CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

022433Orig1s029

Trade Name:	BRILINTA tablets
Generic or Proper Name:	ticagrelor
Sponsor:	AstraZeneca Pharmaceuticals LP.
Approval Date:	November 05, 2020
Indication:	To reduce the risk of stroke in patients with acute ischemic stroke (NIH Stroke Scale score ≤5) or high-risk transient ischemic attack (TIA).

CENTER FOR DRUG EVALUATION AND RESEARCH

022433Orig1s029

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	X
Other Action Letters	
Labeling	X
REMS	
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	X
Clinical Review(s)	X
Product Quality Review(s)	
Non-Clinical Review(s)	
Statistical Review(s)	X
Clinical Microbiology / Virology Review(s)	
Clinical Pharmacology Review(s)	
Other Reviews	X
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022433Orig1s029

APPROVAL LETTER

NDA 22433/S-029

SUPPLEMENT APPROVAL

AstraZeneca Pharmaceuticals LP
Attention: 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 May 5, 2020, received May 5, 2020, 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 stroke in patients with acute ischemic stroke (NIH Stroke Scale score ≤5) or high-risk transient ischemic attack (TIA).

As part of this supplement, changes were made to Sections 1 INDICATIONS AND USAGE, 2 DOSING AND ADMINISTRATION, 5 WARNINGS AND PRECAUTIONS, 6 ADVERSE REACTIONS, and 14 CLINICAL STUDIES of the Package Insert as well as the Medication Guide. Additional editorial revisions were made throughout the label.

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.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We acknowledge your request to waive the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. As conveyed to you during labeling negotiation, we are denying your request because the HIGHLIGHTS section does not exceed ½ page.

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.

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 acute ischemic stroke as a disease entity is not applicable to the pediatric population. As such, performance of clincal trials in the pediatric population would be highly impractical if not impossible.

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]

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

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]

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

[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

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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
11/05/2020 01:25:48 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022433Orig1s029

LABELING

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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 IN PATIENTS WITH ACS
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 IN PATIENTS WITH ACS

- **Maintenance doses of aspirin above 100 mg daily reduce the effectiveness of BRILINTA and should be avoided. (2, 5.2, 14.1)**

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

Indications and Usage (1.2)	05/2020
Indications and Usage (1.3)	11/2020
Dosage and Administration (2.3)	11/2020
Dosage and Administration (2.2)	05/2020
Warnings and Precautions (5.1, 5.2, 5.3, 5.4)	11/2020

---------- 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)
- to reduce the risk of stroke in patients with acute ischemic stroke (NIH Stroke Scale score ≤5) or high-risk transient ischemic attack (TIA). (1.3)

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

- ACS or History of MI
  - Initiate treatment with 180 mg oral loading dose of BRILINTA. 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 BRILINTA twice daily. (2.2)
- Acute Ischemic Stroke
  - Initiate treatment with a 180 mg loading dose of BRILINTA then continue with 90 mg twice daily for up to 30 days. (2.3)

Use BRILINTA with a daily maintenance dose of aspirin of 75-100 mg. (2, 5.2)

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

- 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: 11/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

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For current labeling information, please visit https://www.fda.gov/drugsatfda

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

FULL PRESCRIBING INFORMATION

WARNING: (A) BLEEDING RISK, and (B) ASPIRIN DOSE AND BRILINTA EFFECTIVENESS IN PATIENTS WITH ACS

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 IN PATIENTS WITH ACS

- **Maintenance doses of aspirin above 100 mg daily reduce the effectiveness of BRILINTA and should be avoided (2, 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 (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 *[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).

1.3 Acute Ischemic Stroke or Transient Ischemic Attack (TIA)

BRILINTA is indicated to reduce the risk of stroke in patients with acute ischemic stroke (NIH Stroke Scale score ≤5) or high-risk transient ischemic attack (TIA) *[see Clinical Studies (14.3)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Acute Coronary Syndrome or a History of Myocardial Infarction

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

Use BRILINTA with a daily maintenance dose of aspirin of 75 to 100 mg *[see Warnings and Precautions (5.2) and Clinical Studies (14)]*.

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2.2 Coronary Artery Disease but No Prior Stroke or Myocardial Infarction

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

Use BRILINTA with a daily maintenance dose of aspirin of 75 to 100 mg *[see Warnings and Precautions (5.2) and Clinical Studies (14)]*.

2.3 Acute Ischemic Stroke or Transient Ischemic Attack (TIA)

Initiate treatment with a 180 mg loading dose of BRILINTA and then continue with 90 mg twice daily for up to 30 days. The treatment effect accrued early in the course of therapy *[see Clinical Studies (14)]*.

Use BRILINTA with a loading dose of aspirin (300 to 325 mg) and a daily maintenance dose of aspirin of 75 to 100 mg *[see Warnings and Precautions (5.2) and Clinical Studies (14)]*.

2.4 Administration

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

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 Risk of Bleeding

Drugs that inhibit platelet function including BRILINTA increase the risk of bleeding *[see Adverse Reactions (6.1) and Warnings and Precautions (5.4)].*

Patients treated for acute ischemic stroke or TIA

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Patients at NIHSS >5 and patients receiving thrombolysis were excluded from THALES and use of BRILINTA in such patients is not recommended.

5.2 Concomitant Aspirin Maintenance Dose for Patients Being Treated for ACS

In the management of patients with ACS, the use of BRILINTA with maintenance doses of aspirin above 100 mg decreased the effectiveness of BRILINTA. In such patients, use a maintenance dose of aspirin of 75-100 mg *[see Dosage and Administration (2.1) and Clinical Studies (14.1)]*.

5.3 Dyspnea

In clinical trials, about 14% (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), 1.0% (THALES), 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 in Patients Treated for Coronary Artery Disease

Discontinuation of BRILINTA will increase the risk of myocardial infarction, stroke, and death in patients being treated for coronary artery disease. 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.

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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

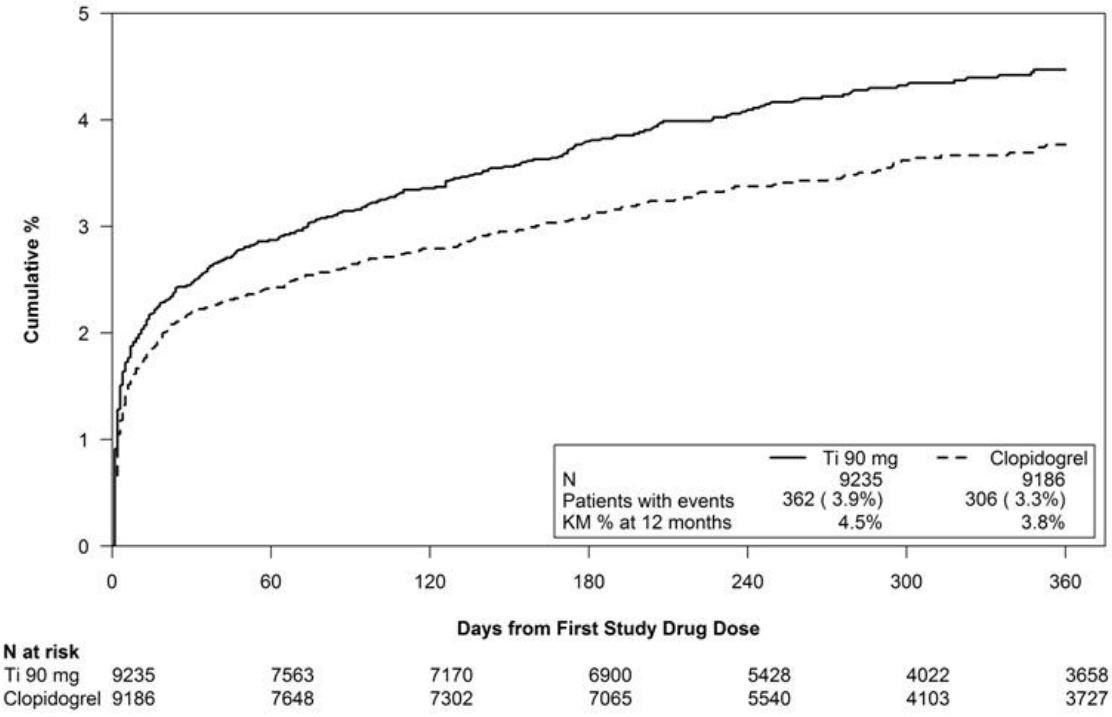
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

BRILINTA has been evaluated for safety in more than 58,000 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.

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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.

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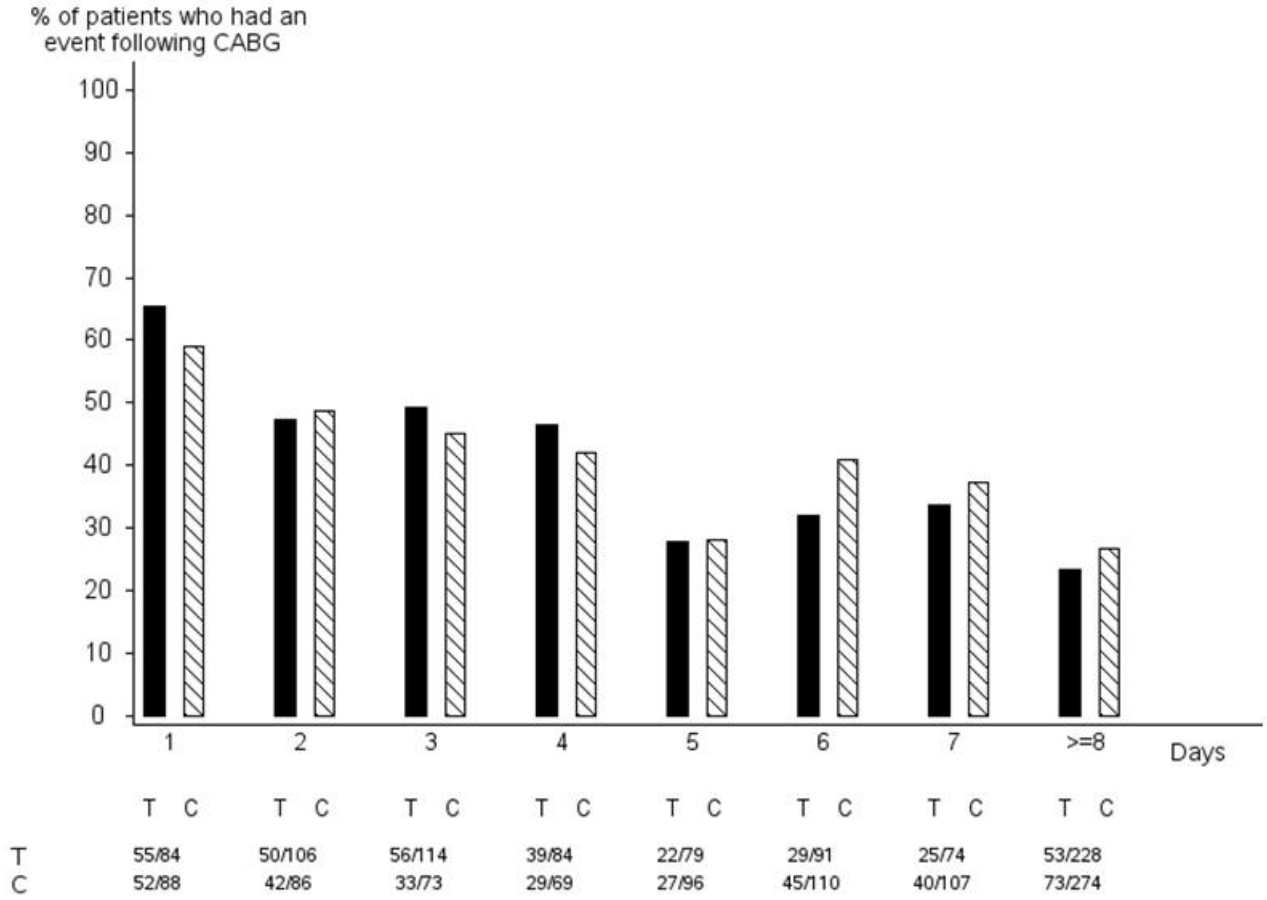
Figure 2 – 'Major fatal/life-threatening' CABG-related bleeding by days from last dose of study drug to CABG procedure (PLATO)



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.

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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

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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)

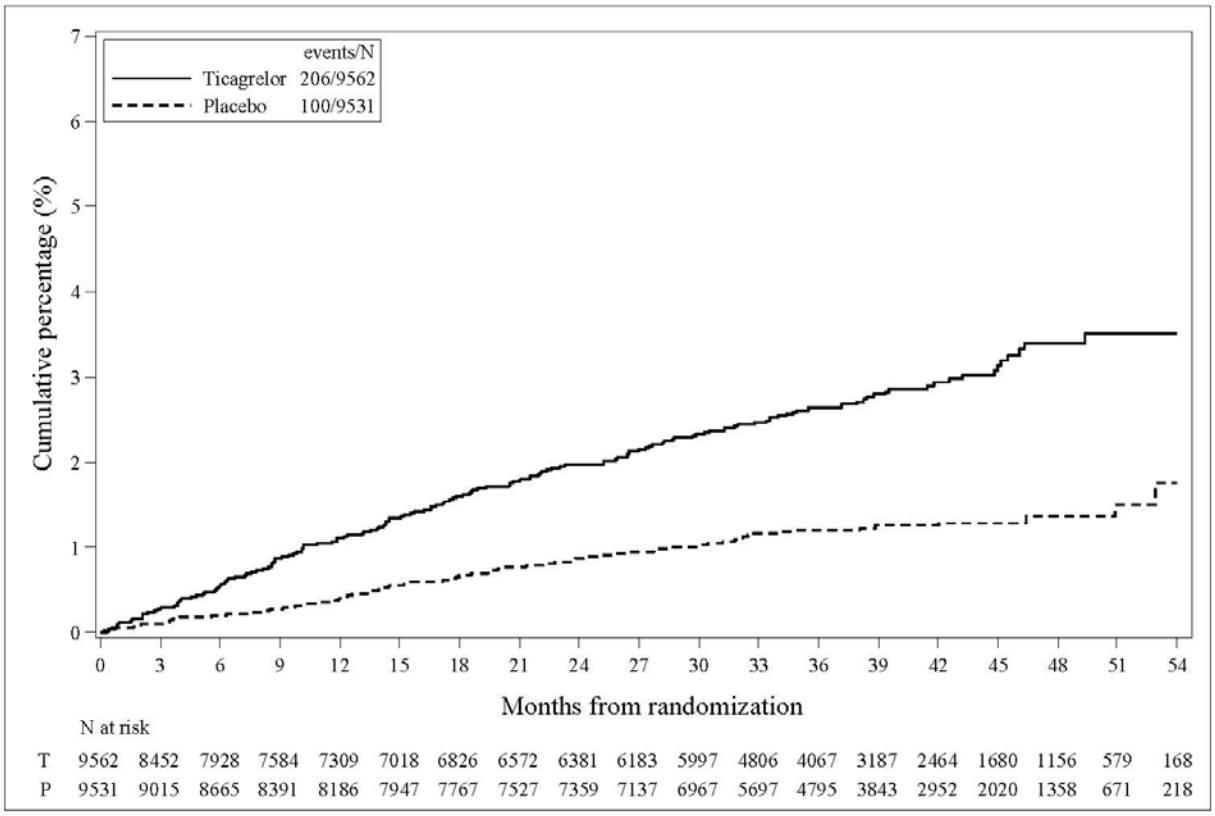
	BRILINTA* **N=6958**	**Placebo N=6996**
Dyspnea	14.2%	5.5%
Dizziness	4.5%	4.1%
Diarrhea	3.3%	2.5%

*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.

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For current labeling information, please visit https://www.fda.gov/drugsatfda

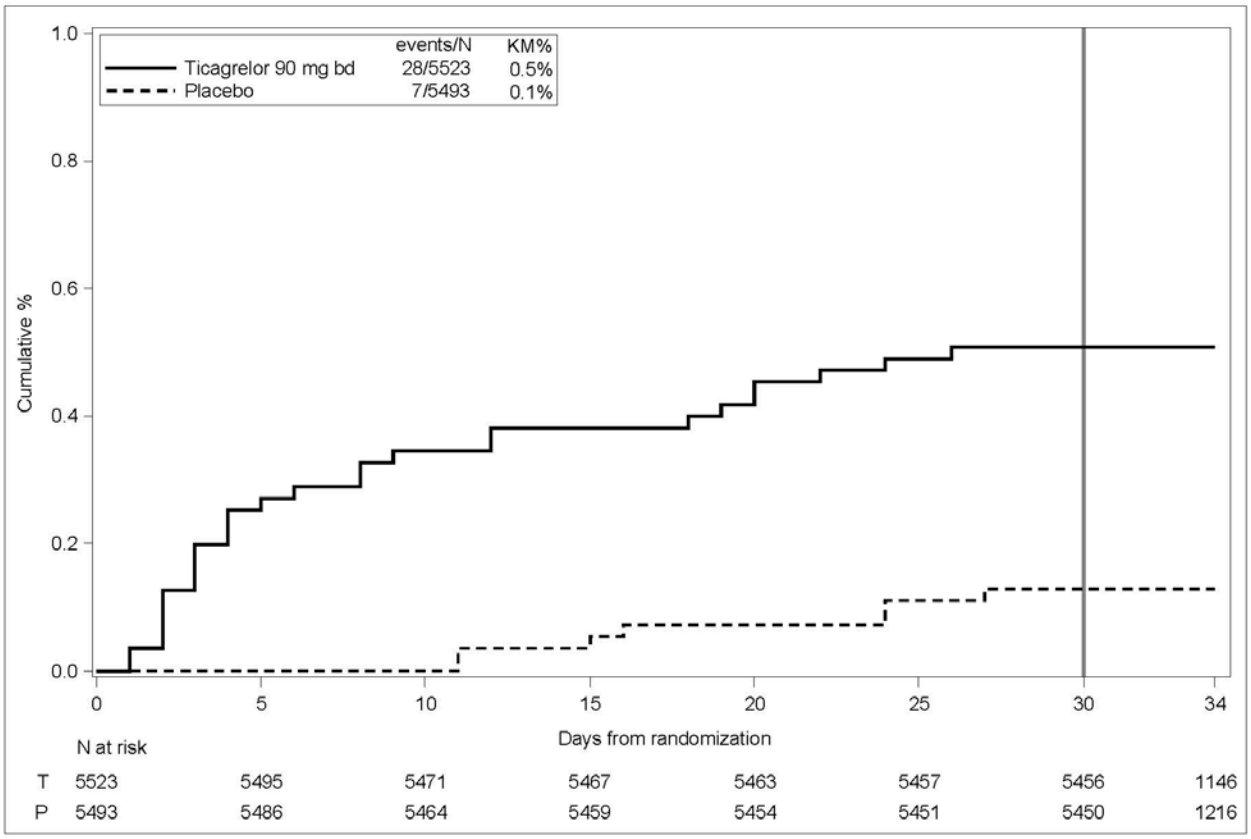
Table 6 – Bleeding events (THEMIS)

	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

Bleeding in THALES (Reduction in risk of stroke in patients with acute ischemic stroke or TIA)

The Kaplan-Meier curve of time course of GUSTO severe bleeding events is presented in Figure 4.

Figure 4 - Time course of GUSTO severe bleeding events



KM%: Kaplan-Meier percentage evaluated at Day 30; T = Ticagrelor; P = placebo; N = Number of patients

GUSTO Severe: Any one of the following: fatal bleeding, intracranial bleeding (excluding asymptomatic hemorrhagic transformations of ischemic brain infarctions and excluding microhemorrhages < 10 mm evident only on gradient-echo magnetic resonance imaging), bleeding that caused hemodynamic compromise requiring intervention (eg, systolic blood pressure <90 mmg Hg that required blood or fluid replacement, or vasopressor/inotropic support, or surgical intervention).

Intracranial bleeding and fatal bleeding in THALES: In total, there were 21 intracranial hemorrhages (ICHs) for BRILINTA and 6 ICHs for placebo. Fatal bleedings, almost all ICH, occurred in 11 for BRILINTA and in 2 for placebo.

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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, THEMIS and THALES 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)]*.

Respiratory Disorders: Central sleep apnea, Cheyne-Stokes respiration

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,

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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

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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, THEMIS, and THALES were ≥65 years of age and at least 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 efficacy and safety in patients with ESRD on dialysis as were seen in PLATO, PEGASUS, THEMIS and THALES.

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10 OVERDOSAGE

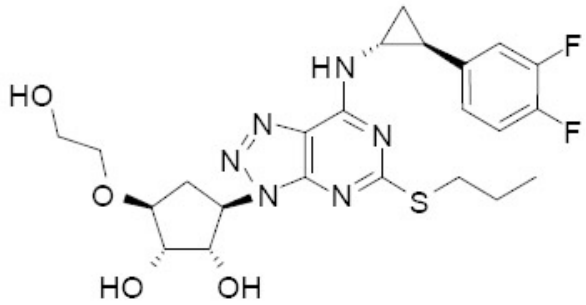
There is currently no known treatment to reverse the effects of BRILINTA, and ticagrelor is not dialyzable. Treatment of overdose should follow local standard medical practice. Bleeding is the expected pharmacologic effect of overdosing. If bleeding occurs, appropriate supportive measures should be taken.

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.

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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 5, 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 6, mean maximum IPA following the last dose of ticagrelor was 88% and 62% for clopidogrel. The insert in Figure 6 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 5 – Mean inhibition of platelet aggregation (±SE) following single oral doses of placebo, 180 mg ticagrelor or 600 mg clopidogrel

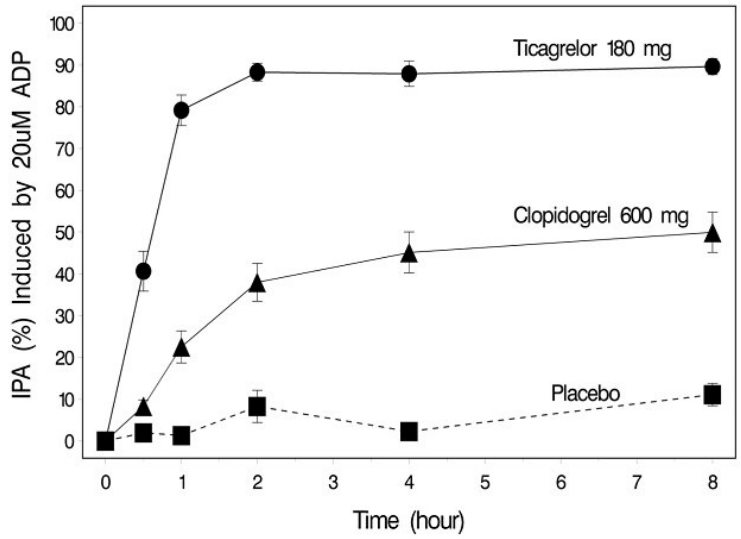

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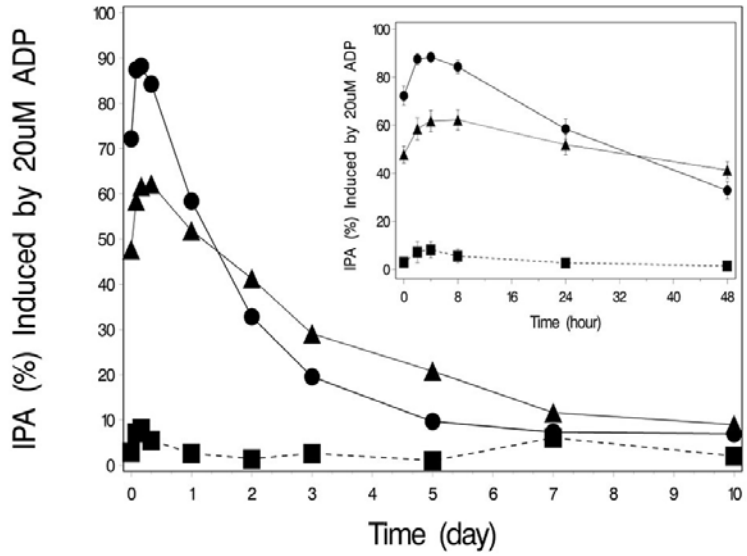
Figure 6 – Mean inhibition of platelet aggregation (IPA) following 6 weeks on placebo, ticagrelor 90 mg twice daily, or clopidogrel 75 mg daily



● **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%).

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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.

