433\0524\m1\us\annotated-draft-label-themis-new-indication.docx

[h] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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