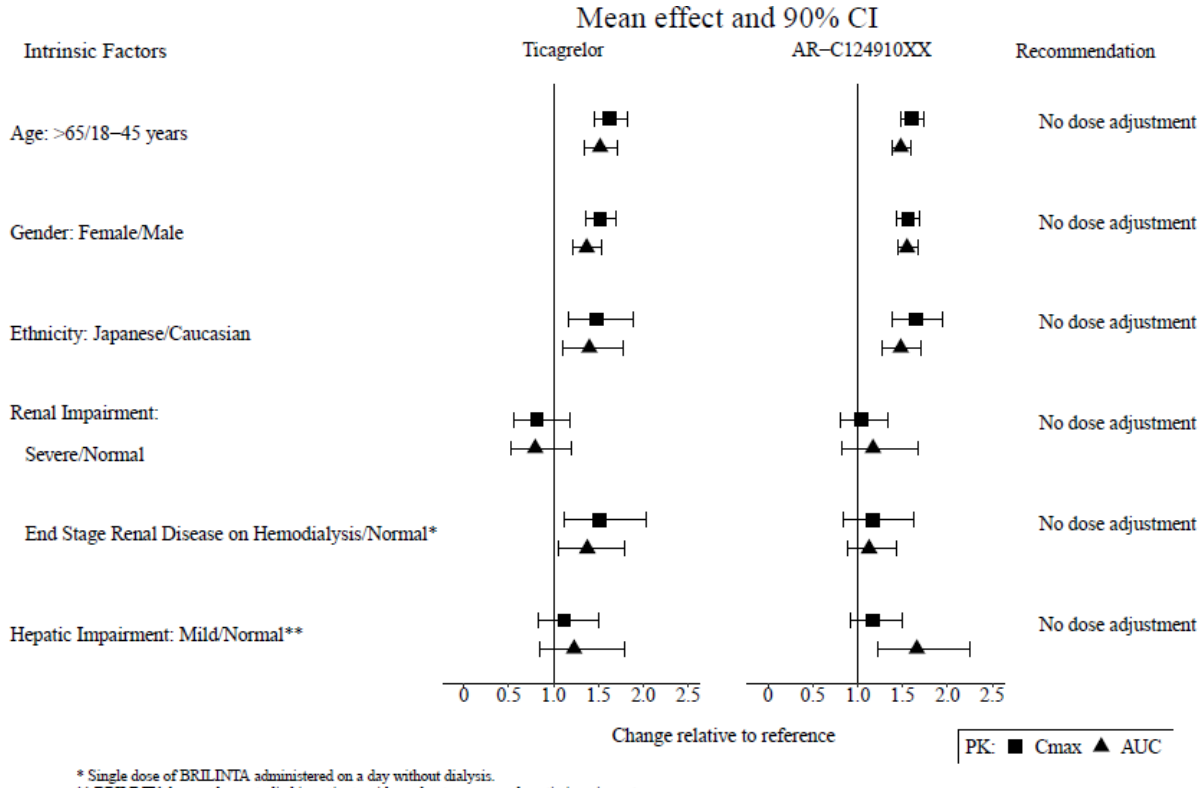
Specific Populations

The effects of age, gender, ethnicity, renal impairment and mild hepatic impairment on the pharmacokinetics of ticagrelor are presented in Figure 7. 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 7 – 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.

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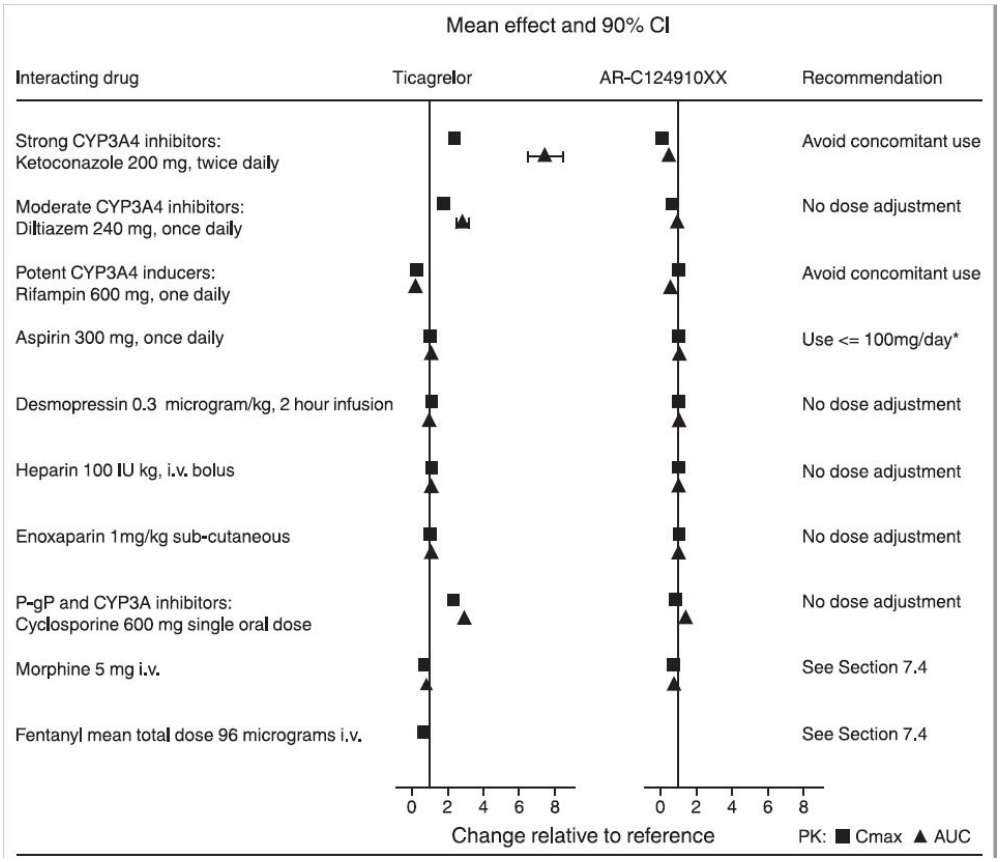
Effects of Other Drugs on BRILINTA

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 8 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 8 – 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

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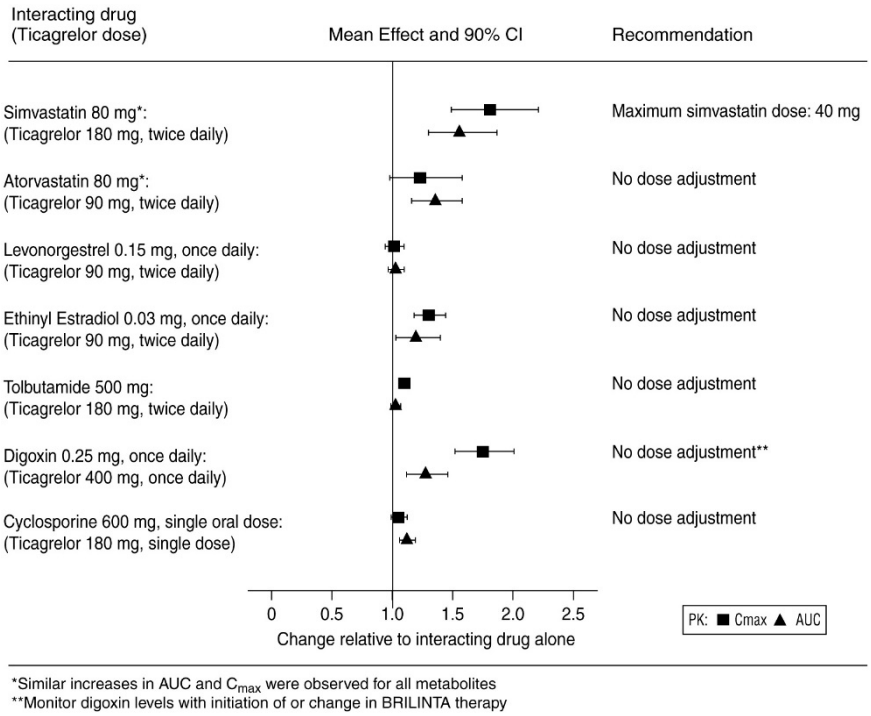
have no inhibitory effect on human CYP1A2, CYP2C19, and CYP2E1 activity. For specific *in vivo* effects on the pharmacokinetics of simvastatin, atorvastatin, ethinyl estradiol, levonorgesterol, tolbutamide, digoxin and cyclosporine, see Figure 9.

Figure 9 – 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.

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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.

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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†				
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

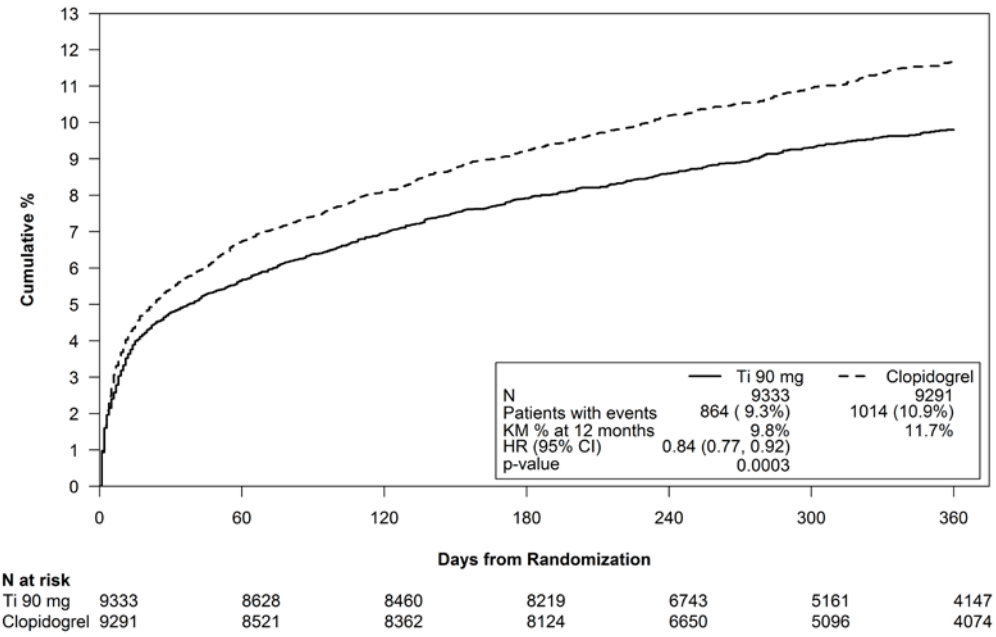
*Dosed at 90 mg bid.

†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 10) 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 10 – 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.

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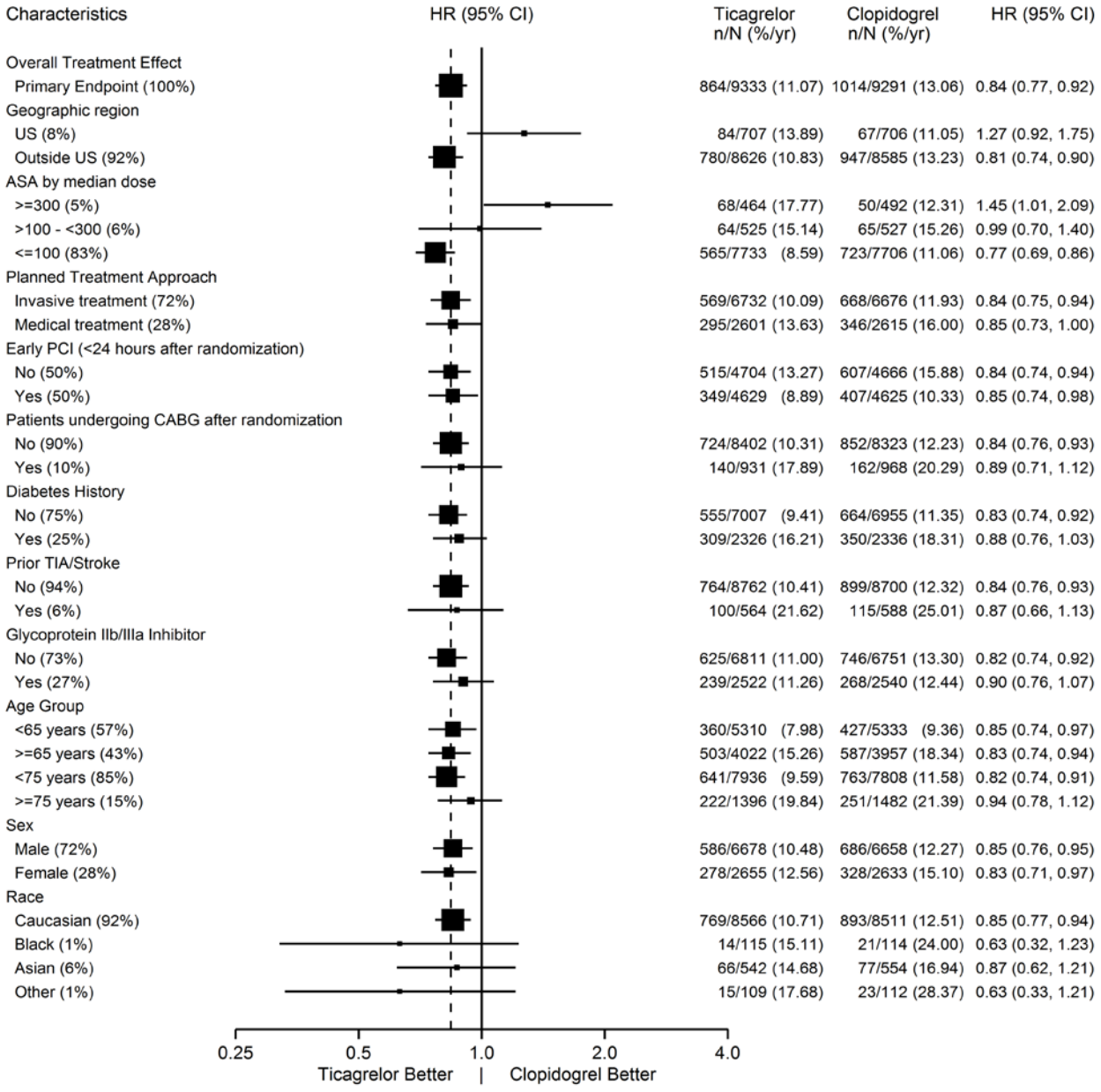
A wide range of demographic, concurrent baseline medications, and other treatment differences were examined for their influence on outcome. Some of these are shown in Figure 11. Such analyses must be interpreted cautiously, as differences can reflect the play of chance among a large number of analyses. 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 11 – 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.

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Regional Differences

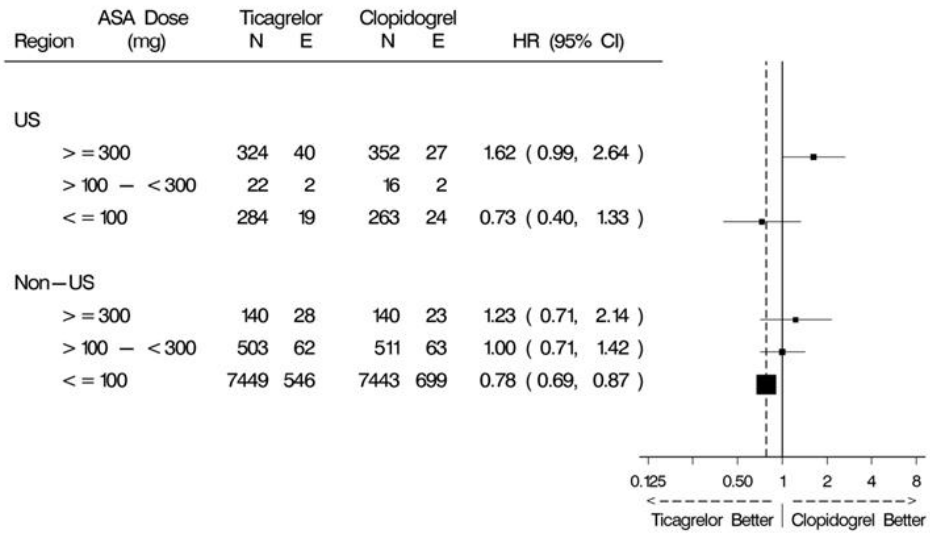
Results in the rest of the world compared to effects in North America (US and Canada) show a smaller effect in North America, numerically inferior to the control and driven by the US subset. The statistical test for the US/non-US comparison is statistically significant (p=0.009), and the same trend is 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 12 shows results by region and dose.

Figure 12 – 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.

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PEGASUS

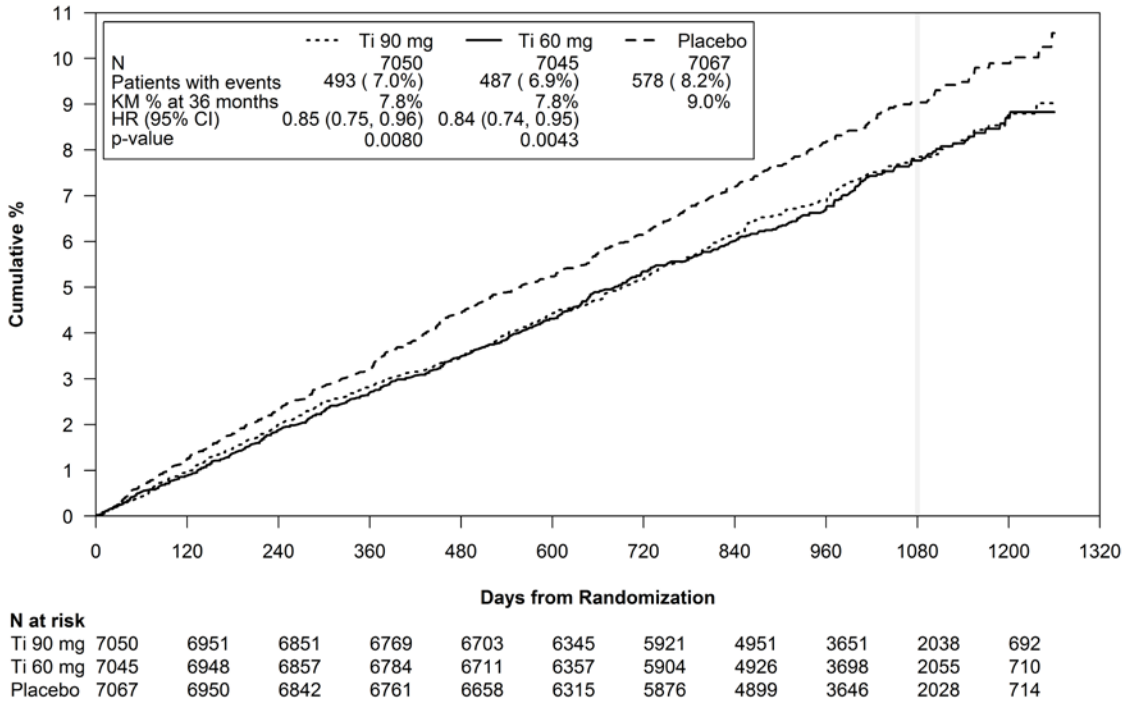
The PEGASUS TIMI-54 study (NCT01225562) was a 21,162-patient, randomized, double-blind, placebo-controlled, parallel-group study. Two doses of ticagrelor, either 90 mg twice daily or 60 mg twice daily, co-administered with 75-150 mg of aspirin, were compared to aspirin therapy alone in patients with 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.

The Kaplan-Meier curve (Figure 13) shows time to first occurrence of the primary composite endpoint of CV death, non-fatal MI or non-fatal stroke.Figure 13 – 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

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1.27% and 1.19% for the 60 and 90 mg regimens, respectively. Although the efficacy profiles of the two regimens were similar, the lower dose had lower risks of bleeding and dyspnea.

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

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

	BRILINTA[*] 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 14.

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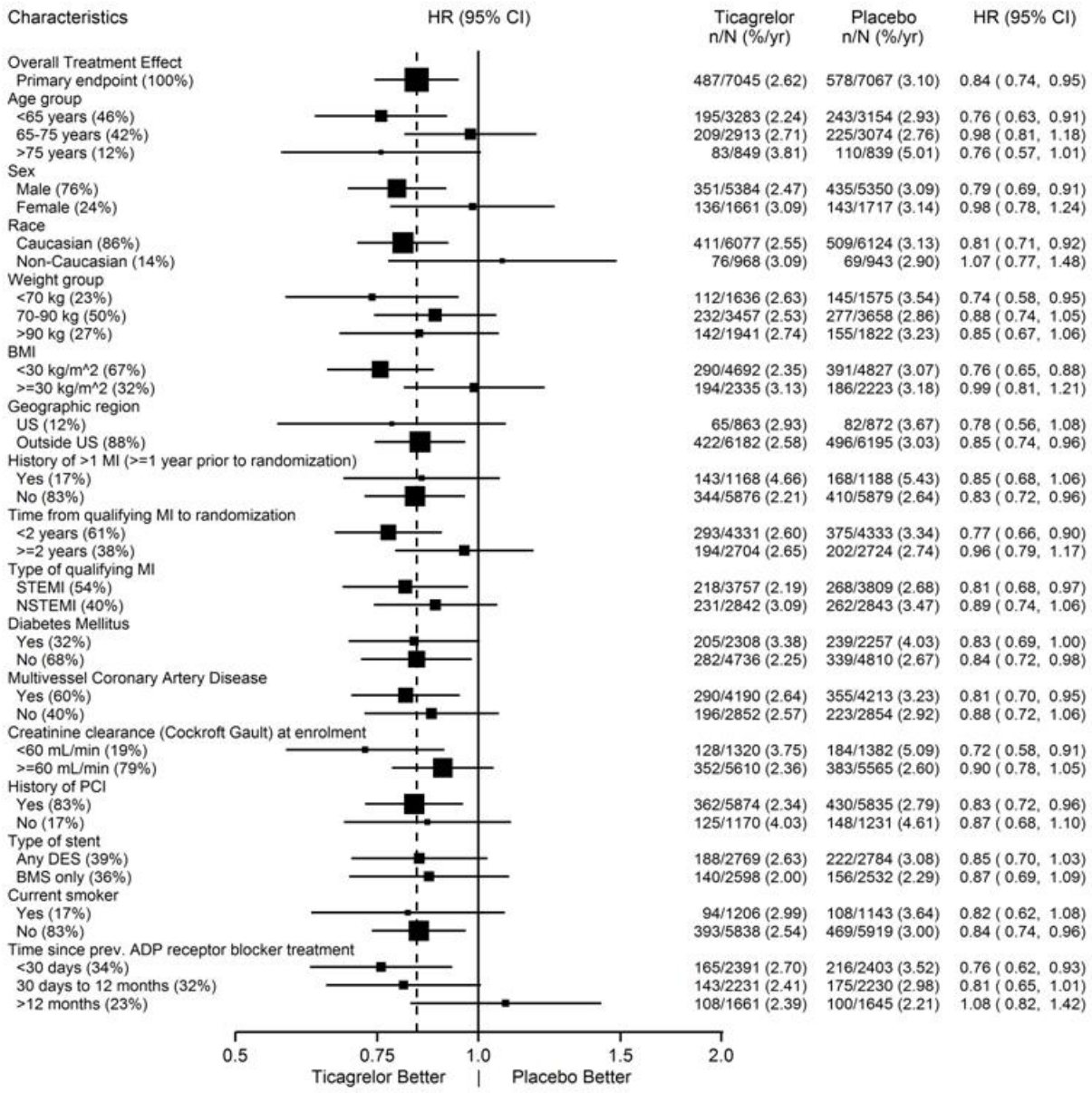
Figure 14 – Subgroup analyses of ticagrelor 60 mg (PEGASUS)



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

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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.

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 9.

Table 9 – 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.

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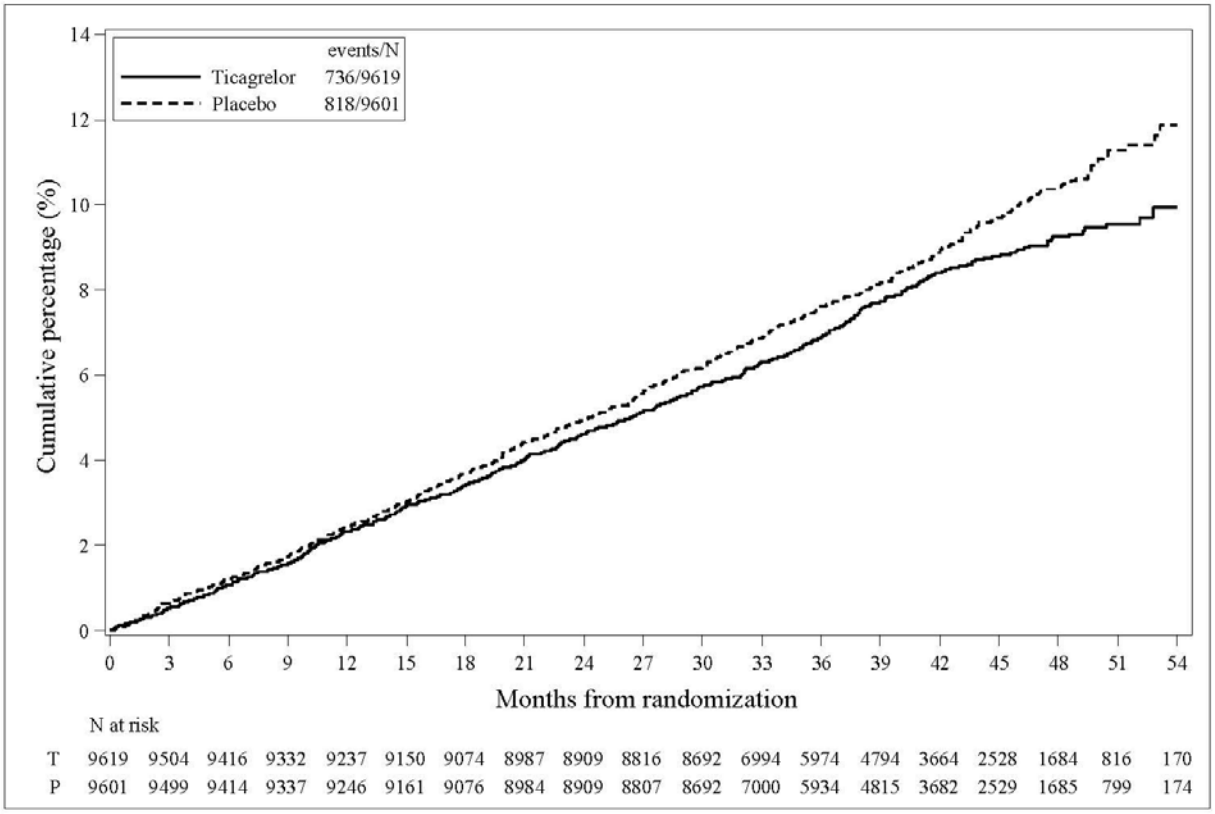
The Kaplan-Meier curve (Figure 15) shows time to first occurrence of the primary composite endpoint of CV death, MI, or stroke.

Figure 15 - 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 16.

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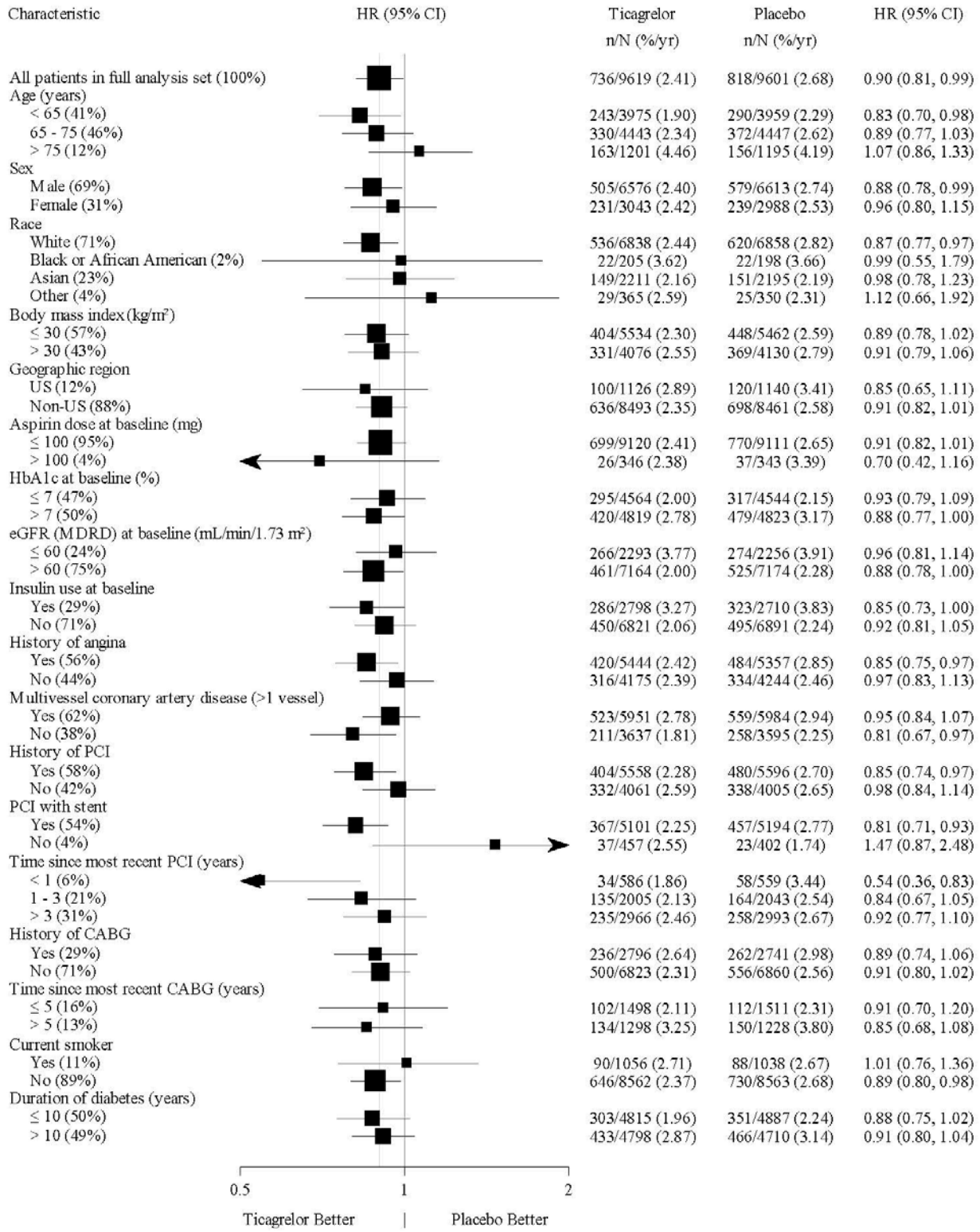
Figure 16 –Subgroup analyses of ticagrelor (THEMIS)



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.

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14.3 Acute Ischemic Stroke or Transient Ischemic Attack (TIA)

THALES

The THALES study (NCT03354429) was a 11016-patient, randomized, double-blind, parallel-group study of BRILINTA 90 mg twice daily versus placebo in patients with acute ischemic stroke or transient ischemic attack (TIA). The primary endpoint was the first occurrence of the composite of stroke and death up to 30 days. Ischemic stroke was assessed as one of the secondary endpoints.

Patients were eligible to participate if they were ≥40 years old, with non-cardioembolic acute ischemic stroke (NIHSS score ≤5) or high-risk TIA (defined as $ABCD^2$ score ≥6 or ipsilateral atherosclerotic stenosis ≥50% in the internal carotid or an intracranial artery). Patients who received thrombolysis or thrombectomy within 24 hours prior to randomization were not eligible.

Patients were randomized within 24 hours of onset of an acute ischemic stroke or TIA to receive 30 days of either BRILINTA (90 mg twice daily, with an initial loading dose of 180 mg) or placebo, on a background of aspirin initially 300-325 mg then 75-100 mg daily. The median treatment duration was 31 days.

BRILINTA was superior to placebo in reducing the rate of the primary endpoint (composite of stroke and death), corresponding to a relative risk reduction (RRR) of 17% and an absolute risk reduction (ARR) of 1.1% (Table 10). The effect was driven primarily by a significant reduction in the stroke component of the primary endpoint (19% RRR, 1.1% ARR).

Table 10 - Incidences of the primary composite endpoint, primary composite endpoint components, and secondary endpoint (THALES)

	BRILINTA N=5523		**Placebo N=5493**		**HR (95% CI)**	***p*-value**
	n (patients with event)	**KM%**	**n (patients with event)**	**KM%**		
Time to first Stroke or Death	303	5.4%	362	6.5%	0.83 (0.71, 0.96)	0.015
Time to first Stroke*	284	5.1%	347	6.3%	0.81 (0.69, 0.95)	
Time to Death*	36	0.6%	27	0.5%	1.33 (0.81, 2.19)	
Secondary Endpoint						
Time to first Ischemic Stroke	276	5.0%	345	6.2%	0.79 (0.68, 0.93)	0.004

CI = Confidence interval; HR = Hazard ratio; KM = Kaplan-Meier percentage calculated at 30 days; N = Number of patients
*The number of patients with the event of interest. In the time to first stroke, patients who died are censored at the time of death.

The Kaplan-Meier curve (Figure 17) shows the time to first occurrence of the primary composite endpoint of stroke and death.

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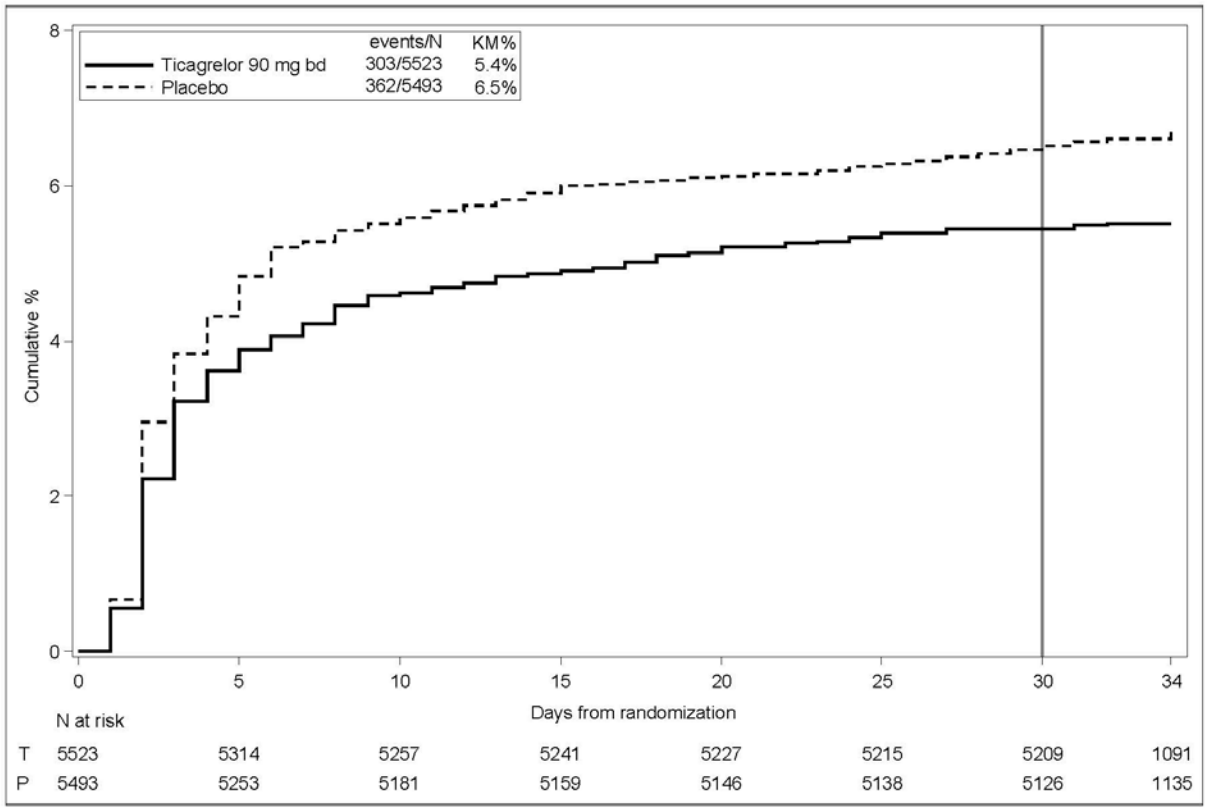
Figure 17 – Time to First Occurrence of Stroke or Death (THALES)



KM%: Kaplan-Meier percentage evaluated at Day 30; T=Ticagrelor; P=placebo; N=Number of patients

BRILINTA's treatment effect on stroke and on death accrued over the first 10 days and was sustained at 30 days. Although not studied, this suggests that shorter treatment could result in similar benefit and reduced bleeding risk.

The treatment effect of BRILINTA was generally consistent across pre-defined subgroups (Figure 18).

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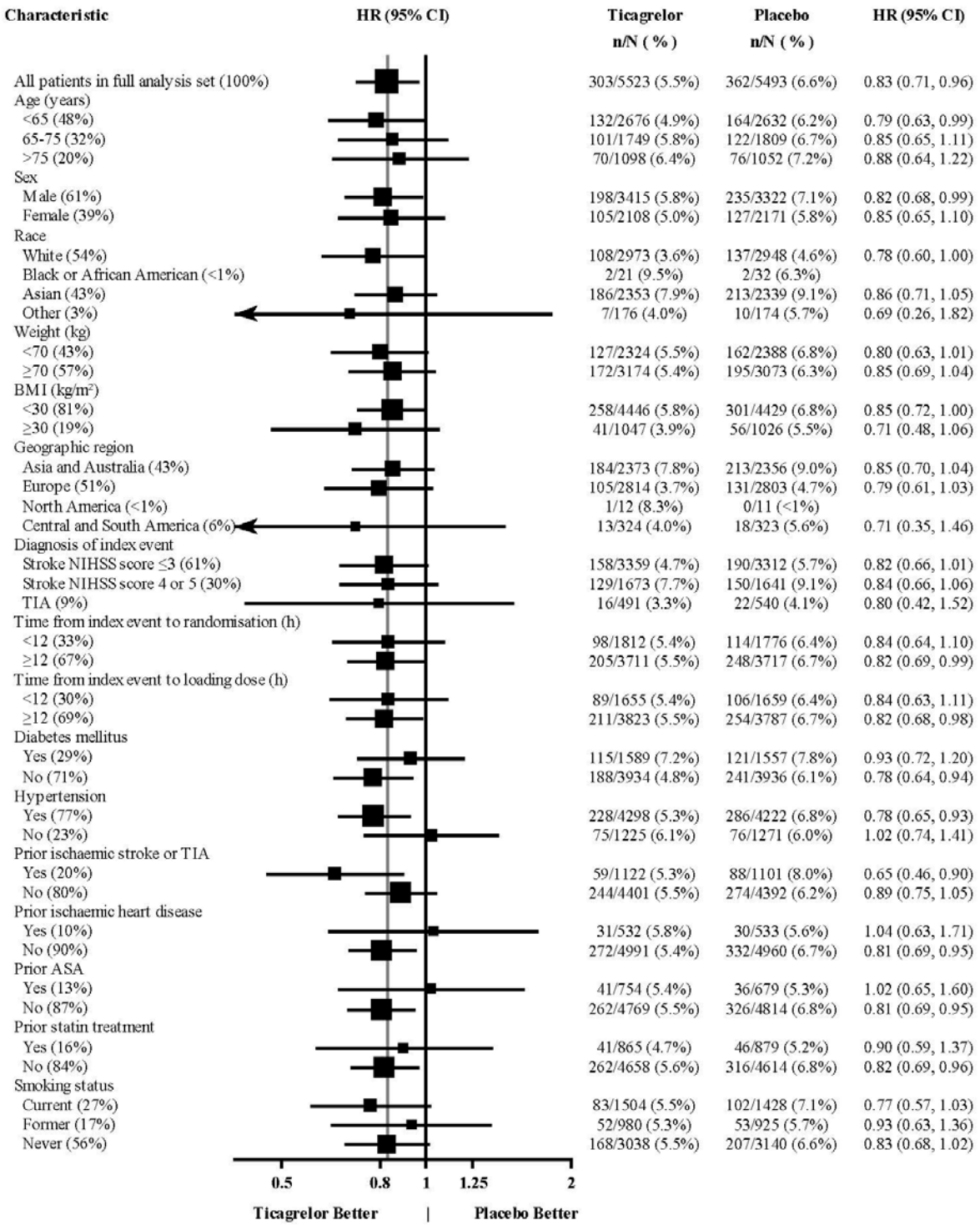
Figure 18 – Subgroup analyses of ticagrelor 90 mg (THALES)



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

At Day 30, there was an absolute reduction of 1.2% (95% CI: -2.1%, -0.3%) in the incidence of non-hemorrhagic stroke and death (excluding fatal bleed) favoring ticagrelor (294 events: 5.3%) over placebo (359 events: 6.5%) in the intention-

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to-treat population. In the same population, there was an absolute increase of 0.4% (95% CI: 0.2%, 0.6%) in the incidence of GUSTO severe bleeding unfavorable to ticagrelor arm (28 events: 0.5%) compared to the placebo arm (7 events: 0.1%).

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)]*.

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Distributed by: AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850

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MEDICATION GUIDE
BRILINTA® (brih-LIN-tah)
(ticagrelor) Tablets

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

BRILINTA is used to lower your chance of having, or dying from, a heart attack or stroke. **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. In most cases, 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.
- decrease your risk of stroke in people who are having a stroke (acute ischemic stroke) or mini-stroke (transient ischemic attack or TIA).

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

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- 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 aspirin as directed by your doctor.
- 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.

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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: 11/2020

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022433Orig1s029

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	22 OCT 2020
From	Fred Senatore MD, PhD, FACC
NDA/BLA # and Supplement#	NDA 22433 / Supplement 029 / Submission 0565
Applicant	Astra Zeneca
Date of Submission	05 MAY 2020
PDUFA Goal Date	05 NOV 2020
Proprietary Name	Brilinta®
Established or Proper Name	Ticagrelor
Dosage Form(s)	Film-coated tablets
Applicant Proposed Indication(s)/Population(s)	Reduce the risk of stroke in patients with acute ischemic stroke or transient ischemic attack
Applicant Proposed Dosing Regimen(s)	Loading dose 90 mg PO x2; followed by 90 mg PO BID
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Reduce the risk of ischemic stroke in patients with acute mild ischemic stroke or transient ischemic attack
Recommended Dosing Regimen(s) (if applicable)	Same as applicant's proposed dosing regimen

Reference ID: 4691882

This secondary review is based on the following reviews, consults, and meeting minutes:

Materials Reviewed		
Reviews		
#	**Discipline (Date)**	**Reviewers**
1	Clinical and Biometrics	Lars Johannesen PhD & Christine Garnett PharmD (Clinical Analysis, DCN); William Koh, PhD & Jialu Zhang, PhD (Biometrics)
2	Clinical Memo	Steven Grant MD, DCN (retired)
Consults		
1	DMEPA / Labeling	Hina Mehta, PharmD
2	Patient Labeling	Morgan Walker, PharmD, MPA, CPH
3	Neurology	Lawrence Rodichock MD, ON/DN2
4	OPDP	Zarna Patel, PharmD

APPEARS THIS WAY ON ORIGINAL

Reference ID: 4691882

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

The benefit-risk assessment of ticagrelor in the THALES trial focused on preventing recurrent strokes against incurring major bleeding events in patients who experienced a mild acute ischemic stroke. The number of subjects needed to be treated for preventing a recurrent stroke was lower than the number needed to be treated to cause a severe bleed, suggesting a net clinical benefit for ticagrelor in this patient population. Also, the cumulative difference in the number of non-hemorrhagic strokes between ticagrelor and placebo favoring ticagrelor was greater than the cumulative difference between the two arms for GUSTO severe bleed unfavorable to ticagrelor.

The numerical assessment of the benefit-risk evaluation that favored ticagrelor was supplemented by a qualitative assessment of the importance of avoiding a recurrent stroke at the expense of a severe bleed. The data were modeled by varying the weight of the stroke event relative to the weight of the severe bleeding event. We evaluated several weights in the model: 1) one recurrent stroke was as important as two severe bleeds; 2) one recurrent stroke was as important as one severe bleed; and 3) two recurrent strokes were as important as one severe bleed. Based on the data, when the importance of one GUSTO severe bleed was considered twice as important as a recurrent stroke, the net clinical benefit approached neutrality. When both stroke and severe bleed were given equal weight, the benefit of reducing the incidence of recurrent stroke outweighed the risk of a severe bleed. These analyses ignored bleeding of lesser severity.

The review team's position is that a known risk of a severe bleed is undersirable, but the concern about a recurrent stroke after experiencing the disabling symptoms of an acute ischemic stroke will likely yield a favorable benefit-risk profile for ticagrelor.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Acute ischemic stroke is the 4th leading cause of death and the leading cause of adult disability. The annual incidence of new and recurrent stroke is approximately 795,000 (Bansal, 2013). In 2018, 1 of every 6 deaths from cardiovascular disease was due to stroke; someone in the USA has a stroke every 40 seconds; someone dies of a stroke every 4 minutes; nearly 1 of 4 strokes are in people who had a previous	None.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	stroke; 87% of all strokes are ischemic (cdc.gov/stroke/facts.htm). • Acute ischemic stroke commonly occurs by pathophysiological mechanisms in common with that of acute coronary syndrome. • Atherosclerotic obstruction of a cerebral artery leads to irreversible brain injury and subsequent focal neurological deficits. • A transient ischemic attack is a reversable neurological deficit based upon transient blockage of a cerebral artery, analogous to unstable angina. Transient ischemic attacks are forerunners of an ischemic stroke.	
Current Treatment Options	•The current treatment paradigm as described in the current guidelines focuses on management of the acute phase of ischemic stroke followed by post-stroke. •Administration of IV alteplase in eligible patients without initially obtaining an MRI to exclude cerebral microbleeds (CMB) is a Class I, LOE B-NR recommendation from the most recent guidelines (Powers, 2019). Based on meta-analyses, the risk of an intracranial hemorrhage in patients with > 10 CMBs (30%-47%) is consistently reported as significantly greater than in those with no CMBs (1%-4%). However, these data are based on < 50 patients. There are no randomized clinical trials of IV alteplase with baseline MRI. Therefore, there is a paucity of data on the effect of baseline CMB on the treatment effect of alteplase. In the absence of direct evidence that IV alteplase provides no benefit or produces harm in ischemic stroke patients with CMBs, withholding treatment on the basis of the presence of CMBs could lead to the exclusion of patients who would benefit from treatment (Powers, 2019). •IV alteplase should be administered as quickly as possible-within	• The mainstay of treatment includes thrombolytic therapy for an acute ischemic stroke and dual antiplatelet therapy within 24 hours of symptom onset and continued for 21 days. • There is antecedent data to support dual antiplatelet therapy (aspirin and clopidogrel), started within 24 hours after symptom onset and continued for 21 days to reduce recurrent ischemic stroke for a period of 90 days from symptom onset (Class I, LOE A). However, there is no antecedent approval of a single antiplatelet agent for the reduction of stroke. •For patients with noncardioembolic acute ischemic stroke, the use of antiplatelet agents rather than oral anticoagulation is recommended to reduce the risk of recurrent stroke and other cardiovascular events (Class I, LOE A).

	3 hours of stroke symptom onset (Class I, LOE A). •Hypotension and hypovolemia should be corrected to maintain systemic perfusion levels necessary to support organ function (Class I, LOE – expert opinion). •For patients with a non-disabling stroke (NIHSS score 0-5), IV alteplase is not recommended for patients who could be treated within 3 hours of ischemic stroke symptom onset (Class III-no benefit, LOE C-limited data). •The efficacy of anti-platelet IV glycoprotein IIb/IIIa inhibitors tirofiban and eptifibatide co-administered with IV alteplase is not well established. (Class IIb, LOE B-R). Abciximab or IV aspirin should not be administered within 90 minutes after the start of IV alteplase (Class III-harm, LOE B-R). •The risk of antithrombotic therapy (other than IV aspirin) within the first 24 hours after treatment with IV alteplase is uncertain (Class IIb, LOE B-NR). A retrospective analysis of consecutive ischemic stroke patients admitted to a single center in Seoul, South Korea, found no increased risk of hemorrhage with early initiation of antiplatelet or anticoagulant therapy (< 24 hours) after IV alteplase compared to initiation > 24 hours. However, this study was criticized for possible selection bias. •Administration of aspirin is recommended in patients with AIS within 24 to 48 hours after onset. For those treated with IV alteplase, aspirin administration is generally delayed until 24 hours later but might be considered in the presence of concomitant conditions for which such treatment given in the absence of IV alteplase is known to provide substantial benefit or withholding such treatment is known to cause substantial risk (Class I, LOE A). • In patients presenting with minor noncardioembolic ischemic stroke (NIHSS score ≤3) who did not receive IV alteplase, treatment with dual antiplatelet therapy (aspirin and clopidogrel) started within 24 hours after symptom	

Reference ID: 4691882

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	onset and continued for 21 days is effective in reducing recurrent ischemic stroke for a period of up to 90 days from symptom onset (Class I, LOE A). •Ticagrelor is <u>not recommended</u> in lieu of aspirin for the treatment of patients with minor acute stroke (Class III-no benefit, LOE B-R). This was based on the SOCRATES trial (Acute Stroke or Transient Ischemic Attack Treated With Aspirin or Ticagrelor and Patient Outcomes), which was a randomized, double-blind, placebo-controlled trial of ticagrelor versus aspirin begun within 24 hours in patients with minor stroke (NIHSS score ≤5) or TIA (ABCD2 score ≥4). With a primary outcome of time to the composite end point of stroke, MI, or death up to 90 days, ticagrelor was not found to be superior to aspirin (HR, 0.89 [95% CI, 0.78–1.01]; *P*=0.07). However, because there were no significant safety differences in the 2 groups, ticagrelor may be a reasonable alternative in stroke patients who have a contraindication to aspirin. •For patients with noncardioembolic AIS, the use of antiplatelet agents rather than oral anticoagulation is recommended to reduce the risk of recurrent stroke and other cardiovascular events (Class I, LOE A). •For early secondary prevention in patients with noncardioembolic AIS, the selection of an antiplatelet agent should be individualized on the basis of patient risk factor profiles, cost, tolerance, relative known efficacy of the agents, and other clinical characteristics (Class I. LOE C-expert opinion). • For patients who have a noncardioembolic AIS while taking aspirin, increasing the dose of aspirin or switching to an alternative antiplatelet agent for additional benefit in secondary stroke prevention is not well established (Class IIb, LOE B-R). In patients with a noncardioembolic ischemic stroke, the therapeutic benefit of aspirin is similar across a wide range of doses, but the hemorrhagic risk increases with higher doses. In patients taking aspirin at the time of the incident stroke, the benefit of switching to an alternative antiplatelet agent or combination therapy is not	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	well established. The SPS3 RCT (Secondary Prevention of Small Subcortical Strokes) found no benefit from adding clopidogrel to aspirin compared with placebo in patients with a recent small vessel, lacunar stroke taking aspirin at the time of their index event. However, the median time from the qualifying event to enrollment in the SPS3 trial was >40 days, so results may have underestimated benefit in the early poststroke period. A recent meta-analysis of 5 studies, including 3 RCTs and 2 observational registries, of patients with noncardioembolic stroke taking aspirin at the time of the index event found a decreased risk of major cardiovascular events and recurrent stroke in patients switching to an alternative antiplatelet agent or combination antiplatelet therapy. This analysis included data from aspirin failure subgroups in the CHANCE trial of dual antiplatelet therapy in patients with minor stroke or TIA and the SOCRATES trial of aspirin versus ticagrelor. However, there was significant heterogeneity among the included studies, and results may have been driven by data from registries susceptible to unmeasured confounders and bias (Powers, 2019).	
Benefit	Evidence: Ticagrelor + aspirin vs placebo + aspirin was studied in an adequate and well-controlled randomized clinical trial, demonstrating a statistically significant reduction in recurrent stroke (no mortality benefit) in a 30 day period following an index mild acute ischemic stroke where thrombolytic therapy was not provided (Hazard Ratio 0.8, 95% confidence interval 0.71—0.96). The results were consistent across pre-specified subgroups. Although the trial was conducted entirely outside the USA, the standard of care at the sites where the trial was conducted was determined to be equivalent to that in the USA. Uncertainties: 1) The systemic pattern of under-represented patient populations,	Having met the primary endpoint, it can fairly and responsibly be concluded that the applicant presented substantial evidence of effectiveness from the THALES trial to support approval of ticagrelor, as an adjunct to aspirin, for the following indication: to reduce the incidence of recurrent stroke in patients who experienced a mild acute ischemic stroke for which thrombolytic therapy was not provided. However, there was

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	endemic to clinical trials, was also evident in the THALES trial. There was a paucity of black patients who are at particular risk of stroke relative to the white population. The less than 1% black subjects who participated in THALES showed a similar outcome to the remainder of the ITT population, but the sample size was too small to be conclusive. Patient under-representation is an issue beyond the scope of the THALES trial and is currently being addressed by working groups whose membership span academia, regulatory and industry. 2) The THALES trial was not designed to evaluate secondary stroke severity and was underpowered to do so. Analysis of the primary endpoint across the spectrum of recurrent stroke severity as measured by the modified Rankin Scale, although inconclusive, showed numerical decreases in the incidence of the primary endpoint across all severity categories except for the worst category where the secondary strokes resulted in death	no evidence that ticagrelor reduced the severity of recurrent stroke.
Risk and Risk Management	Evidence: Bleeding events were significantly higher in the ticagrelor arm compared to the placebo arm. This included GUSTO severe bleeds, intracranial hemorrhage or fatal bleeds, fatal bleeds as an independent variable, intracranial hemorrhage as an independent variable, GUSTO moderate/severe bleeds, and premature discontinuations due to bleeding. Uncertainties: Following an acute ischemic stroke, those patients at higher risk for a hemorrhagic stroke should be identified to avoid morbidity or mortality from a recurrent hemorrhagic stroke due to ticagrelor treatment.	Bleeding is a well-known side effect of ticagrelor based on its antiplatelet effect and it is described in the label as a warning. The label should include a warning about post stroke patients at risk for a hemorrhagic transformation.

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Reference ID: 4691882

2. Background

Ticagrelor is a $P2Y_{12}$ platelet inhibitor and inhibits platelet activation and aggregation mediated by the $P2Y_{12}$ ADP-receptor.

On July 20, 2011, ticagrelor 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, ticagrelor 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, ticagrelor also reduced the rate of stent thrombosis.

On September 3, 2015, ticagrelor received US marketing 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 May 30, 2020, ticagrelor received US marketing approval for the same indication in patients with CAD and T2DM (but no prior stroke or MI) who have undergone PCI. The application was filed and classified as a standard review. This indication was based on the THEMIS trial (The Effect of **T**icagrelor on **H**ealth outcomes in diab**E**tes **M**ellitus patients **I**ntervention **S**tudy). The approved dose for this indication was 60 mg twice daily with a daily maintenance dose of aspirin of 75-100 mg.

The Applicant proposes to market ticagrelor to reduce the incidence of ischemic stroke in patients who experienced an acute ischemic stroke or transient ischemic attack (TIA) (secondary prevention). The basis of this proposed indication is the THALES trial (Acute S**T**roke or Transient Isc**H**emic Attack Treated with Tic**A**gre**L**or and ASA for Pr**E**vention of **S**troke and Death).

The design of the THALES trial was based on findings from two trials (CHANCE and POINT) showing clopidogrel to be effective in patients with acute ischemic stroke.

The CHANCE trial (Wang, 2013) was a randomized, double blind, placebo-controlled study conducted at 114 Chinese sites. A total of 5170 patients were randomized within 24 hours of experiencing a minor ischemic stroke or a high-risk TIA to clopidogrel or placebo on a background of aspirin for 90 days. The incidence of stroke was 8.2% in the clopidogrel arm and 11.7% in the placebo arm (HR 0.68, 95% CI 0.57—0.81). The incidence of death and bleeding were similar in each arm. At 90 days, patients who experienced a stroke had a

Reference ID: 4691882

modified Rankin Scale (mRS) score ≥ 2 in 254 subjects (9.9%) in the clopidogrel arm vs 299 subjects (11.6%) in the placebo arm.

MRS scores *(New, PW et al., 2006, Neuroepidemiology, 26:4-15)* are characterized as: 0 (asymptomatic); 1 (no significant disability-able to carry out activities of daily living); 2 (slight disability requiring some help but able to carry out activities of daily living without assistance; 3 (moderate disability requiring some help but able to walk without assistance; 4 (moderately severe disability with inability to walk without assistance and unable to attend to bodily needs without assistance); 5 (severe disability-bedridden, incontinent and requiring constant nursing care /attention); and 6 (dead).

The POINT trial (Claiborne-Johnston, 2018) was a randomized, double-blind, placebo-controlled study conducted at 269 international sites (83% of the sites in the US, including 20% black patients). Eligible subjects were enrolled within 12 hours of experiencing an ischemic stroke or high risk TIA to receive either clopidogrel or placebo on a background of aspirin for 90 days. The composite primary efficacy endpoint of ischemic stroke, MI, or ischemic death occurred in 5.0% in the clopidogrel arm and 6.5% in the placebo arm (HR 0.75, 95% CI 0.59—0.95). Deaths occurred in 18 patients in the clopidogrel arm and 12 patients in the placebo arm. Major hemorrhage (intracranial hemorrhage, death, transfusion with 2 units of packed RBC, or hospitalization for bleeds) occurred in 23 subjects (0.9%) in the clopidogrel arm and 10 subjects (0.4%) in the placebo arm. At 90 days, the mRS score ≥ 2 occurred in 13.3% in the clopidogrel arm vs 13.7% in the placebo arm (HR 0.97, 95% CI 0.82—1.14).

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.

Reference ID: 4691882

7. Clinical/Statistical- Efficacy

THALES Trial Description

Study Design: The THALES study was a randomized, double-blind, placebo controlled, event driven trial. A total of 11,016 subjects were enrolled at approximately 400 sites in 28 countries (not USA). The study treatment period was 30 days; a follow-up period was 30 days for a total of 60 days. The study schedule included randomization (Day 1), a telephone contact or on-site visit at Day 7, an on-site visit at Day 30; and a follow-up on-site visit or telephone contact at Day 60 (see Figure 1).

Objective: The primary objective was to demonstrate superior efficacy of ticagrelor and aspirin compared to placebo and aspirin to prevent a subsequent stroke at 30 days in patients experiencing an acute ischemic stroke/TIA.

Patient Population: The study population was defined as patients ≥ 40 years of age who have experienced a non-cardioembolic acute ischemic stroke with an NIHSS (National Institute of Health Stroke Scale) ≤ 5 or high-risk TIA (ABCD score ≥ 6 or ipsilateral atherosclerotic stenosis in an extra/intracranial artery) who could be randomized within 24 hours of symptom onset. ABCD is a clinical score based on age (≥ 60 years: 1 point), blood pressure (≥ 140/90 mmHg: 1 point), clinical features (speech disturbance without weakness: 1 point; unilateral weakness: 2 points), duration of TIA (10-59 minutes: 1 point; ≥ 60 minutes: 2 points) and diabetes (2 points). Exclusion criteria were 1) thrombolysis or thrombectomy; 2) antiplatelet therapy other than aspirin; 3) anticoagulation therapy; and 4) history of previous intracranial hemorrhage.

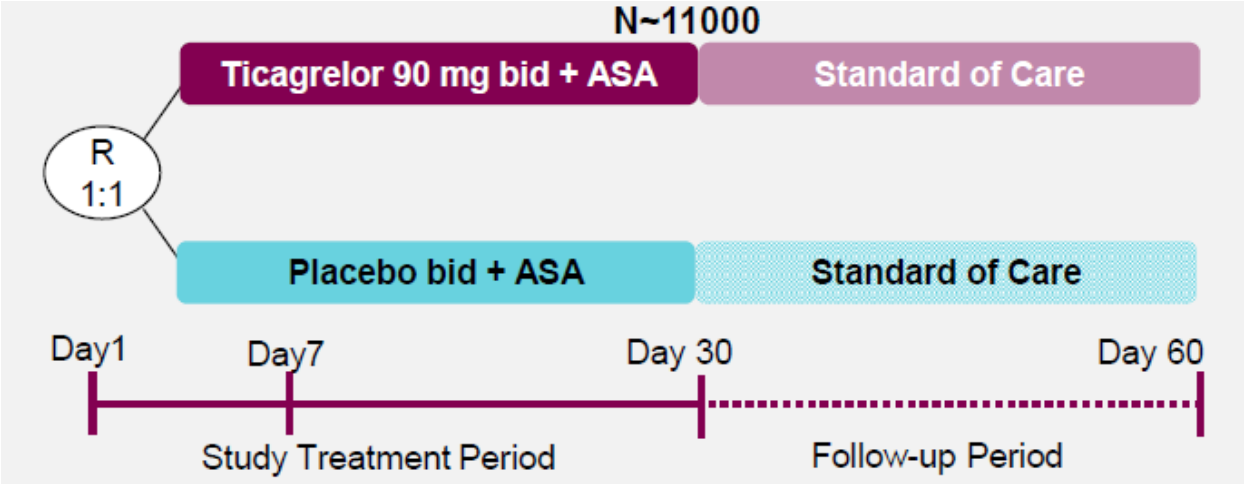
Primary Efficacy Endpoint: The primary endpoint was all stroke (ischemic and hemorrhagic) or death.

Primary Safety Endpoints: The primary safety endpoints were: 1) GUSTO Severe Bleeding; 2) SAEs; and 3) DAEs (discontinuation due to adverse events). GUSTO severe bleed is defined as fatal, intracranial, or causative of hemodynamic compromise requiring intervention. GUSTO moderate bleed is defined as requiring transfusion but without hemodynamic compromise. GUSTO mild bleed is defined as not requiring blood transfusion and no hemodynamic compromise.

Statistical Considerations: Assuming a 6.7% primary endpoint event rate in the placebo arm at 30 days, the trial had 85% power to detect 770 primary endpoint events to show an HR of 0.805.

Reference ID: 4691882

Figure 1; THALES Study Design



Source: Applicant's Top-Line Presentation, 25 FEB 2020

Trial Results

Study Metrics: The recruitment period occurred between January 2018 and October 2019. The last patient visit was 13 DEC 2019.

Patient Characteristics: Demographic characteristics were balanced between treatment groups. Medical history was representative of the target population and balanced between the treatment groups.

Index Event: In the Intention-To-Treat (ITT) Population, 61% had an index stroke with an NIHSS score ≤ 3; 30% had a stroke with an NIHSS score 4-5; and 9% had a TIA. An NIHSS score of ≤ 5 defines a population that may be discharged home after the index event; a score of 6-13 defines a population requiring acute in-patient rehabilitation; and a score ≥ 14 defines a population requiring long-term care in a nursing facility.

Time to Randomization: Time from symptom onset to randomization was > 12 hours in 67% of the ITT population and ≤ 12 hours in 33% of the population. The type of index event and time from symptom onset to randomization were balanced between treatment groups.

Efficacy Results:
Subject disposition (Table 1) showed that virtually all of the 11,000 randomized subjects received study drug and approximately 87% completed treatment. A total of 941 (8.5%) subjects discontinued study drug due to an adverse event (numerically higher in the ticagrelor arm).

The occurrence of the primary efficacy endpoint was statistically significantly lower in the ticagrelor arm compared to the placebo arm (Table 2). These results were driven by the stroke component of the composite endpoint. The incidence of recurrent stroke was 5.1% in the

Reference ID: 4691882

ticagrelor arm and 6.3% in the placebo arm. There were 9 more deaths in the ticagrelor arm compared to the placebo arm (36 vs 27). This result was assessed to be similar between the arms of the study because of the low percentages (0.7% vs 0.5%, respectively).

Stroke characterization (Table 3) showed 4 cases of ischemic stroke with hemorrhagic transformation (HT) (1 in the ticagrelor arm and 3 in the placebo arm). These results were consistent with excluding subjects with a high risk for HT (e.g., cardioembolic stroke, administration of thrombolytics, previous intracranial hemorrhage, use of anticoagulation therapy, and mild stroke suggestive of a relatively small penumbra). The 4 subjects with a HT were combined with those subjects who had a recurrent hemorrhagic stroke (Neurology Consult, Rodichok, 5 OCT 2020).

The Kaplan Meier curve (Figure 2) showed the greatest impact (i.e., efficacy and bleeding risk) at 7 days post treatment, beyond which the curves remained parallel.

The THALES trial was not designed to detect a difference in 30-day mRS between the arms of the study and was underpowered to do so. The mRS score was measured in all treated patients, scheduled at Day 30 and measured on the average 25 days after the index stroke. However, there was an absence of baseline mRS. Although approximately 700 subjects reported a recurrent stroke, some 7000 subjects had mRS scores > 0 based on the index stroke. It would therefore have been difficult to detect the effect of ticagrelor on the severity of the recurrent stroke under these conditions. From previously reported neuroprotectant trials, the number of recurrent strokes in this trial was too small to detect a statistically significant treatment effect based on a severity score (Neurology Consult, Rodichok, 5 OCT 2020).

The cumulative distribution curve (Figure 3) of subjects across the mRS range of scores showed that the THALES subjects who did not have a recurrent stroke (~ 90%) had a low overall disability score (mRS $\leq$ 2) at 30 days, consistent with the index event of a mild stroke. Those subjects who experienced a recurrent stroke, however, had worse mRS scores (50% of those subjects having a recurrent stroke had mRS $\geq$ 3 at 30 days). This was consistent with further neurological deficit from a recurrent stroke.

A categorical analysis of mRS scores between the ticagrelor and placebo arms in those subjects who had a recurrent stroke (Figure 4) showed a numerically lower number of subjects in each mRS category across the entire mRS scale except for the mRS score of 6 (stroke death). In subjects who died of stroke (mRS score of 6), the number of deaths trended against ticagrelor (36 in the ticagrelor arm of which 8 were hemorrhagic vs 27 in the placebo arm of which 1 was hemorrhagic). The hemorrhagic stroke deaths were presumed to be attributed to ticagrelor.

A question to our neurology colleagues was whether the mRS measured at 30 days was a reasonable timepoint, compared to a later point in time. The Neurology consultation memo stated mRS is typically measured 90 days after an event because at that point, the mRS score

Reference ID: 4691882

tends to plateau. However, there is reasonable correlation between an earlier mRS score, such as 30 days, with the outcome at 90 days.

In summary, THALES was an adequate and well-controlled pivotal trial designed to evaluate the effect of ticagrelor on the reduction in the incidence of recurrent stroke or death in patients experiencing a mild acute ischemic stroke. The trial met its primary endpoint, driven by stroke with no significant difference in death.

Table 1: THALES Patient Disposition

	Number (%) of Patients		
	Ticagrelor	Placebo	Total
Patients Randomized	5523 (100.0)	5493 (100.0)	11016 (100.0)
Patients who received treatment	5506 (99.7)	5470 (99.6)	10976 (99.6)
Patients who completed treatment	4715 (85.4)	4825 (87.8)	9540 (86.6)
Patients who discontinued treatment due to an AE	530 (9.6)	411 (7.5)	941 (8.5)
Patients who withdrew consent	8 (0.1)	7 (0.1)	15 (0.1)
Patients lost to follow-up	1 (0.0)	0 (0.0)	1 (0.0)

Source: Applicant's CSR

Table 2: THALES Primary Endpoint

	Ticagrelor 90 mg BID (N=5523)		Placebo (N=5493)				
Primary Endpoint	Patients with events (%)	KM%	Patients with events (%)	KM (%)	HR	95%CI	p-value
Stroke/Death	303 (5.5%)	5.4	362 (6.6%)	6.5	0.83	0.71-0.96	0.015
Stroke	284 (5.1%)	5.1	347 (6.3%)	6.3	0.81	0.69-0.95	0.008
Death	36 (0.7%)	0.6	27 (0.5%)	0.5	1.33	0.81-2.19	0.264

Source: Applicant's Clinical Overview

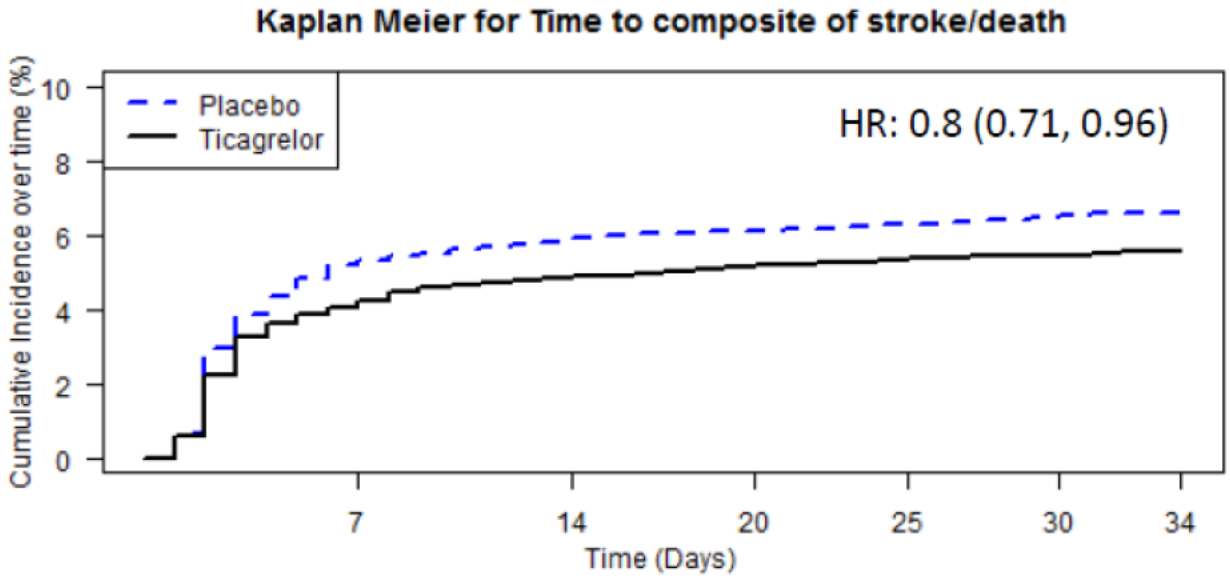
Table 3: Stroke Characterization

	Number (%) of First Events in Each Group	
	Ticagrelor 90 mg BID (N= 5523)	Placebo (N=5493)
Stroke	284 (5.1)	347 (6.3)
Ischemic Stroke	262 (4.7)	332 (6.0)
Ischemic Stroke without Hemorrhagic Transformation	261 (4.7)	330 (6.0)

--Fatal	8 (0.1)	7 (0.1)
--Non-fatal	254 (4.6)	324 (5.9)
Ischemic Stroke with Hemorrhagic Transformation	1 (0.0)	3 (0.1)
--Fatal	0 (0.0)	0 (0.0)
--Non-Fatal	1 (0.0)	3 (0.0)
Hemorrhagic Stroke	10 (0.2)	2 (0.0)
--Fatal	8 (0.1)	1 (0.0)
--Non-fatal	2 (0.0)	1 (0.0)
Undetermined	14 (0.3)	14 (0.3)
--Fatal	1 (0.0)	0 (0.0)
--Non-fatal	13 (0.2)	14 (0.3)

Source: Applicant's CSR

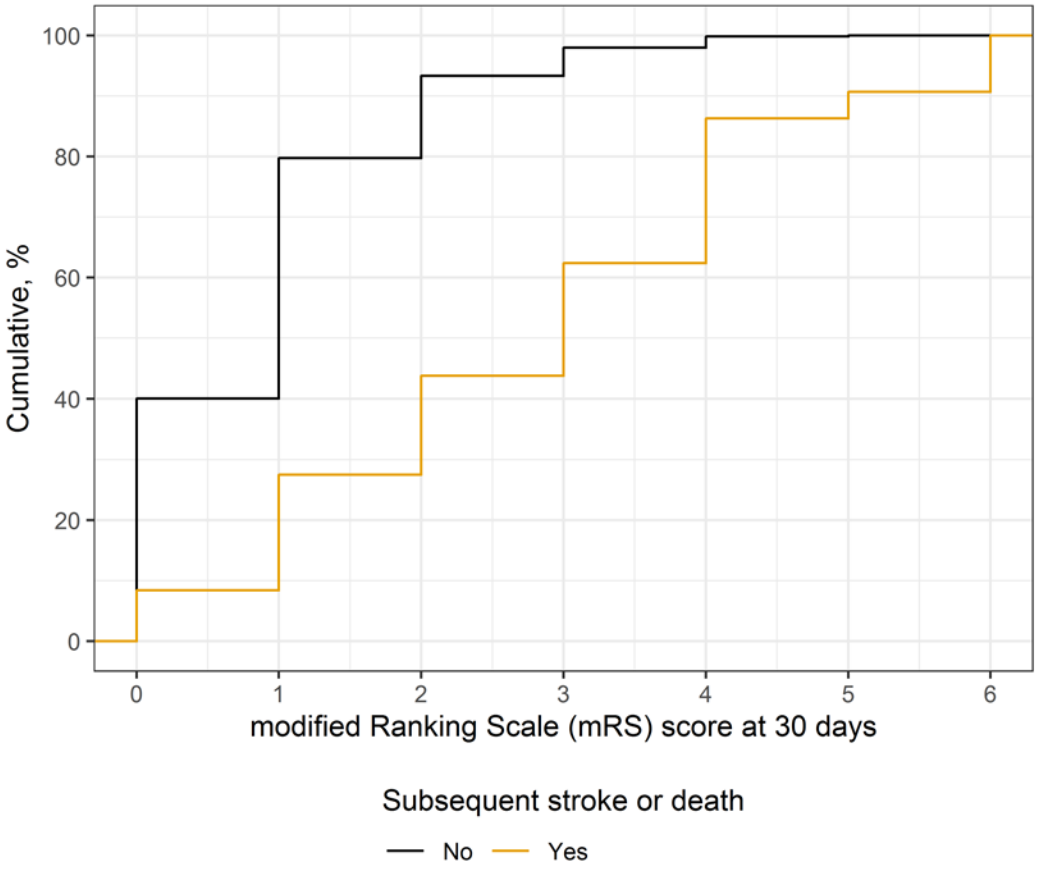
Figure 2: Kaplan Meier Curve for Time to the Primary Efficacy Endpoint (Stroke or Death)



Number of Events						
Placebo	290	324	336	345	358	362
Ticagrelor	233	269	287	297	300	303
Number at Risk						
Placebo	5204	5165	5146	5138	5126	1135
Ticagrelor	5289	5243	5227	5215	5209	1091
Cumulative Incidence (%)						
$\hat{F}_{Placebo}$	5.28	5.90	6.12	6.28	6.52	6.69
$\hat{F}_{Ticagrelor}$	4.22	4.88	5.20	5.38	5.44	5.52

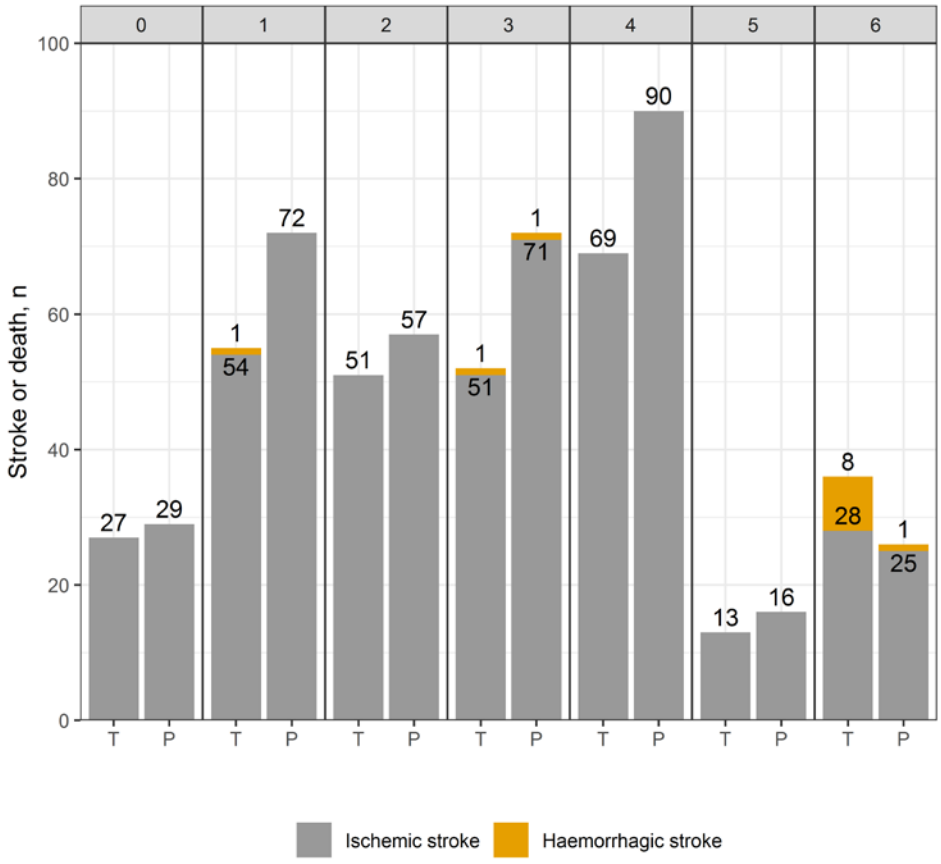
Source: Clinical/Statistics Primary Review, Johannesen et al., 21 OCT 2020

Figure 3: Cumulative Distribution Curve of mRS Score in Subjects Experiencing /Not Experiencing Subsequent Stroke



Source: Clinical/Statistics Primary Review, Johannesen et al., 21 OCT 2020

Figure 4: Primary Endpoint between Ticagrelor and Placebo by mRS score of Stroke Endpoint



Source: Clinical/Statistics Primary Review, Johannesen et al., 21 OCT 2020

8. Safety

The number of any adverse event with an outcome of death, any serious adverse event (including death), any adverse event leading to premature discontinuation were similar between the arms of the THALES trial (Table 4). An outstanding finding, however, was a much larger number of any bleeding (serious or non-serious adverse event) leading to premature permanent discontinuation of investigational drug.

Bleeding events were significantly higher in the ticagrelor arm compared to the placebo arm (Table 5). This included GUSTO severe bleeds, intracranial hemorrhage or fatal bleeds, fatal bleeds as an independent variable, intracranial hemorrhage as an independent variable, GUSTO moderate/severe bleeds, and premature discontinuations due to bleeding.

Bleeding is a well-known side effect of ticagrelor based on its antiplatelet effect and it is described in the label as a warning.

Reference ID: 4691882

In the previous trials, ticagrelor and clopidogrel had similar bleeding rates (PLATO); major bleeding was approximately twice as frequent with ticagrelor (~ 2%) compared to placebo (~1%) (PEGASUS-TIMI 54 and THEMIS).

- 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*).

Table 4: THALES Adverse Event Profile

	Number (%) of Patients	
	Ticagrelor 90 mg BID	Placebo
	N = 5523	N = 5493
Any AE with outcome of death	40 (0.7)	32 (0.6)
Any SAE (including death)	571 (10.3)	609 (11.1)
Any AE leading to premature discontinuation	535 (9.7)	415 (7.6)
Any bleeding SAE or AE leading to premature permanent discontinuation of investigational drug	183 (3.3)	41 (0.7)

Source: Table 14.3.2.1.1 CSR

Table 5: THALES Bleeding Events

	Ticagrelor 90 mg BID		Placebo				
	N= 5523		N=5493				
Variable	Patients with Events (%)	KM %	Patients with Events (%)	KM %	HR	95%CI	p-value
GUSTO Severe	28 (0.5)	0.5	7 (0.1)	0.1	4.0	1.7-9.1	0.001
ICH or Fatal Bleeding	22 (0.4%)	0.4	6 (0.1)	0.1	3.7	1.5-9.0	0.005
Fatal Bleeding	11 (0.2)		2 (0.0)				
ICH	20 (0.4)	0.4	6 (0.1)	0.1	3.3	1.3-8.3	0.010
GUSTO Moderate/Severe	36 (0.7)	0.6	11 (0.2)	0.2	3.27	1.7-6.4	<0.001
Premature discontinuation of study drug due to bleeding	152 (2.8)	2.9	32 (0.6)	0.6	4.80	3.3-7.0	<0.001

Reference ID: 4691882

Source: Applicant's CSR, Table 14.3.2.2.1

9. Benefit-Risk Discussion

The net clinical benefit of ticagrelor from the THALES trial was evaluated by ascertaining the benefit of reducing the incidence of non-bleeding death or secondary ischemic stroke (classified as disabling ischemic strokes defined as a mRS > 2, or any stroke) versus the risk of a severe bleed (classified as GUSTO severe bleed, or all bleeds classified as a serious adverse event, or all bleeds classified as adverse events leading to discontinuation).

The results (Figure 5) showed the number needed to treat to produce a benefit was lower than the number needed to treat to produce a harm for all classifications except for the classification of all strokes vs bleeding adverse events leading to discontinuation.

The cumulative difference in the number of events between ticagrelor and placebo for non-hemorrhagic stroke or death favoring ticagrelor was greater than the cumulative difference between the two arms for GUSTO severe bleed unfavorable to ticagrelor (Figure 6).

In addition to the numerical assessment, the benefit-risk evaluation also incorporated a qualitative assessment of the importance of reducing the incidence of a secondary stroke versus the importance of avoiding a bleed. The willingness to pay a price for the accrued benefit is often subjective, and is dependent upon perception and personal preference. Consequently, Dr. Johannesen modeled the net clinical benefit by weight as shown in Figure 6. The net clinical benefit understandably decreased as a function of increasing the weight that was placed on the severe bleed. When the importance of one GUSTO severe bleed was considered twice as important as a recurrent stroke, the net clinical benefit approached neutrality. When a GUSTO severe bleed was considered equally as important to a recurrent stroke, ticagrelor showed a net clinical benefit.

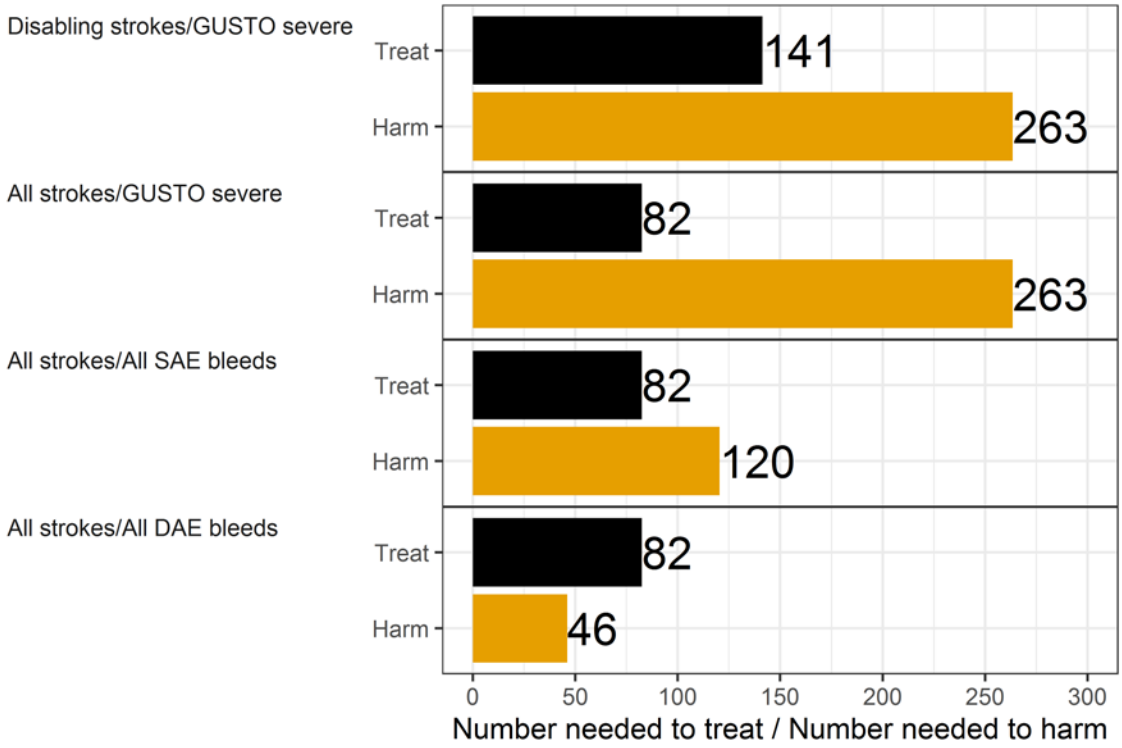
The benefit-risk evaluation of the THALES data was assessed in the setting of the antecedent benefit-risk assessment of the data from the THEMIS trial. THEMIS was designed to evaluate ticagrelor compared to placebo to reduce the incidence of major adverse cardiac events (stroke, myocardial infarction, cardiovascular death) in patients with established coronary artery disease, but with no history of myocardial infarction or stroke. In the THEMIS trial, the number of patients needed to treat for a benefit (reduction in major adverse cardiac events) was twice as large as the number of patients needed to treat for harm (TIMI major bleed defined as an intracranial hemorrhage or a $\geq$ 5 g/dL decrease in hemoglobin or a $\geq$ 15% absolute decrease in hematocrit). The numerical-based net harm for ticagrelor in the THEMIS population may have resulted in non-approval for ticagrelor despite having met the THEMIS efficacy endpoint. Application of a multi-criteria decision analysis (MCDA) that incorporated personal preferences and perceptions pointed to a willingness to be treated with ticagrelor to reduce the risk of a major adverse cardiac event at the risk of a major bleeding event. The major bleeding risk of ticagrelor was well known

Reference ID: 4691882

from antecedent approvals and carries a warning in the label. Based on the MCDA and the precedence in accepting the known bleeding risk, the review team recommended approval.

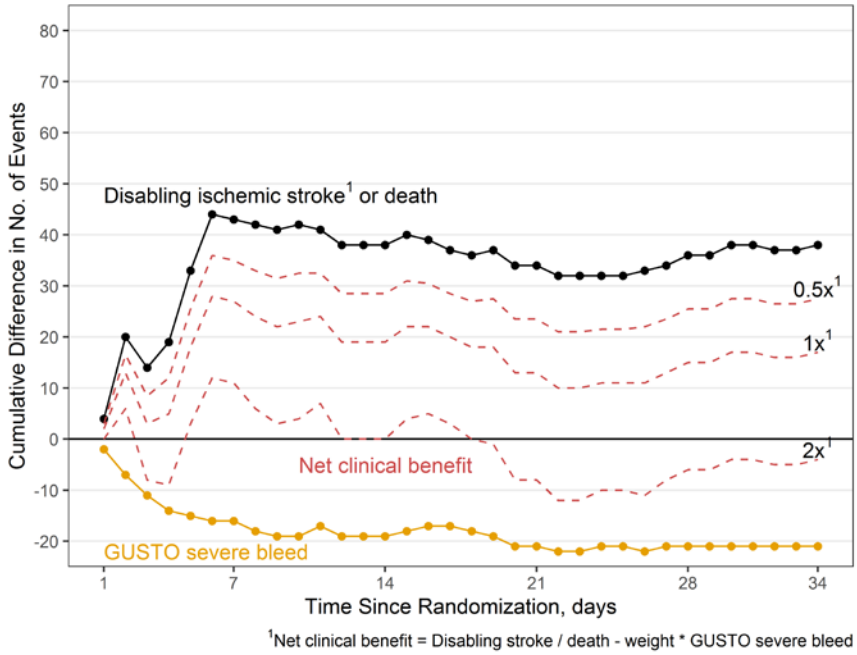
The review team recognized the possibility that disabling symptoms of an acute ischemic stroke, even if mild, may foster a significant concern about a recurrent stroke. This led to the judgment that patients may be willing to take a drug with a proven benefit despite the risk of a bleeding event. This assessment in the setting of an established net clinical benefit led the team to recommend approval of ticagrelor for the secondary stroke indication.

Figure 5: Net Clinical Benefit (Day 30): Number Needed to Treat vs Number Needed to Harm



Source: Clinical Review (DAE: adverse events resulting in discontinuation)

Figure 6: Cumulative Distribution Curves and Net Clinical Benefit as a Function of Subjective Attribution of Importance of Stroke vs Bleed



Source: Clinical Review

10. 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.

11. Pediatrics

A PeRC meeting was held on 15 SEP 2020. The Division and PeRC agreed with the Applicant's request for a full waiver of pediatric studies based on issues of practicality.

12. Other Relevant Regulatory Issues

- Financial Disclosures and Good Clinical Practice: There were no issues regarding conflicts of interest based on financial disclosure.

- Office of Scientific Investigations: A site-level evaluation took place in joint meeting between clinical and OSI. It was determined that there was no individual site or a cluster

of sites that impacted the outcome of the THALES trial. Based on a lack of outlier signal, the Clinical / OSI team concluded that site inspections were not necessary.

- Proprietary Name Review: Not applicable.

- Uncertainties Identified in a memo authored by Dr. Stephen Grant: Prior to retirement, Dr. Grant was the primary clinical reviewer through the mid-cycle meeting and authored a memo (Grant, 30 SEP 2020) that identified two potential uncertainties: 1) The clinical trial was performed completely outside the USA thus raising a question of applicability to the US population; and 2) There was under-representation of black patients (< 1% of the intention-to-treat population). Our conclusions on these matters are:

  - We concur with our neurology consultants that the practice paradigm is similar in the US and Europe.
  - While African Americans may be at higher risk of recurrent stroke than are Caucasians, there is no evidence in other trials of ticagrelor of a disparity in response to treatment.

13. 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.

14. Postmarketing Recommendations

None.

15. Recommended Comments to the Applicant

None.

16. Appendices

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Reference ID: 4691882

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Reference ID: 4691882

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022433Orig1s029

CLINICAL REVIEW(S)

Clinical-Statistical Joint Review

L. Johannesen, C. Garnett, F. Senatore, W. Koh, J. Zhang

NDA 22433/s029

Brilinta (ticagrelor)

CLINICAL REVIEW

Application Type	Efficacy supplement
Application Number(s)	NDA 22433
Priority or Standard	Priority
Submit Date(s)	5/5/2020
Received Date(s)	5/5/2020
PDUFA Goal Date	11/5/2020
Division/Office	DCN / OCHEN
Reviewer Name(s)	**Clinical** Lars Johannesen, PhD, Christine Garnett, PharmD, Fred Senatore, MD, PhD, FACC (CDTL) **Statistics** William Koh, PhD, Jialu Zhang, PhD
Review Completion Date	10/12/2020
Established/Proper Name	Ticagrelor
(Proposed) Trade Name	BRILINTA
Applicant	AstraZeneca
Dosage Form(s)	Oral tablets
Applicant Proposed Dosing Regimen(s)	180 mg loading dose followed by 90 mg twice daily for 30 days together with a loading dose of aspirin (300 – 325 mg) followed by 75-100 mg aspirin once a day.
Applicant Proposed Indication(s)/Population(s)	To reduce the risk of stroke in patients with acute ischemic stroke or transient ischemic attack (TIA)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	BRILINTA is indicated to reduce the risk of stroke in patients with acute mild ischemic stroke (NIH Stroke Scale score ≤ 5) or transient ischemic attack (TIA)

Link to submission: \\CDSESUB1\evsprod\NDA022433\0565\

Clinical-Statistical Joint Review

L. Johannesen, C. Garnett, F. Senatore, W. Koh, J. Zhang

NDA 22433/s029

Brilinta (ticagrelor)

Table of Contents

Reference ID: 4689224

Reference ID: 4689224

Table of Tables

Reference ID: 4689224

Table of Figures

Glossary

AC	advisory committee
ACS	acute coronary syndrome
ADP	adenosine diphosphate
AIS	acute ischemic stroke
AE	adverse event
ASA	Acetylsalicylic acid
CAD	coronary artery disease
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CHANCE	Clopidogrel in High-risk patients with Acute Nondisabling Cerebrovascular Events trial
CSR	clinical study report
CSP	clinical study protocol
DAE	Premature permanent discontinuation of investigational product due to adverse event
DMC	data monitoring committee
EC	Executive Committee
FAS	full analysis set
FDA	Food and Drug Administration
GCP	good clinical practice
GUSTO	global utilization of streptokinase and Tpa for occluded arteries
HR	hazard ratio
ICH	International Council for Harmonization

Reference ID: 4689224

IEC	independent ethics committee
IND	Investigational New Drug Application
IRB	institutional review board
ITT	intent to treat
LOE	level of evidence
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
mRS	modified Rankin scale
NDA	new drug application
NIHSS	NIH Stroke Scale
OSI	Office of Scientific Investigation
POINT	Platelet-Oriented Inhibition in New TIA and minor ischemic stroke trial
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SOCRATES	Acute Stroke or Transient Ischemic Attack Treated With Aspirin or Ticagrelor and Patient Outcomes
TEAE	treatment emergent adverse event
THALES	Acute STroke or Transient IscHaemic Attack Treated with TicAgreLor and ASA for PrEvention of Stroke and Death
TIA	transient ischemic attack

Reference ID: 4689224

2. Executive Summary

2.1. 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); patients with a history of myocardial infarction (MI); and to reduce the risk of a first MI or stroke in patients with coronary artery disease (CAD) at high risk for such events.

2.2. Conclusions on the Substantial Evidence of Effectiveness

The THALES (Acute STroke or Transient IscHaemic Attack Treated with TicAgreLor and ASA for PrEvention of Stroke and Death) 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 death and stroke (hazard ratio (HR) 0.8; 95% confidence interval 0.71 – 0.96). The results were driven by a reduction in any stroke, with consistent significant findings in key secondary endpoint for ischemic stroke, and prespecified subgroups.

The evidence of effectiveness is clinically meaningful to the extent that it expanded the spectrum of benefit to include a reduction in the risk of stroke in patients with acute mild ischemic stroke (NIH Stroke Scale (NIHSS) score ≤5) or transient ischemic attack (TIA).

2.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

The THALES study was a double-blind, two-arm, randomized, placebo-controlled trial designed to evaluate ticagrelor in patients either with an acute mild stroke (NIHSS score of ≤ 5) or high-risk TIA. The trial was designed to evaluate whether ticagrelor can reduce the incidence of the primary endpoint comprised of recurrent stroke or death.

A total of 11,073 patients were randomized to receive ticagrelor 90 mg PO twice daily or placebo (50% of the patients).

Efficacy analysis showed a statistically significant absolute reduction of -1.1% in the risk of the composite endpoint favoring ticagrelor over placebo. This corresponded to a relative risk reduction of 20% (hazard ratio 0.8; 95% confidence interval 0.71 – 0.96). The results were driven by a reduction in any stroke, with consistent significant findings in key secondary endpoint for ischemic stroke, and prespecified subgroups. Based on the Kaplan Meier curves, the benefit in reducing recurrent ischemic stokes occurred early during the trial.

Ticagrelor did not reduce the severity of strokes. Results based on the proportion of patients with modified Rankin score (mRS) greater than one was not statistically significant on day 30. A post-hoc analysis of the mRS score showed patients with a subsequent stroke were associated with a worse overall disability outcome compared to patients without a subsequent stroke at the end of the study. The mRS analysis involves post-randomization subgroup comparison and interpretation of the results can be limited.

Safety analysis showed bleeding-related serious adverse events occurred more frequently in the ticagrelor arm. There were more adverse events that resulted in discontinuation of treatment in the ticagrelor group and the difference was driven by bleeding related adverse events and shortness of breath (dyspnea).

The Global Utilization Of Streptokinase And Tpa For Occluded Arteries (GUSTO) bleeding criteria was used. GUSTO severe bleeding events were more frequent in the ticagrelor group (26 of 5508 patients: 0.5%) compared to placebo group (6 of 5468 patients: 0.1%) at 30 days. Fatal bleeds were more frequent in the ticagrelor group (9 patients: 0.2%) compared to placebo group (1 patient: <0.1%) and was driven by hemorrhagic strokes. Like fatal bleeds, there were more intracranial hemorrhages in the ticagrelor treatment group (20 patients: 0.4%) compared to the placebo group (6 patients: 0.1%). The risk of GUSTO severe bleeding began immediately upon initiation and most of difference between the treatment groups were observed early in the trial.

Serious bleeding risk and dyspnea are described in the current label as warnings.

The benefit-risk assessment compared the reduction of the primary endpoint to the risk of GUSTO severe bleeds. A simple calculation showed that 90 patients required treatment with ticagrelor to prevent 1 primary endpoint event. Similarly, 263 patients required treatment with ticagrelor to cause 1 GUSTO severe bleed. From this strict numerical perspective, the benefit outweighed the risk.

Additional benefit-risk analysis using different weights for benefit (reduction in ischemic stroke or death not due to bleeding) vs. risk (increase in GUSTO severe bleeds) supported a positive benefit-risk for ticagrelor that was primarily observed early in the study and was maintained throughout the study duration. While, there was a positive benefit-risk in THALES, it is unknown if the findings can be extrapolated to patients with more severe strokes (NIHSS score > 5), who might be at an increased risk for intracranial hemorrhage (ICH). Therefore, the indication will be limited to reduction in the risk of stroke in patients with acute mild ischemic stroke (NIHSS score ≤5).

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Acute ischemic stroke is the 4th leading cause of death and the leading cause of adult disability. The annual incidence of new and recurrent stroke is approximately 795,000 (Bansal, 2013). In 2018, 1 of every 6 deaths from cardiovascular disease was due to stroke; someone in the US has a stroke every 40 seconds; someone dies of a stroke every 4 minutes; nearly 1 of 4 strokes are in people who had a previous stroke; 87% of all strokes are ischemic (www.cdc.gov>stroke>facts). • Acute ischemic stroke (AIS) commonly occurs by pathophysiological mechanisms in common with that of acute coronary syndrome. • Atherosclerotic obstruction of a cerebral artery leads to irreversible brain	None.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	injury and subsequent focal neurological deficits. • A TIA is a reversable neurological deficit based upon transient blockage of a cerebral artery, analogous to unstable angina. TIAs are a forerunner of an ischemic stroke.	
Current Treatment Options	• Individuals who have experienced AIS or TIA are at high risk for subsequent strokes, and the aim of treatment is both to minimize disability from the initial event and prevent the occurrence of subsequent strokes. Current treatment options were obtained from the most recent guideline on treatment of acute stroke (Powers, 2019). • IV alteplase (0.9 mg/kg, maximum dose 90 mg over 60 minutes with initial 10% of dose given as bolus over 1 minute) is recommended for selected patients who can be treated within 3 hours of ischemic stroke symptom onset or patient last known well or at baseline state (Class I, LOE A). • For patients with a non-disabling stroke (NIHSS score 0–5), IV alteplase is not recommended for patients who could be treated within 3 hours of ischemic stroke symptom onset (Class III-no benefit, LOE C-limited data). • Administration of aspirin is recommended in patients with AIS within 24 to 48 hours after onset. For those treated with IV alteplase, aspirin administration is generally delayed until 24 hours later but might be considered in the presence of concomitant conditions for which such treatment given in the absence of IV alteplase is known to provide substantial benefit or withholding such treatment is known to cause substantial risk (Class I, LOE A). • In patients presenting with minor non-cardioembolic ischemic stroke (NIHSS score ≤3) who did not receive IV alteplase, treatment with dual antiplatelet	• The mainstay of treatment includes thrombolytic therapy for an AIS and dual antiplatelet therapy within 24 hours of symptom onset and continued for 21 days. • There is antecedent data to support dual antiplatelet therapy (aspirin and clopidogrel), started within 24 hours after symptom onset and continued for 21 days to reduce recurrent ischemic stroke for a period of 90 days from symptom onset (Class I, LOE A). However, there is no antecedent approval of an antiplatelet agent for the reduction of stroke. • For patients with non-cardioembolic AIS, the use of antiplatelet agents rather than oral anticoagulation is recommended to reduce the risk of recurrent stroke and other cardiovascular events (Class I, LOE A).

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	therapy (aspirin and clopidogrel) started within 24 hours after symptom onset and continued for 21 days is effective in reducing recurrent ischemic stroke for a period of up to 90 days from symptom onset (Class I, LOE A).	
Benefit	Evidence • The THALES study showed a statistically significant absolute reduction of -1.1% in the risk of the composite primary endpoint favoring ticagrelor over placebo. This corresponded to a relative risk reduction of 20% (hazard ratio 0.8; 95% confidence interval 0.71 – 0.96). The results were driven by a reduction in any stroke. • The results of primary endpoint were consistent across pre-specified subgroups (e.g., age, sex, geographic region, severity of index stroke, time of index stroke to randomization or loading dose). • There was a statistically significant reduction in the risk of ischemic stroke, a key secondary endpoint, comparing ticagrelor arm with placebo with an estimated HR of 0.8 (95% CI: 0.68, 0.93; p=0.004). Uncertainties • There were numerical trends in risk of death in the ticagrelor arm (36 (0.7%)) relative to placebo arm (27 (0.5%)). • The proportions of patients with a mRS score > 1 for ticagrelor (23.8%) and placebo (24.1%) were numerically similar and the OR was 0.98 (95% CI: 0.89, 1.07; p=0.61). Therefore, treatment with ticagrelor plus aspirin did not reduce the severity in strokes (all strokes) compared to placebo plus aspirin. • THALES was conducted outside the US. However, the findings from THALES	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 risk of stroke in patients with acute mild ischemic stroke (NIHSS score ≤5) or TIA.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	are expected to be applicable to US practice because the treatment guidelines for stroke and TIA listed in these countries are generally similar to the US guidelines. • The systemic pattern of under-represented patient populations, endemic to clinical trials, was also evident in the THALES trial. There was a paucity of black patients who are at particular risk of stroke relative to the white population. The less than 1% black subjects who participated in THALES showed a similar outcome to the remainder of the ITT population, but the sample size was too small to be conclusive. Patient under-representation is an issue beyond the scope of the THALES trial and is currently being addressed by working groups whose membership spans academia, regulatory and industry.	
Risk and Risk Management	Evidence • There were no differences between the ticagrelor arm and the placebo arm for serious adverse events or adverse events leading to discontinuation except for bleeding related adverse events and shortness of breath (dyspnea) that occurred more frequently in the ticagrelor arm. • Severe bleeding events (GUSTO definition) occurred 4x as often in the ticagrelor arm compared to placebo. The imbalance in severe bleeding events was driven by ICH bleeds. • There was a low incidence of fatal bleeds (9 in the ticagrelor group and 1 in the placebo). The imbalance in fatal bleeds was driven by hemorrhagic strokes. Uncertainties • Following an AIS, those patients at higher risk for a hemorrhagic stroke	• Dyspnea also already caries a warning in the ticagrelor label. • Bleeding is a well-known adverse event of ticagrelor based on its antiplatelet effect and it is described in the label as a warning. • The label should include a warning about post stroke patients at risk for a hemorrhagic transformation.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	should be identified to avoid mortality from a recurrent hemorrhagic stroke due to ticagrelor treatment.	

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2.4. Patient Experience Data

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	

Reference ID: 4689224

	□ Other: (Please specify)	
x	Patient experience data was not submitted as part of this application.	

3. Therapeutic Context

3.1. Analysis of Condition

AIS is the 4th leading cause of death and the leading cause of adult disability. The annual incidence of new and recurrent stroke is approximately 795,000 (Bansal, 2013). In 2018, 1 of every 6 deaths from cardiovascular disease was due to stroke; someone in the USA has a stroke every 40 seconds; someone dies of a stroke every 4 minutes; nearly 1 of 4 strokes are in people who had a previous stroke; 87% of all strokes are ischemic (www.cdc.gov>stroke>facts).

AIS commonly occurs by pathophysiological mechanisms in common with that of acute coronary syndrome.

Atherosclerotic obstruction of a cerebral artery leads to irreversible brain injury and subsequent focal neurological deficits.

A TIA is a reversable neurological deficit based upon transient blockage of a cerebral artery, analogous to unstable angina. TIAs are a forerunner of an ischemic stroke

3.2. Analysis of Current Treatment Options

The mainstay of treatment of AIS includes thrombolytic therapy for an AIS.

There is antecedent data to support dual antiplatelet therapy (aspirin and clopidogrel), started within 24 hours after symptom onset and continued for 21 days to reduce recurrent ischemic stroke for a period of 90 days from symptom onset (Class I, LOE A). However, there is no antecedent approval of an antiplatelet agent for the reduction of stroke. For patients with non-cardioembolic AIS, the use of antiplatelet agents rather than oral anticoagulation is recommended to reduce the risk of recurrent stroke and other cardiovascular events (Class I, LOE A).

For patients with a non-disabling stroke (NIHSS score 0 - 5), IV alteplase is not recommended for patients who could be treated within 3 hours of ischemic stroke symptom onset (Class III-no benefit, LOE C-limited data). In patients presenting with minor non-cardioembolic ischemic stroke (NIHSS score ≤3) who did not receive IV alteplase, treatment with dual antiplatelet therapy (aspirin and clopidogrel) started within 24 hours after symptom onset and continued

for 21 days is effective in reducing recurrent ischemic stroke for a period of up to 90 days from symptom onset (Class I, LOE A).

Ticagrelor is not recommended in lieu of aspirin for the treatment of patients with minor acute stroke (Class III-no benefit, LOE B-R). This was based on the SOCRATES trial (Acute Stroke or Transient Ischemic Attack Treated With Aspirin or Ticagrelor and Patient Outcomes) (Johnston, 2016), which was a randomized, double-blind, placebo-controlled trial of ticagrelor versus aspirin begun within 24 hours in patients with minor stroke (NIHSS score ≤5) or TIA ($ABCD^2$ score ≥4). With a primary outcome of time to the composite end point of stroke, MI, or death up to 90 days, ticagrelor was not found to be superior to aspirin (HR, 0.89 [95% CI, 0.78–1.01]; *P*=0.07). However, because there were no significant safety differences in the 2 groups, ticagrelor may be a reasonable alternative in stroke patients who have a contraindication to aspirin.

For early secondary prevention in patients with non-cardioembolic AIS, the selection of an antiplatelet agent should be individualized on the basis of patient risk factor profiles, cost, tolerance, relative known efficacy of the agents, and other clinical characteristics (Class I. LOE C-expert opinion).

4. Regulatory Background

4.1. 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 – 100 mg PO daily.

Based on the THEMIS trial, ticagrelor was approved by the US FDA in May 2020 for the reduction of the risk of a first MI or stroke in patients with CAD at high risk for such events.

The labeled dosing instruction is 60 mg PO twice daily concomitantly with aspirin 75 – 100 mg PO daily.

The current sNDA for the proposed indication to reduce the risk of stroke in patients with acute ischemic stroke or TIA.

4.2. Summary of Presubmission/Submission Regulatory Activity

The Division held two meetings with the Applicant: pre-phase 3 meeting for THALES (10/27/2016) and topline results discussion (02/25/2020). Written responses concerning the format and content of sNDA were also provided prior to submission of the sNDA (07/25/2020).

At the pre-phase 3 meeting the Division noted that it is possible that the indication resulting from THALES could include a time limitation and be limited to a subset of patients like those enrolled or appeared to have benefit. The Division also encouraged inclusion of a lower maintenance dose (60 mg twice daily) based on the findings in PEGASUS of a comparable efficacy and reduced risk for bleeding and dyspnea. The inclusion of a 60 mg group could be achieved by including it in addition to 90 mg and group the two arms together for the primary analysis or allow for a dose reduction to 60 mg for patients unable to tolerate 90 mg. The Division also agreed to selective safety monitoring. Lastly, it was noted that avoiding bias in capturing of endpoints and use of pharmacotherapy like what is recommended in US and European guidelines would be important to ensure that the study results are applicable to the US population and that randomization should be stratified by region.

The Division questioned whether the 30-day duration was longer than needed at the topline results based on the information presented and encouraged exploration of net benefit as a function of time in the submission. The Applicant agreed to evaluated this but noted that it could be challenging due to the small number of safety events. The Division also reminded the Applicant that an explanation of the applicability of foreign data to US practice should be included in the submission and asked the Applicant to provide monitoring reports across regions due to concern about potential under-reporting.

4.3. 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 as in the USA and based on the same pivotal trials. Ticagrelor and aspirin is not approved anywhere for the reduction of risk of recurrent stroke.

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

5.1. 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 the treatment arms. This was accomplished by the site-selection tool designed to display outliers and thus facilitate site selection for inspection.

The evaluation showed that no single site impacted the overall results of THALES. Hence, the review team concluded that routine or for-cause site inspections would not be informative and were not required.

5.2. Product Quality

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

5.3. Nonclinical Pharmacology/Toxicology

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

5.4. Clinical Pharmacology

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

5.5. Devices and Companion Diagnostic Issues

Not applicable.

5.6. Consumer Study Reviews

Not applicable.

6. Sources of Clinical Data and Review Strategy

6.1. Table of Clinical Studies

The THALES trial served as the sole basis for supporting the proposed indication in this sNDA (Table 1).

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Table 1: 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
THALES D5134C 00003	03354429	Randomized, Double-Blind, Placebo controlled	Ticagrelor: 180 mg PO loading followed by 90 mg PO BID ASA: 300 – 325 mg PO loading followed by 75 - 100 mg PO BID	Time to event: composite of subsequent stroke or death	30 days of treatment followed by an additional 30 days of standard of care	11,073	Patients ≥40 years with a non-cardioembolic acute ischemic stroke (NIHSS ≤ 5) or high-risk TIA	28 countries in North America (excluding US), South America, Asia, Australia and Europe; 414 participating sites

Source: Applicant's CSR.

6.2. Review Strategy

The efficacy analysis from the Applicant was confirmed by the team statistician.

Safety evaluation focused on GUSTO severe bleeding events, serious adverse events and adverse events leading to discontinuation.

Benefit-risk evaluation was conducted by comparing the reduction in ischemic strokes and death not due to bleeding (benefit) versus risk (GUSTO severe bleeding events) using different weights (appendix 14.4). Post-hoc comparison of the distribution of mRS scores for patients with and without subsequent strokes were also conducted (appendix 14.5).

7. Review of Relevant Individual Trials Used to Support Efficacy

7.1. THALES study (D5134C00003)

7.1.1. Study Design

Overview and Objective

The primary objective of the THALES study was to determine the efficacy and safety of ticagrelor and acetylsalicylic acid (ASA) compared to placebo and ASA in the prevention of the composite of stroke and death in patients with AIS or TIA.

The key secondary objectives included comparing ticagrelor and ASA with placebo and ASA in the (1) prevention of ischemic stroke at 30 days and (2) in reducing overall disability at 30 days.

Trial Design

THALES was a randomized, parallel-group, placebo-controlled, multi-center, double-blind clinical trial (Figure 1).

The study was conducted in 414 sites across 28 countries defined by geographical regions, namely, Asia and Australia, Europe, Central and South America, and North America (Table 2). There were no participating sites or randomized patients from USA.

Table 2: List of Countries in the Geographical Regions defined in THALES

Geographical Regions	Countries	# of Sites
Central and South America	Argentina, Brazil, Mexico, Peru	43
Asia and Australia	China, Hong Kong, Indonesian, Korea, Taiwan, Thailand, Vietnam, Australia	145
Europe	Belgium, Bulgaria, Czech, France, Germany, Hungary, Italy, Poland, Romania, Russia, Slovakia, Spain, Sweden, Ukraine, Saudi Arabia[1]	221
North America	Canada	5

1: Saudi Arabia is categorized as coming from Europe by the Applicant even those this country is not geographically considered to be part of Europe.
[Source: Statistical Reviewer]

The clinical reviewer noted that even though the study did not include any US sites, the findings from THALES are expected to be applicable to US practice for the following reasons. Firstly, the treatment guidelines for stroke and TIA listed in these countries are similar to the US (see Table 4 in Applicability of Foreign Data document). Secondly, the baseline characteristics of the THALES population are similar to a comparable population in the US (Section 10) with respect to risk factors for an ischemic event — hypertension, dyslipidemia, cardiovascular disease, diabetes mellitus, tobacco use, and overweight/obesity. However, the THALES trial enrolled a low percentage of blacks or African Americans (<1%), which is not consistent with US demographics.

Eligible patients were at least 40 years of age who have experienced a non-cardioembolic acute ischemic stroke (NIHSS score ≤5) OR high-risk TIA (defined as ABCD[2] score[1] ≥6 or ipsilateral atherosclerotic stenosis ≥50% in an extra/intracranial artery) who could be randomized within 24 hours of symptom onset.

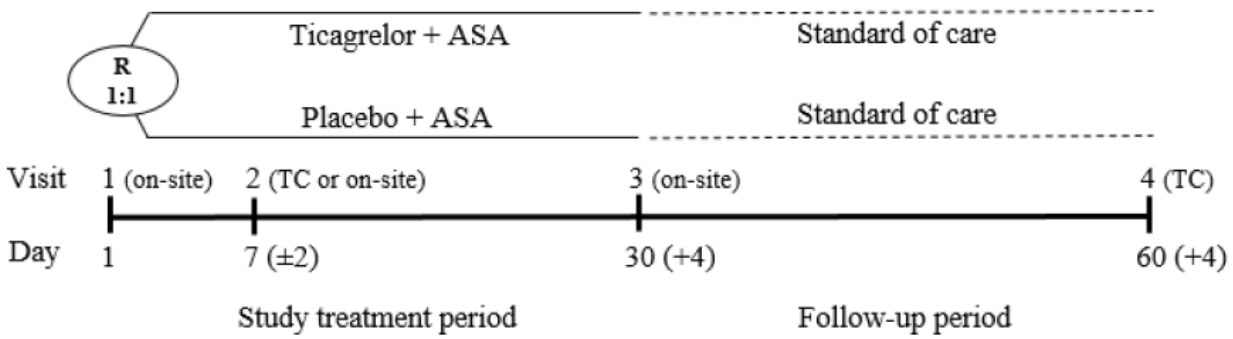
The key exclusion criteria were 1) need for dual antiplatelet therapy with ASA and $P2Y_{12}$ antagonists, antiplatelets other than ASA, or anticoagulants; 2) previous atrial fibrillation/flutter, ventricular aneurysm, or suspicion of other cardioembolic pathology for TIA or stroke; 3) planned to receive intravenous or intra-arterial thrombolysis or mechanical thrombectomy; 4) planned carotid endarterectomy; 5) history of bleeding (intracerebral or GI);

[1] A 7-point risk assessment tool designed to improve the prediction of stroke risk after a TIA (composite of age, blood pressure, clinical features, duration of symptoms, diabetes history). A higher score indicates a higher risk.

6) Known risk of bradycardic events; 7) hyper-sensitivity to ticagrelor or ASA; 8) known bleeding diathesis or coagulation disorder; 9) severe liver disease or renal failure requiring dialysis.

Patients were given a loading dose of 180 mg ticagrelor or placebo at Day 1 after randomization. All patients received open-label ASA. Patients were also given a loading dose of ASA (recommended to be 300 mg to 325 mg). Thereafter, patients received ASA 75 mg to 100 mg once daily.

Figure 1: Study Design, THALES



ASA (concomitant medication) = open-label. Loading dose at the Investigator's discretion (300 to 325 mg recommended) followed by 75 to 100 mg once daily.
Ticagrelor (investigational product) = 180 mg loading dose followed by 90 mg twice daily
Abbreviations: ASA=acetylsalicylic acid; R=randomization; TC=telephone contact
[Source: Module 5.3.5.1; Protocol Version 3.0]

Study Endpoints

The primary efficacy endpoint was the time from randomization to first subsequent stroke or death.

The secondary efficacy endpoints, presented hierarchically, were:

1. Time from randomization to first subsequent ischemic stroke;
2. The proportion of patients with a modified Rankin score greater than 1 at Visit 3

The study listed the following exploratory safety endpoints:

- Time from randomization to first bleeding event that fulfils serious adverse event (SAE) criteria and is categorized as GUSTO Severe[2]
- Time from randomization to first intracranial hemorrhage or fatal bleeding event
- Time from randomization to first bleeding event that fulfils SAE criteria and is categorized as GUSTO Moderate[3]/Severe
- Time from randomization to premature permanent discontinuation of IP due to bleeding
- Occurrence of SAE
- Occurrence of DAE (Premature permanent discontinuation of investigational product due to adverse event)

Statistical Analysis Plan

The statistical analysis plan (SAP) was first drafted on February 9, 2017 and finalized on December 9, 2019. There was a total of four revisions.

The full analysis set (FAS) consisted of all patients randomized. Patients were analyzed according to their randomized assignment regardless of whether they have discontinued the treatment. The safety analysis set is based on all patients who received at least one dose of randomized treatment. Patients will be analyzed based on the actual treatment received. If patients received both ticagrelor and placebo, then the treatment assignment will be based on the randomized assignment. Unless otherwise specified, all statistical analyses on efficacy endpoints were based on the FAS including all randomized patients.

The primary endpoint is the time from randomization to first subsequent stroke or death. Patients who have not experienced either of these events will be censored at Visit 3, i.e., Day 34, or the date of last event assessment, whichever occurs earlier. If Visit 3 has occurred within the visit window, Day 30 to 34, events will be included up to the date of Visit 3 (inclusive). If Visit 3 has occurred outside of the visit window (or is missing), it will be replaced by Day 34 for event inclusion and censoring.

Cox proportional hazards (PH) regression was used to analyze the primary efficacy timepoint adjusting for treatment group, and Efron's method for ties. The estimated hazard ratio (HR), Wald-based 95% CI, and Wald-based p-value were reported from the regression model. In

[2] GUSTO Severe Bleeding includes a fatal, intracranial (excludes asymptomatic haemorrhagic transformations of ischemic brain infarctions and excludes microhaemorrhages <10 mm evident only on gradient-echo MRI), or bleeding that that caused haemodynamic compromise requiring intervention

[3] GUSTO Moderate include Bleeding requiring transfusion of whole blood or packed red blood cells without hemodynamic compromise

addition, Kaplan-Meier estimates of the cumulative incidence were reported at specific time points and at Day 30. The estimated risk difference based on cumulative incidence will be reported with respective 95% CI.

To address for potential missing vital status at Day 30, the SAP specified that a tipping point analysis may be conducted by adding events to the ticagrelor arm until a non-significant result is obtained.

Subgroup analysis was conducted for the primary efficacy endpoint. Within each subgroup category, the same Cox PH model is applied and the HR, respectively 95% CI are reported within each subgroup category provided at least 15 events have occurred in total.

The following subgroup variables and categories were assessed:

- Age (<65, 65-75, >75 years)
- Sex (Male, Female)
- Race (White, Black, Asian, Other)
- Weight (<70, ≥70 kg)
- BMI (<30, ≥30 kg/m^2)
- Geographic region (Asia and Australia, Europe, North America, Central and South America)
- Diagnosis of index event (Stroke NIHSS score ≤3, Stroke NIHSS score >3, TIA)
- Time from index event to randomization (<12, ≥12 hours)
- Time from index event to loading dose (<12, ≥12 hours)
- Diabetes mellitus (Yes, No)
- Hypertension (Yes, No)
- Prior ischemic stroke or TIA (Yes, No)
- Prior ischemic heart disease [defined as any of coronary artery bypass grafting,
- myocardial infarction, percutaneous coronary intervention, or coronary artery disease]
- (Yes, No)
- Prior ASA (Yes, No)
- Prior statin treatment (Yes, No)
- Smoking status (Current, Former, Never)

The key secondary endpoint, time to first ischemic stroke, was analyzed in a similar manner as a primary endpoint. Patients who died prior to the event will be censored at the time of death.

The proportion of patients with mRS score > 1 at Visit 3 was analyzed using a logistic regression model fit to the binary endpoint adjusting for treatment group, history of stroke, and baseline NIHSS score. Patients with missing NIHSS score were excluded from the regression model. As a sensitivity analysis, the analysis was repeated by imputing missing mRS scores as >1.

The safety variables were analyzed similarly as the primary efficacy endpoints. The components of the primary efficacy endpoint were analyzed using the same Cox PH model described. Patients who died prior to observing other events of interest, except death, were censored at time of death. For example, in the time to any stroke endpoint, patients who died were not counted as an event and have their survival time censored at the time of death.

An interim analysis was planned after 453 planned primary events have been accrued during the study. The efficacy stopping boundary, estimated using the Haybittle-Peto procedure, at the interim is based on a 2-sided p-value of < 0.001, corresponding to a critical value of 0.734. With this interim analysis, the final p-value to be used will be based on a significance level of 4.996% if the study proceeds to the final analysis. The overall Type 1 error is controlled at 5.00%.

Additional Statistical Reviewer's Analyses

To facilitate understanding of the risk-benefit, the statistical reviewer reported differences in risk based on incidence rates at various timepoints and Day 30 and respective 95% CI for the time to event endpoints, namely, stroke and death, death, stroke, and GUSTO Severe bleeding event.

For the analysis of mRS, the statistical reviewer did not agree with the Applicant's approach to excluding patients without mRS at Day 30 from the analysis since these patients are not missing at random. Despite that, the proportion of patients without mRS at Day 30 were 2%. As a supportive analysis, the statistical reviewer included cumulative responder curves to describe the proportion of patients with a mRS score greater than some values at Day 30. Patients without mRS score were included as a separate category with mRS greater than 5 but not 6. During the review, the statistical reviewer noted that patients without mRS at Day 30 had a vital status of being alive. For simplicity, the statistical reviewer included them as a separate category together with patients with mRS score greater than some value but not six.

Protocol Amendments

There were three protocol amendments dated 15 October 2018, 5 February 2019 and 8 May 2019. The first protocol amendment relates to changes in the interim analysis and inclusion of a futility analysis as recommended by the Data Monitoring Committee (DMC) prior to start of patient recruitment. The second amendment was an administrative update (corrected date of clinical study protocol or CSP). The third protocol amendment described changes in the adjusted assumed HR and power based on a recommendation from the Executive Committee (EC) that the original assumptions were too conservative. All protocol amendments were approved after the start of patient recruitment. As discussed in subsequent sections, the changes to the planned analysis, and SAP, are not expected to impact the interpretation of the study results.

7.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant stated that the THALES study was conducted in accordance with the Declaration of Helsinki that were consistent with the International Council for Harmonization / Good Clinical Practice (GCP) and applicable regulatory requirements.

Independent ethics committees and Institutional Review Boards (IRBs) approved the study protocol, including the informed consent form and any other written information and/or materials to be provided to patients**.**

During conduct of the study, standard-of-care treatment in Canada changed and the comparator (ASA alone) was no longer considered appropriate. As a result, IRBs/IECs in Canada withdrew the ethical approval of the study and recruitment was halted at all Canadian sites (last patient recruited July 4th, 2018).

Clinical Reviewer's Comment: The withdrawal of the ethical approval was likely due to the positive findings from POINT (Johnston, 2018) and CHANCE trials (Wang, 2013), which also caused the withdrawal of support for THALES from the Canadian Stroke Consortium.

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 2508 investigators of which 413 were designated as principle investigators. One principle investigator disclosed that his spouse was an employee of the Applicant.

There were 4 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 4 investigators the information required under 21 CFR part 54.4.

In total there were 5 investigators out of 2508 representing 176 out of 11016 randomized patients with a disclosure or unknown disclosure status, which did not impact the clinical review.

Patient Disposition

A total of 11016 screened patients were randomized in a 1:1 ratio to ticagrelor (n=5523) or placebo (n=5493). A total of 87% of the patients completed randomized treatment (Table 3). There were no numerical differences between the number of patients who discontinued randomized treatment across treatment arms. Adverse event was the most common reason for

discontinuing randomized treatment. All but one patient's vital status was ascertained at Visit 3, the primary efficacy time-point, Day 30.

Table 3: Disposition of Patients, THALES

	Ticagrelor	Placebo	Total
Patients randomized	5523 (100%)	5493 (100%)	11016 (100%)
Patients who did not received treatment	17 (< 1%)	23 (< 1%)	40 (< 1%)
Patients who received treatment	5506 (99.7%)	5470 (99.6%)	10976 (99.6%)
Patients who completed treatment	4732 (86%)	4848 (88%)	9580 (87%)
Died	20 (< 1%)	14 (< 1%)	34 (< 1%)
Patients who did not complete treatment	791 (14%)	645 (12%)	1436 (13%)
Adverse Event	530 (10%)	411 (8%)	941 (9%)
Other	84 (2%)	89 (2%)	173 (2%)
Subject Decision	177 (3%)	145 (3%)	322 (3%)
Patients who completed the study	5516 (99.9%)	5487 (99.9%)	11003 (99.9%)
Vital Status: Alive	5479 (99.2%)	5460 (99.4%)	10939 (99.3%)
Vital Status: Dead	36 (< 1%)	27 (< 1%)	63 (< 1%)
Vital Status: Unknown	1 (< 1%)	-	1 (< 1%)
Patients who did not completed study	7 (< 1%)	6 (< 1%)	13 (< 1%)
Vital Status: Alive	7 (< 1%)	6 (< 1%)	13 (< 1%)

Counts and percentages in parenthesis.
[Source: Statistical Reviewer]

Protocol Violations/Deviations

Important protocol deviations were defined as: 1) patients who were randomized but violated eligibility criteria; 2) patients who developed criteria for permanent discontinuation but continued treatment; 3) patients who received the wrong investigational product; 4) patient who received an overdose (more than 4 tables of IP per day); 5) patients who received

Reference ID: 4689224

prohibited concomitant medication[4] and 6) patients who were randomized but did not receive IP.

Patients with protocol violations were not excluded from efficacy or safety analysis.

A total of 10% of patients had at least 1 important protocol violation (Table 4). Most of the protocol violations were in the category of prohibited concomitant medication (ticagrelor: 7.7% vs placebo: 7.9%). The most common prohibited medication administered in violation of the protocol were platelet aggregation inhibitors excluding heparin. Given the relatively low percentage of individual key protocol violations that occurred at similar frequencies between the arms, it is unlikely that such violations significantly impacted the study results.

Table 4: Important protocol deviations, full analysis set

Important protocol deviations	Ticagrelor (n = 5523)	Placebo (n = 5493)
Number of patients with at least 1 important deviation[1]	519 (9.4%)	535 (9.7%)
Patients who were randomized but did not meet all inclusion criteria or fulfilled any exclusion criteria	93 (1.7%)	89 (1.6%)
Patient developed criteria for permanent discontinuation of investigational product, but IP was continued	5 (<0.1%)	9 (0.2%)
Patient received the wrong investigational product	1 (<0.1%)	3 (<0.1%)
Patient received an overdosed IP (more than 4 tablets of IP per day)	0 (0%)	2 (<0.1%)
Patient received prohibited concomitant medication	426 (7.7%)	435 (7.9%)
Patient was randomized but took no IP	22 (0.4%)	26 (0.5%)

Source: adprodev**; Software:** R

Abbreviations: IP, Investigational Product

[1]Patients may have more than one important deviation

Demographic Characteristics

The baseline demographics and anthropometric variables were similar between the arms (Table 5). The THALES trial population was mainly male (61%). The mean and median age of the

[4]Prohibited concomitant medications were: antiplatelet agents other than ASA (e.g., GPIIb/IIIa inhibitors, clopidogrel, ticlopidine), anticoagulants (e.g., warfarin, oral thrombin and factor Xa inhibitors), strong CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin) and traditional/herbal medication known to have antiplatelet or anticoagulant properties.

patient population was 65 years. The patient population were ex-US with 51% of the patients from Europe and 43% of the patients from Asia and Australia. A total of 54% of the patients in the THALES trial were white and Asian (43%) was the second most represented race. Less than 1% of the patient population studied was in African Americans.

Table 5: Baseline Demographic Characteristics

	Ticagrelor (N=5523)	Placebo (N=5493)	All (N=11016)
Sex			
Male	3415 (62%)	3322 (60%)	6737 (61%)
Female	2108 (38%)	2171 (40%)	4279 (39%)
Age[1]	65 (11.0); (n=5523)	65 (11.1); (n=5493)	65 (11.0); (n=11016)
< 65	2676 (48%)	2632 (48%)	5308 (48%)
[65, 75)	1654 (30%)	1674 (30%)	3328 (30%)
≥ 75	1193 (22%)	1187 (22%)	2380 (22%)
Baseline Weight (kg) [1]	73 (15.3); (n=5498)	73 (15.3); (n=5461)	73 (15.3); (n=10959)
Baseline Height (cm) [1]	166 (8.9); (n=5495)	166 (8.9); (n=5460)	166 (8.9); (n=10955)
Baseline BMI (kg/m^2) [1]	26.4 (4.6); (n=5493)	26.3 (4.6); (n=5455)	26.4 (4.6); (n=10948)
BMI < 30	4446 (80%)	4429 (81%)	8875 (81%)
BMI ≥ 30	1047 (19%)	1026 (19%)	2073 (19%)
Missing BMI	30 (<1%)	38 (<1%)	68 (<1%)
Geographical Region			
Europe	2814 (51%)	2803 (51%)	5617 (51%)
Central and South America	324 (6%)	323 (6%)	647 (6%)
Asia and Australia	2373 (43%)	2356 (43%)	4729 (43%)
North America (Only Canada)	12 (<1%)	11 (<1%)	23 (<1%)
Race			
White	2973 (54%)	2948 (54%)	5921 (54%)
Black or African American	21 (<1%)	32 (<1%)	53 (<1%)
Asian	2353 (43%)	2339 (43%)	4692 (43%)
Other	176 (3%)	174 (3%)	350 (3%)
Ethnicity			
Hispanic or Latino	517 (9%)	504 (9%)	1021 (9%)

Not Hispanic or Latino	5006 (91%)	4989 (91%)	9995 (91%)

1: Means and standard deviation are on the first line; n=Number of non-missing observations
All other variables are counts and percentages relative to N.
Abbreviations: BMI=body mass index; ASA= acetylsalicylic acid; N=total number of patients randomized
[Source: Statistical Reviewer]

Other Baseline Characteristics

The baseline diagnosis and severity of the index stroke event were similar between treatment arms (Table 6).

Table 6: Baseline Index Event

	Ticagrelor (N=5523)	Placebo (N=5493)	All (N=11016)
Diagnosis of Index Event			
TIA	491 (9%)	540 (10%)	1031 (9%)
ACT	5032 (91%)	4953 (90%)	9985 (91%)
NIHSS Total Score			
< 3	2629 (48%)	2610 (48%)	5239 (48%)
4, 5	1681 (30%)	1646 (30%)	3327 (30%)
> 5	2 (<1%)	-	2 (<1%)
Persistent signs or symptoms	4905 (89%)	4798 (87%)	9703 (88%)
Acute ischaemic brain lesion	2510 (45%)	2490 (45%)	5000 (45%)
Missing	39 (<1%)	48 (<1%)	87 (<1%)
ABCD^2 Total Score			
≤ 5	60 (1%)	71 (1%)	131 (1%)
6	377 (7%)	395 (7%)	772 (7%)
7	54 (<1%)	74 (1%)	128 (1%)
Symptomatic intracranial arterial occlusive disease [a]	42 (<1%)	40 (<1%)	82 (<1%)
Internal carotid arterial occlusive disease [b]	71 (1%)	73 (1%)	144 (1%)
Index Event rel to randomization (hrs)			
≤ 6	524 (9%)	535 (10%)	1059 (10%)
(6, 12]	1289 (23%)	1242 (23%)	2531 (23%)
(12, 18]	1298 (24%)	1386 (25%)	2684 (24%)

(18, 24]	2407 (44%)	2327 (42%)	4734 (43%)
> 24	5 (<1%)	3 (<1%)	8 (<1%)
Missing	-	-	-
Index Event rel to onset of loading dose (hrs)			
≤ 6	439 (8%)	435 (8%)	874 (8%)
(6, 12]	1266 (23%)	1261 (23%)	2527 (23%)
(12, 18]	1272 (23%)	1310 (24%)	2582 (23%)
(18, 24]	2420 (44%)	2360 (43%)	4780 (43%)
> 24	81 (1%)	80 (1%)	161 (1%)
Missing	45 (<1%)	47 (<1%)	92 (<1%)

a: Stenosis ≥ 50% in intracranial artery supplying the ischemic field known at randomization
b**: Stenosis ≥ 50% in carotid artery supplying the ischemic field known at randomization**
Counts and percentages relative to N are presented.
Abbreviations: NIHSS=National Institutes of Health Stroke Scale; ASA= acetylsalicylic acid
[Source: Statistical Reviewer]

Baseline disease characteristics were similar between treatment arms (Table 7).

Table 7: Baseline Disease Characteristics, THALES

	Ticagrelor (N=5523)	**Placebo (N=5493)**	**All (N=11016)**
Smoking Status			
Current Smoker	1504 (27%)	1428 (27%)	2932 (27%)
Former Smoker	980 (18%)	925 (18%)	1905 (17%)
Angina Pectoris	192 (3%)	205 (3%)	397 (4%)
Atrial Fibrillation	5 (<1%)	7 (<1%)	12 (<1%)
Cerebrovascular Accident Nos	2 (<1%)	-	2 (<1%)
Chronic Kidney Disease	196 (4%)	228 (4%)	424 (4%)
Congestive Heart Failure	207 (4%)	204 (4%)	411 (4%)
Coronary Artery Bypass Grafting	38 (<1%)	42 (<1%)	80 (<1%)
Coronary Artery Disease	452 (8%)	459 (8%)	911 (8%)

Dyslipidaemia	2098 (38%)	2049 (38%)	4147 (38%)
Haemorrhagic Stroke	8 (<1%)	3 (<1%)	11 (<1%)
Hypertension	4298 (78%)	4222 (78%)	8520 (77%)
Ischemic Stroke	901 (16%)	914 (16%)	1815 (16%)
Myocardial Infarction	169 (3%)	177 (3%)	346 (3%)
Percutaneous Coronary Intervention	112 (2%)	117 (2%)	229 (2%)
Peripheral Arterial Occlusive Disease	102 (2%)	102 (2%)	204 (2%)
Transient Ischemic Attack	275 (5%)	240 (5%)	515 (5%)
Type 1 Diabetes Mellitus	32 (<1%)	36 (<1%)	68 (<1%)
Type 2 Diabetes Mellitus	1557 (28%)	1521 (28%)	3078 (28%)

Abbreviations: ASA= acetylsalicylic acid
[Source: Statistical Reviewer]

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Recordings of concomitant medications were made at the randomization visit, 1 week (±2 days), day 30 – 34 (end of treatment) and day 60 – 64 (end of follow-up period).

Antithrombotic and selected non-antithrombotic medication affecting stroke risk factors were balanced between treatment groups at baseline (Table 8) and post-baseline (Table 9). There was a notable increase in medication affecting stroke risk factors from baseline to post-baseline, e.g. an increase in anti-hypertensives of ~38% to ~74%, and use of proton pump inhibitors which was similar across both treatment arms and observed across all regions in THALES (Table 6 in Applicability of Foreign Data). The increase in concomitant medications is not expected to impact study results interpretation because it is balanced across treatment arms.

Compliance with study drug was evenly distributed between the two arms of the study (Table 10). The mean compliance was 99% (standard deviation of 50%). 91% of the full analysis set were >80% compliant with study drug and 85% were >90% compliant.

Table 8: Concomitant medication during baseline, full analysis set

Category[1]	**Ticagrelor (n=5523)**	**Placebo (n=5493)**
Antiplatelets	822 (14.9%)	749 (13.6%)
ASA	754 (13.7%)	678 (12.3%)

Reference ID: 4689224

Category[1]	Ticagrelor (n=5523)	Placebo (n=5493)
ASA (any dose)	754 (13.7%)	678 (12.3%)
ADP receptor blocker	76 (1.4%)	75 (1.4%)
Clopidogrel	75 (1.4%)	75 (1.4%)
Antihypertensives	2135 (38.7%)	2117 (38.5%)
ACE inhibitor	836 (15.1%)	825 (15%)
ARB blocker	735 (13.3%)	741 (13.5%)
Beta blockers	741 (13.4%)	735 (13.4%)
Calcium channel blockers	792 (14.3%)	783 (14.3%)
Nitrates	67 (1.2%)	64 (1.2%)
Other	467 (8.5%)	448 (8.2%)
Lipid lowering agents	921 (16.7%)	933 (17%)
Statins	865 (15.7%)	879 (16%)
Other	94 (1.7%)	105 (1.9%)
Blood glucose lowering drugs	965 (17.5%)	956 (17.4%)
Insulin	241 (4.4%)	257 (4.7%)
Other	859 (15.6%)	853 (15.5%)
Proton pump inhibitors	403 (7.3%)	406 (7.4%)

Source: adcm**; Software:** R

Abbreviations: ASA, Acetylsalicylic acid; ADP, adenosine diphosphate; ACE, Angiotensin converting enzyme; ARB, Angiotensin II receptor

[1]At least one dose 2-7 days prior to randomization, only including rows with at least 100 patients combined across treatment groups

Table 9: Concomitant medication during study, full analysis set

Category[1]	Ticagrelor (n=5523)	Placebo (n=5493)
Antiplatelets	5508 (99.7%)	5469 (99.6%)
ASA	5501 (99.6%)	5464 (99.5%)
ASA (any dose)	5501 (99.6%)	5464 (99.5%)
ASA (>150 mg)	130 (2.4%)	130 (2.4%)
ADP receptor blocker	213 (3.9%)	228 (4.2%)

Reference ID: 4689224

Category[1]	Ticagrelor (n=5523)	Placebo (n=5493)
Clopidogrel	207 (3.7%)	224 (4.1%)
Alprostadil	132 (2.4%)	130 (2.4%)
Heparin	496 (9%)	489 (8.9%)
Direct thrombin inhibitors	49 (0.9%)	54 (1%)
Direct Xa inhibitors	64 (1.2%)	59 (1.1%)
Antihypertensives	4122 (74.6%)	4057 (73.9%)
ACE inhibitor	1969 (35.7%)	1904 (34.7%)
ARB blocker	1521 (27.5%)	1554 (28.3%)
Beta blockers	1217 (22%)	1171 (21.3%)
Calcium channel blockers	1788 (32.4%)	1761 (32.1%)
Nitrates	131 (2.4%)	125 (2.3%)
Other	945 (17.1%)	882 (16.1%)
Lipid lowering agents	4643 (84.1%)	4602 (83.8%)
Statins	4608 (83.4%)	4567 (83.1%)
Other	171 (3.1%)	161 (2.9%)
Blood glucose lowering drugs	1517 (27.5%)	1526 (27.8%)
Insulin	590 (10.7%)	640 (11.7%)
Other	1336 (24.2%)	1332 (24.2%)
Proton pump inhibitors	2430 (44%)	2403 (43.7%)

Source: adcm**; Software:** R

Abbreviations: ASA, Acetylsalicylic acid; ADP, adenosine diphosphate; ACE, Angiotensin converting enzyme; ARB, Angiotensin II receptor

[1]Excluding day of randomization, only including rows with at least 100 patients combined across treatment groups

Table 10: Study treatment compliance, full analysis set

Compliance (%) with study drug[1]	Ticagrelor (n=5523)	Placebo (n=5493)
Mean (SD)	98.5 (43.1)	99.4 (55.8)
Median	98	99
Compliance > 80%[2]	91.5	90.9

Compliance (%) with study drug[1]	Ticagrelor (n=5523)	Placebo (n=5493)
Compliance > 90%[2]	85.2	85.1

Source: adsl**; Software:** R

Abbreviations: SD, Standard Deviation

[1]Compliance is defined as 100 * estimated number of pills / planned number of pills taken

[2]Patients with missing data are counted as not meeting compliance threshold

Efficacy Results – Primary Endpoint

A total of 303 patients (5.5%) in the ticagrelor arm and 362 subjects (6.6%) in the placebo arm experienced a primary endpoint (Table 11). The estimated HR comparing ticagrelor arm with placebo was 0.8 (95% CI: 0.71, 0.96; p=0.015), with an observed separation in the Kaplan Meier curves early in the study (Figure 2). The primary results were driven by stroke (HR: 0.8; 95% CI: 0.69, 0.95; p=0.008) (Figure 8). There were numerical trends in risk of death in the ticagrelor arm relative to placebo arm (Figure 9).

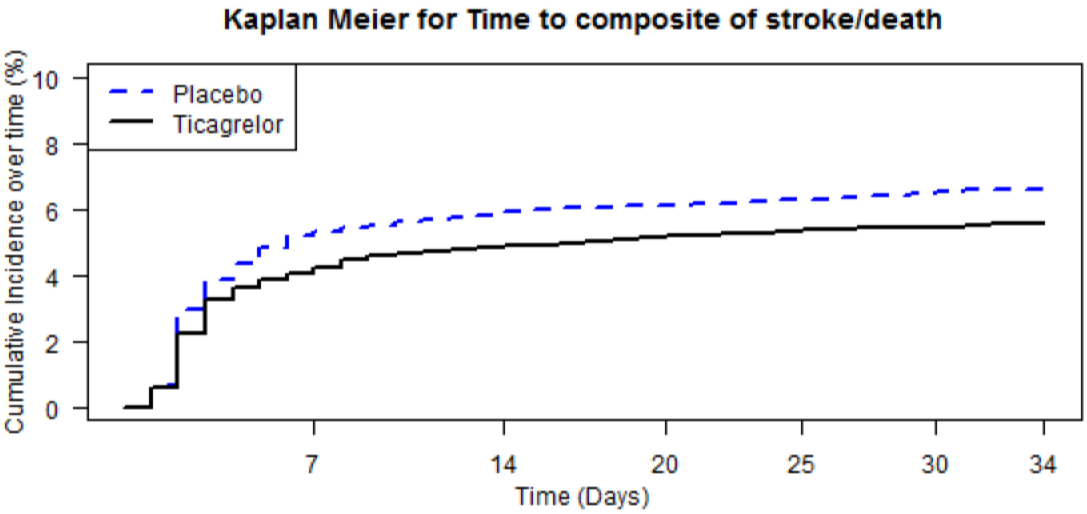
At Day 30, the estimated incidence rate of composite stroke and/or death was 5.44% and 6.52% in the ticagrelor arm and placebo arm respectively. The estimated risk difference comparing ticagrelor arm with placebo was -1.1% (95% CI: -1.97%, -0.2%).

Table 11: Primary Efficacy Endpoint Results and its Components

	Events (% relative to N)			Incidence Rate (%)[1]		
	Ticagrelor (N=5543)	Placebo (N=5493)	HR (95% CI); p-value	Ticagrelor (N=5543)	Placebo (N=5493)	RD (95% CI)
Time to Composite Stroke/ Death	303 (5.5%)	362 (6.6%)	0.8 (0.71, 0.96); 0.02	5.44%	6.52%	-1.1 (-1.97, -0.20)
Time to Stroke	284 (5.1%)	347 (6.3%)	0.8 (0.69, 0.95); 0.008	5.12%	6.25%	-1.1 (-2.00, -0.27)
Time to Death	36 (0.7%)	27 (0.5%)	1.3 (0.81, 2.19); 0.3	0.62%	0.47%	0.1 (-0.13, 0.42)

1: Incidence rate is based on the Kaplan Meier Estimate at Day 30
Abbreviations: HR=hazard ratio; RD=risk difference; N= total number of patients in the FAS; FAS=full analysis set
[Source: Statistical Reviewer]

Figure 2: Kaplan Meier Curve for the Primary Efficacy Endpoint



Number of Events						
Placebo	290	324	336	345	358	362
Ticagrelor	233	269	287	297	300	303
Number at Risk						
Placebo	5204	5165	5146	5138	5126	1135
Ticagrelor	5289	5243	5227	5215	5209	1091
Cumulative Incidence (%)						
$\hat{F}_{Placebo}$	5.28	5.90	6.12	6.28	6.52	6.69
$\hat{F}_{Ticagrelor}$	4.22	4.88	5.20	5.38	5.44	5.52

Abbreviations: F=cumulative incidence
[Source: Statistical Reviewer]

There was only one patient without a vital status, therefore a tipping point analysis was not conducted during the review.

Data Quality and Integrity

The Applicant submitted all versions of their protocol amendments, SAP, and their Data Monitoring Charter, Executive Committee Charter, and Data Management Plan for review (Table 12). The documents submitted were considered adequate for review.

Table 12: Summary of the Dates of the Initial and Final Versions of the Relevant Documents

	Date of Initial Version	Date of Final Version
Protocol	February 8, 2017	May 08, 2019
Statistical Analysis Plan	February 09, 2017	December 09, 2019
Data Monitoring Charter	January 29, 2018	November 20, 2019
Executive Committee Charter	December 15, 2017	November 20, 2019
Data Management Plan	January 11, 2018	January 16, 2020

[Source: Statistical Reviewer]

The first patient was enrolled on January 22, 2018 and the last visit of the last patient took place on December 13, 2019. The DMC met five times during the study, including the organizational meeting. The unblinded interim analysis was conducted during the 4th DMC meeting on July 17, 2019, based on accrued data through June 28, 2019 specified in the Data Management Plan. The DMC recommended the decision to continue the study as planned. The database lock for the THALES was conducted on January 16, 2020.

During the review, the statistical reviewer identified the following concerns with the interim analysis. It was noted that the prespecified interim analysis and the maximum event size of the study were revised several times during the conduct of the study (Table 13). This raised potential concerns on whether there was any potential knowledge of interim results that could have used to make these proposed changes during the study.

To address concerns on whether these changes could have been due to such knowledge of interim results, the following steps were taken.

1. The statistical reviewer noted that these changes and justifications were documented early in the open session of the DMC meeting minutes. Specifically, the meeting highlighted issues on enrolment challenges after study initiated, ongoing knowledge of results from other studies, and changing clinical guidelines. Modifications to the interim analysis were based on external sources of data.
2. These proposed changes were made prior to the planned interim analysis and presented during the open session of the DMC meetings prior to the planned interim analysis. The interim analysis was later finalized on May 27, 2019 in the SAP, prior to the scheduled interim analysis.
3. The Data Management Plan included adequate firewalls to limit any potential unblinding of interim analysis results between the teams and the study investigators. Therefore, the changes to the interim stopping rule prior to the interim analysis were considered acceptable and not due to potential knowledge of study results.

4. In addition, there were no changes to the planned statistical analyses for the primary and key secondary endpoints after the scheduled interim analysis.

In summary, the revisions to the interim analysis were considered appropriate. Therefore, the final version of the SAP is considered acceptable.

Table 13: Summary of SAP versions and the Respective Changes to the Planned Monitoring Rule

Version	Date	# of subjects	Interim Events	Planned Events	Power	Hazard Ratio	α at Final Analysis	Enrolled	Actual # of Events
1 [1]	February 09, 2017	13000	462	770	85%	0.8	4.76%	-	-
2 [1]	December 14, 2017	13000	462	770	85%	0.8	4.76%	-	-
3 [2]	June 11, 2018	13000	458	764	85%	0.805	4.988%	1629	73
4 [2]	May 27, 2019	11000	453	647	90%	0.775	4.996%	8430	480
5 [2]	December 09, 2019	11000	453	647	90%	0.775	4.996%	11016	665

1: Monitoring boundary is pre-specified using a Lan-Demets-OBF alpha spending function
2: Monitoring boundary is pre-specified using a Haybittle-Peto alpha spending function
Abbreviations: OBF=O'Brien Fleming boundary
[Source: Statistical Reviewer]

The datasets for THALES clinical trials were submitted in both study data tabulation model (SDTM) and analysis dataset model (ADaM) formats. The datasets were appropriately organized and well-documented. The analysis datasets included both derived and enriched data (such as formatted variables, derived endpoint, etc.). The statistical reviewer was able to produce the results on the primary endpoints and key secondary endpoints per the statistical analysis plan.

In summary, the data quality and study conduct were considered appropriate.

Efficacy Results – Secondary and other relevant endpoints

Key Secondary Endpoints

The results for the key secondary endpoint, time to ischemic stroke was consistent with the primary efficacy endpoint. There was a statistically significant reduction in the risk of ischemic stroke comparing ticagrelor arm with placebo with an estimated HR of 0.8 (95% CI: 0.68, 0.93; p=0.004) (Table 14). At Day 30, the incidence rate of ischemic stroke was 5.0% and 6.2% in the ticagrelor and placebo arm respectively, with an estimated risk difference of 1.2% lower (95%CI: -2.1, -0.4) on the absolute scale in ticagrelor arm relative to placebo arm (Figure 3).

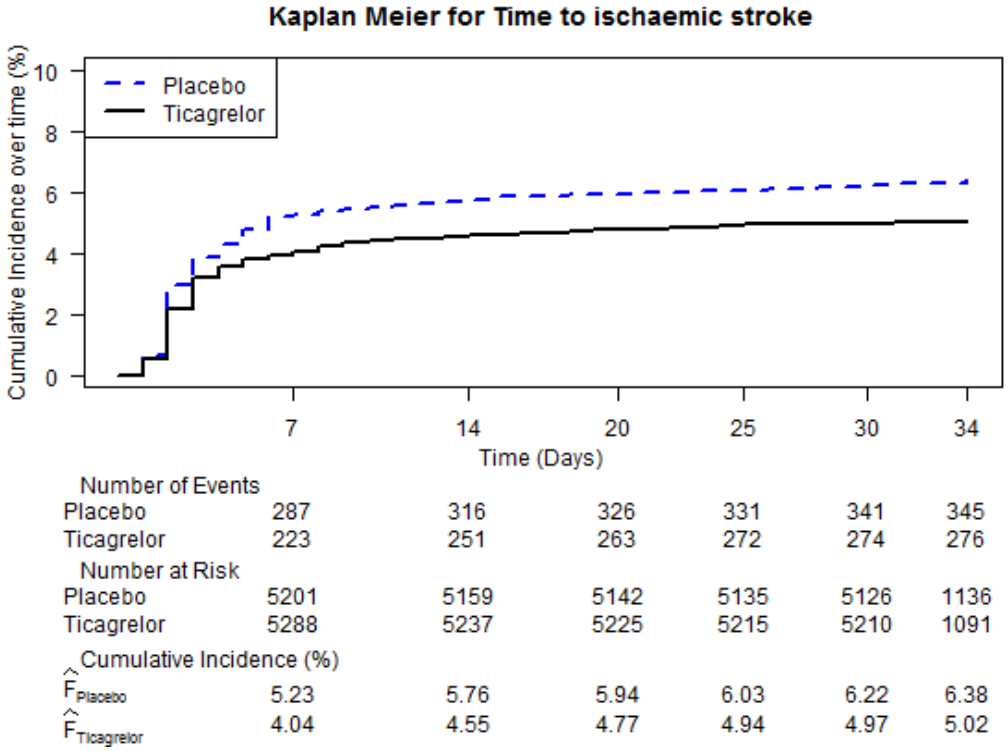
The clinical reviewer notes that there were only few ischemic strokes that where associated with a hemorrhagic transformation (one in ticagrelor and three in placebo). Also, there were more hemorrhagic strokes in the ticagrelor group (10 vs 2), of which the majority were fatal (8/10 in ticagrelor and 1/2 in placebo).

Table 14: Time to Ischemic Stroke Endpoint

Events (% relative to N)			Incidence Rate (%) [1]		RD (95% CI)
Ticagrelor (N=5543)	Placebo (N=5493)	HR (95% CI); p-value	Ticagrelor (N=5543)	Placebo (N=5493)	
276 (5.0%)	345 (6.3%)	0.8 (0.68, 0.93); 0.004	5.0%	6.2%	-1.2 (-2.10, -0.38)

1: Incidence rate is based on the Kaplan Meier Estimate at Day 30
Abbreviations: HR=hazard ratio; RD=risk difference; CI=confidence interval; N=total randomized in the FAS set; FAS=full analysis set
[Source: Statistical Reviewer]

Figure 3: Kaplan Meier Curve for the Time to Ischemic Stroke



[Source: Statistical Reviewer]

Proportion of patients with mRS > 1

Based on the Applicant's prespecified analysis, the proportion of patients with a mRS score > 1 for ticagrelor (23.8%) and placebo (24.1%) were numerically similar and the OR was 0.98 (95% CI: 0.89, 1.07; p=0.61) (Table 15). This result was not statistically significant. The proportion of patients without a mRS score at Visit 3 was less than 2%.

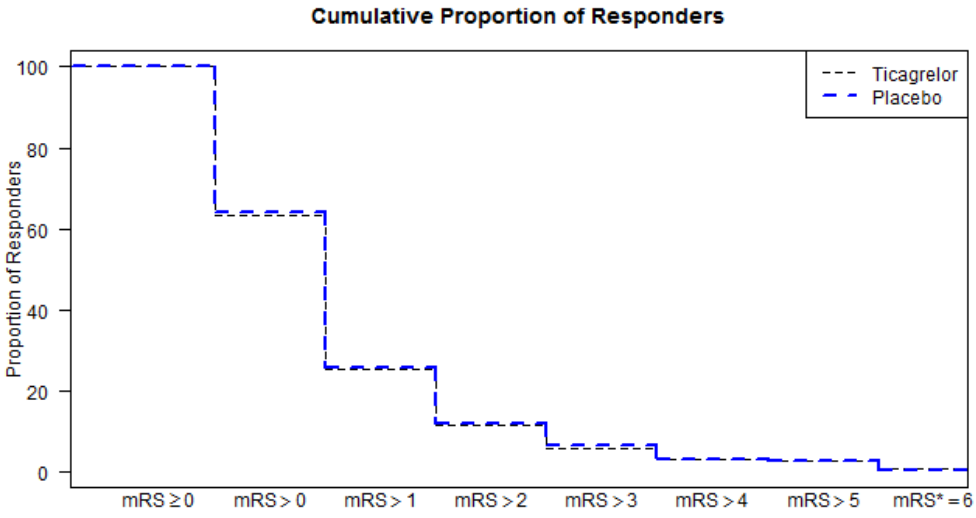
Table 15: Proportion of Patients with mRS Score > 1

	Ticagrelor (N=5543)	Placebo (N=5493)	OR (95% CI); p-value [3]	Difference in Proportions [4]
mRS>1[1]	1287/5386 (23.8%)	1290/5333 (24.1%)	0.98 (0.89, 1.07); p=0.61	0.25% (-1.36%, 1.85%)
mRS≤1[1]	4136/5386 (76.2%)	4090/5333 (75.9%)		
Missing[2]	100 (1.8%)	113 (2.1%)		

1: Counts/number of patients with a mRS score at Visit 3 and percentages relative to patients with mRS score
2: Counts and percentages relative to N
3: Odds ratios, respective 95% CI, and Wald-based p-value from a logistic regression fit to the binary endpoint of mRS > 1 adjusting for treatment group, history of stroke, and baseline NIHSS score. Applicant's pre-specified analysis in the SAP
4: Difference in proportion and respective 95% CI using normal approximation to difference in binomial proportions. Post-hoc analysis conducted by the Statistical Reviewer
Abbreviations: OR=odds ratio; CI=confidence intervals; NIHSS=National Institute of Health Stroke Scale; mRS=modified Rankin score; SAP=statistical analysis plan; N=total randomized in the FAS set; FAS=full analysis set
[Source: Statistical Reviewer]

In a supportive analysis, the statistical reviewer included the cumulative responder curves for the proportion of patients with mRS greater than some value. Patients with missing mRS score were assigned conservatively to be a value greater than five but not six. However, the proportion of patients without mRS at Day 30 were small and this did not impact the findings from the Applicant. In summary, there was a lack of separation between the two treatment arms (Figure 4).

Figure 4: Cumulative Proportion of patients with mRS Score > X



Number (%)								
Ticagrelor	5523 (100.0%)	3503 (63.4%)	1387 (25.1%)	632 (11.4%)	325 (5.9%)	157 (2.8%)	136 (2.5%)	36 (0.7%)
Placebo	5493 (100.0%)	3529 (64.2%)	1403 (25.5%)	648 (11.8%)	346 (6.3%)	164 (3.0%)	140 (2.5%)	27 (0.5%)

Source: Statistical Reviewer
Abbreviations: mRS=modified Rankin Score

Relevant Safety Endpoints

The results for the time to safety endpoints based on the FAS dataset are presented in Table 16. In particular, the risk of GUSTO Severe bleeding comparing ticagrelor arm with placebo at Day 30 was 0.38 (95% CI: 0.17, 0.59) (Figure 11). At Day 30, the remaining safety endpoints showed a consistent increase in risk, precluded 0 in absence of multiplicity, comparing patients on ticagrelor with placebo, consistent with the safety profile of ticagrelor. The reader is deferred to the Safety Section for additional details of the events (Section 9).

Reference ID: 4689224

Table 16: Results for the Time to Safety Exploratory Endpoints using the FAS dataset

	Events			Incidence Rate [1]		
Time to Events	Ticagrelor (N=5543)	Placebo (N=5493)	HR (95% CI);	Ticagrelor (N=5543)	Placebo (N=5493)	RD (95% CI)
GUSTO Severe	28 (0.51%)	7 (0.13%)	4.0 (1.74, 9.14)	0.51%	0.13%	0.38 (0.17, 0.59)
GUSTO Moderate/Severe	35 (0.63%)	10 (0.18%)	3.5 (1.73, 7.06)	0.64%	0.18%	0.45 (0.21, 0.69)
Intracranial haemorrhage /Fatal bleeding	22 (0.40%)	6 (0.11%)	3.7 (1.48, 9.02)	0.40%	0.11%	0.29 (0.10, 0.48)
Fatal bleeding	11 (0.20%)	2 (0.04%)	5.5 (1.21, 24.7)	0.20%	0.04%	0.16 (0.03, 0.29)
Intracranial haemorrhage	20 (0.36%)	6 (0.11%)	3.3 (1.34, 8.28)	0.36%	0.11%	0.25 (0.07, 0.44)
Haemorrhagic stroke	10 (0.18%)	2 (0.04%)	5.0 (1.09, 22.7)	0.18%	0.04%	0.15 (0.02, 0.27)
Premature discontinuation due to bleeding	152 (2.75%)	32 (0.6%)	4.8 (3.28, 7.02)	2.95%	0.63%	2.32 (1.81, 2.83)

1: Incidence rate is based on the Kaplan Meier Estimate at Day 30 multiplied by 100%

Abbreviations: N=total randomized in the full analysis set; HR=hazard ratio; RD=risk difference; CI=confidence interval; FAS=full analysis set; GUSTO=Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries
Source: Statistical Reviewer

Dose/Dose Response

Not applicable.

Durability of Response

Not applicable.

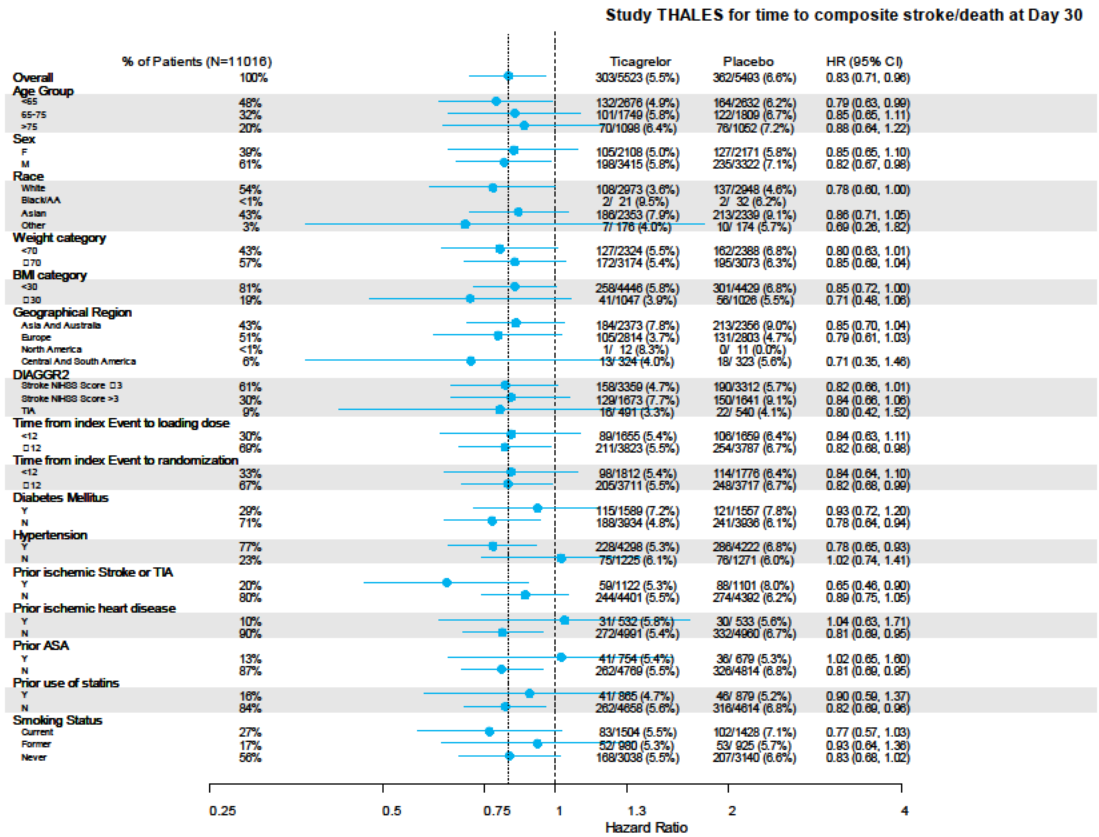
Persistence of Effect

Not applicable.

Additional Analyses Conducted on the Individual Trial

In summary, subgroup analyses by demographics and disease characteristics of interest were consistent with findings in the overall population based on the time to composite stroke and death (Figure 5).

Figure 5: Subgroup Analysis for Primary Efficacy Endpoint



Abbreviations: ASA; AA=African American; BMI=body mass index; TIA=transient ischemic attack; F=female; M=male; NIHSS=National Institute of Health Stroke Scale; CI=confidence interval; HR=hazard ratio
[Source: Statistical Reviewer]

Statistical Considerations

During the review, we identified the following statistical issues

- **Evidence to support the proposed indication based on a single study conducted outside of US**

The FDA Guidance for Industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* indicates situations in which a single study of a new treatment may be combined with independent substantiation from related, supportive study data to provide evidence of effectiveness. In particular, the Guidance notes that supportive data may come from studies of a different dose or studies in a slightly different patient population, depending on the quality and outcomes of such related studies. Ticagrelor has been approved in multiple indications and there is a reasonably large safety database from related indications based on several large-scale cardiovascular studies conducted.

In this submission, the applicant conducted a single pivotal multi-center study THALES to provide evidence of ticagrelor on top of ASA as a treatment for reduction in risk of stroke in patients. The analysis of the primary endpoint of composite stroke and/or death comparing ticagrelor on top of ASA with placebo on top of ASA over 30 days showed a statistically significant effect (HR: 0.8; 95% CI: 0.71, 0.96; p=0.02). The results were driven mainly by the stroke, with numerically more deaths on ticagrelor arm compared to placebo. In addition, the study conduct, despite being ex-US, was acceptable as only one patient did not have a vital status at Day 30. The secondary endpoint, time to first ischemic stroke, was also consistent with the primary efficacy endpoint. Subgroup analysis for this primary efficacy endpoint were also consistent with the primary results.

- Adequacy of race representation in THALES

The African-American population was under-represented in THALES (< 1% of the FAS population), as well as in the antecedent trials. This is in contradiction to the current initiatives from the FDA and academic organizations to provide adequate racial / ethnic representation in clinical trials.

8. Integrated Review of Effectiveness

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

9. Review of Safety

9.1. 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. This is similar to the strategy for safety review approach for the THEMIS study (DARRTS 04/20/2020).

The applicant proposed selective safety data collection (i.e., only reporting SAEs and DAEs) and to classify all bleeding events according to the GUSTO bleeding scale (see appendix 14.1) per the investigator's assessment. This proposal was based on the documentation of the safety profile in SOCRATES (similar patient population) and findings in PLATO (dual antiplatelet therapy with ticagrelor and ASA) in patients with ACS. (IND 115807, eCTD 0434). The Division agreed to the selective safety data collection proposal at the pre-phase 3 study meeting (DARRTS 10/27/2016).

9.2. Review of the Safety Database

9.2.1. Overall Exposure

In the THALES trial, 5523 subjects received ticagrelor 90 mg bid and 5493 subjects received placebo (FAS population). There were 40 patients that were included in the FAS population, who did not receive treatment (17 and 23 randomized to ticagrelor and placebo, respectively). Additionally, there was 1 patient randomized to ticagrelor that received placebo and 3 patients randomized to placebo that received ticagrelor. Therefore, the safety population included 5508 patients in the ticagrelor arm and 5468 patients in the placebo arm.

The mean treatment duration in THALES were 28 and 29 days for ticagrelor and placebo respectively (Table 17). There were numerically more drug discontinuations in the ticagrelor arm compared to placebo, which was maintained during the treatment duration (initial 30 days) with no difference during follow-up (Figure 6).

Table 17: Duration of Exposure, Safety Population

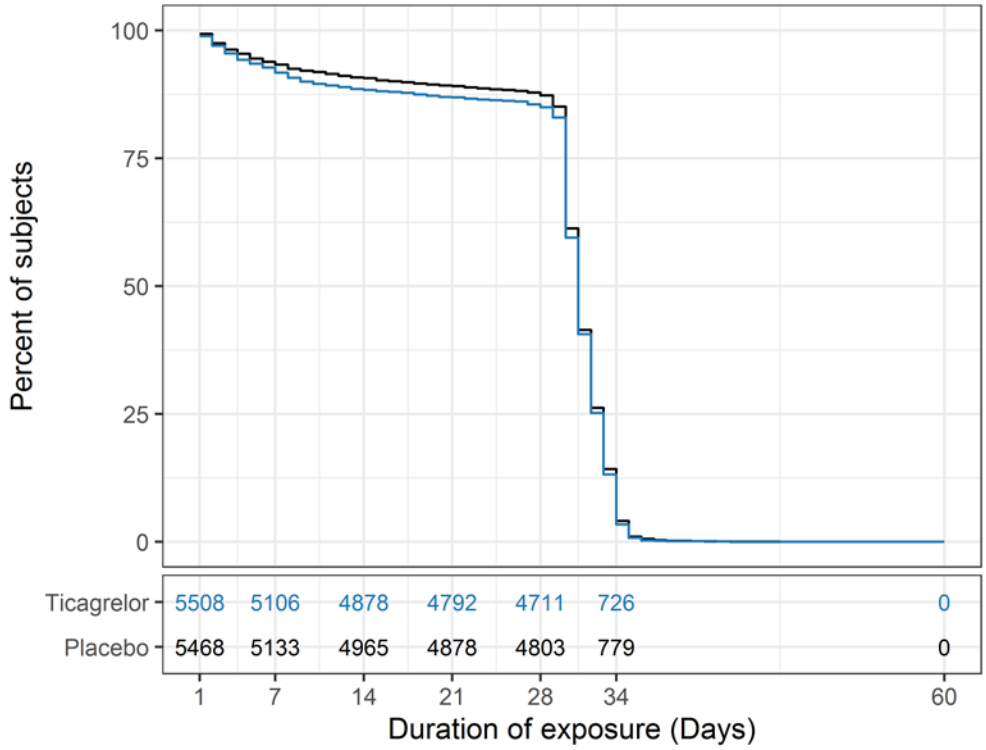
Parameter	Ticagrelor n = 5508	Placebo n = 5468
Duration of treatment, days		
Mean (SD)	28.3 (8.7)	28.9 (8.0)
Median (1st, 3rd Quartile)	31.0 (30.0, 33.0)	31.0 (30.0, 33.0)

Parameter	Ticagrelor n = 5508	Placebo n = 5468
Range	1.0, 58.0	1.0, 46.0

Source: adex.xpt**; Software:** R

Abbreviations: N, number of patients in treatment arm; SD, Standard Deviation

Figure 6: Duration of Exposure, Safety Population



Source: adex.xpt and R

9.3. Safety Results

9.3.1. Adverse Events

As noted in the study report for THALES (e.g., see footnote for Table 26) there was one hemorrhagic stroke in the ticagrelor group (patient (b) (6)) that was reported as a GUSTO severe bleeding, but not included in the ICH category. In all analysis presented in this section, this event has been relabeled as an ICH bleed.

Treatment emergent adverse events for the safety population are shown in Table 18. Bleeding was more frequent in the ticagrelor arm (5.1%) compared to the placebo arm (1.2%).

There were more adverse events that led to discontinuation in the ticagrelor arm (9.7% vs 7.6%), a breakdown by preferred term is provided in Table 19. Differences between treatment arms were observed for adverse events that are consistent with ticagrelor's mechanism of action (i.e., bleeding events) and dyspnea.

A numerically higher rate of death was observed in this study in the ticagrelor arm (n=38 (0.7%) vs n=31 (0.6%)). The incidence of SAEs were overall similar between the two arms. SAEs overall and by preferred term is presented in Table 20 and appear consistent with ticagrelor's safety profile (i.e., associated with bleeding events).

Table 18: Treatment Emergent Adverse Events, Safety Population

Event	Ticagrelor n = 5508	Placebo n = 5468
SAE	574 (10.4%)	610 (11.2%)
SAEs with fatal outcome	38 (0.7%)	31 (0.6%)
SAEs associated with bleeding[2]	69 (1.3%)	23 (0.6%)
AE leading to discontinuation	534 (9.7%)	416 (7.6%)
Any bleed (serious and nonserious)	282 (5.1%)	64 (1.2%)

Source: adae.xpt; **Software:** R

Abbreviations: AE, Adverse Event; SAE, Serious Adverse Event

[1]Treatment emergent AE defined as including up to last day of treatment plus 7 days.

[2]Bleeding SAE defined as GUSTO severe bleeding or belonging to narrow 'Hemorrhage' FMQ version 2020/01/29

Table 19: Patients with AE leading to Discontinuation, Safety Population

Preferred Term	Ticagrelor n = 5508	Placebo n = 5468
Any DAE	534 (9.7%)	416 (7.6%)
Ischaemic stroke	84 (1.5%)	126 (2.3%)
Atrial fibrillation	70 (1.3%)	70 (1.3%)
Dyspnoea	57 (1%)	10 (0.2%)
Ecchymosis	24 (0.4%)	2 (<0.1%)
Epistaxis	20 (0.4%)	1 (<0.1%)
Haematuria	15 (0.3%)	3 (0.1%)
Haemorrhagic transformation stroke	12 (0.2%)	8 (0.1%)

Preferred Term	Ticagrelor n = 5508	Placebo n = 5468
Transient ischaemic attack	7 (0.1%)	9 (0.2%)
Spontaneous haematoma	7 (0.1%)	0 (0.0)
Pulmonary embolism	7 (0.1%)	4 (0.1%)
Increased tendency to bruise	7 (0.1%)	0 (0.0)
Gingival bleeding	7 (0.1%)	1 (<0.1%)
Palpitations	6 (0.1%)	0 (0.0)
Gastrointestinal haemorrhage	6 (0.1%)	2 (<0.1%)
Dizziness	6 (0.1%)	4 (0.1%)
Carotid artery stenosis	6 (0.1%)	4 (0.1%)
Spontaneous haemorrhage	5 (0.1%)	0 (0.0)
Rectal haemorrhage	5 (0.1%)	3 (0.1%)
Haematoma	5 (0.1%)	1 (<0.1%)
Chest discomfort	5 (0.1%)	1 (<0.1%)
Cerebral infarction	5 (0.1%)	2 (<0.1%)
Diarrhoea	4 (0.1%)	7 (0.1%)
Rash	3 (0.1%)	5 (0.1%)
Nausea	1 (<0.1%)	5 (0.1%)
Deep vein thrombosis	1 (<0.1%)	5 (0.1%)

Source: adae.xpt (MedDRA version 22.1)**; Software:** R

Abbreviations: DAE, Premature permanent discontinuation of investigational product due to adverse event

[1]Table includes all preferred term with ≥ 5 events in either treatment group.

Table 20: Patients with Treatment Emergent SAE, Safety Population

Preferred Term	Ticagrelor n = 5508	Placebo n = 5468
Any SAE	574 (10.4%)	610 (11.2%)
Ischaemic stroke	251 (4.6%)	325 (5.9%)
Pneumonia	25 (0.5%)	27 (0.5%)
Atrial fibrillation	18 (0.3%)	15 (0.3%)
Transient ischaemic attack	16 (0.3%)	31 (0.6%)
Haemorrhagic transformation stroke	8 (0.1%)	5 (0.1%)

Preferred Term	Ticagrelor n = 5508	Placebo n = 5468
Haematuria	8 (0.1%)	1 (<0.1%)
Carotid artery stenosis	8 (0.1%)	8 (0.1%)
Pulmonary embolism	7 (0.1%)	5 (0.1%)
Haemorrhagic stroke	7 (0.1%)	1 (<0.1%)
Gastrointestinal haemorrhage	7 (0.1%)	4 (0.1%)
Epistaxis	6 (0.1%)	0 (0.0)
Cerebrovascular accident	6 (0.1%)	7 (0.1%)
Urinary tract infection	5 (0.1%)	7 (0.1%)
Upper gastrointestinal haemorrhage	5 (0.1%)	1 (<0.1%)
Hypertensive crisis	5 (0.1%)	4 (0.1%)
Hypertension	5 (0.1%)	5 (0.1%)
Epilepsy	5 (0.1%)	2 (<0.1%)
Cerebral infarction	5 (0.1%)	7 (0.1%)
Ischaemic cerebral infarction	4 (0.1%)	6 (0.1%)
Acute myocardial infarction	4 (0.1%)	5 (0.1%)
Sepsis	2 (<0.1%)	5 (0.1%)

Source: adae.xpt (MedDRA version 22.1)**; Software:** R

Abbreviations: SAE, Serious Adverse Event

[1]Treatment emergent AE defined as including up to last day of treatment plus 7 days.

[2]Defined as any untoward medical occurrence that, results in death, is immediately life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, is a congenital anomaly or birth defect or is an important medical event that may jeopardize the patient and may require medical intervention to prevent one of the outcomes listed before.

[3]Table includes all preferred term with ≥ 5 events in either treatment group.

There was a low incidence of fatal bleeds (ticagrelor: n=9; placebo: n=1), which were driven by hemorrhagic strokes (Table 21).

Table 21: Treatment Emergent Fatal Bleeds, Safety Population

Event	Ticagrelor n = 5508	Placebo n = 5468
Fatal bleeds	9 (0.2%)	1 (<0.1%)
Nervous system disorders	9 (0.2%)	1 (<0.1%)
Haemorrhagic stroke	6 (0.1%)	0 (0.0%)
Cerebral haemorrhage	3 (0.1%)	1 (<0.1%)

Source: adae (MedDRA version 22.1), fa**; Software:** R

[1]Treatment emergent AE defined as including up to last day of treatment plus 7 days.

Similarly, analysis of intracranial hemorrhage events overall and by system organ class or preferred term revealed an imbalance between ticagrelor (n=20) and placebo (n=6), which was driven by intracranial hemorrhage (Table 22).

Table 22: Treatment Emergent Intracranial Hemorrhage, Safety Population

Event	Ticagrelor n = 5508	Placebo n = 5468
Any ICH	20 (0.4%)	6 (0.1%)
Injury, poisoning and procedural complications	1 (<0.1%)	1 (<0.1%)
Traumatic intracranial haemorrhage	0 (0.0%)	1 (<0.1%)
Subdural haematoma	1 (<0.1%)	0 (0.0%)
Nervous system disorders	19 (0.3%)	5 (0.1%)
Subarachnoid haemorrhage	2 (<0.1%)	0 (0.0%)
Haemorrhagic transformation stroke	4 (0.1%)	2 (<0.1%)
Haemorrhagic stroke	7 (0.1%)	1 (<0.1%)
Haemorrhage intracranial	2 (<0.1%)	0 (0.0%)
Cerebral haemorrhage	3 (0.1%)	2 (<0.1%)
Basal ganglia haemorrhage	1 (<0.1%)	0 (0.0%)

Source: adae (MedDRA version 22.1), fa**; Software:** R

Abbreviations: ICH, Intracranial haemorrhage

[1]Treatment emergent AE defined as including up to last day of treatment plus 7 days.

9.3.2. Bleeding Adverse Events

There were approximately four times as many bleeds classified as GUSTO severe or moderate/severe (all fulfilling the SAE criteria) in the ticagrelor treatment arm compared to the placebo arm (Table 23). Imbalances for ICH or fatal bleeds and premature discontinuation due to bleed were also observed. Except for GUSTO mild bleeding (which were not required to be reported), bleeds classified as trauma or procedural provocation were evenly distributed between the treatment arms (Table 24).

Table 23: Summary of Treatment Emergent Bleeding Events, Safety Population

Bleeding variable	Ticagrelor n = 5508	Placebo n = 5468
GUSTO severe	26 (0.5%)	6 (0.1%)
ICH or fatal bleed	20 (0.4%)	6 (0.1%)
Fatal bleed	9 (0.2%)	1 (<0.1%)
ICH	20 (0.4%)	6 (0.1%)
GUSTO moderate/severe[2]	35 (0.6%)	8 (0.1%)
Premature permanent discontinuation due to bleed	152 (2.8%)	32 (0.6%)

Source: adtte; **Software:** R

Abbreviations: GUSTO, Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries (see Appendix 14.1); ICH, Intracranial haemorrhage

[1]Treatment emergent AE defined as including up to last day of treatment plus 7 days.

[1]Fulling SAE criteria see footnote 2 of Table 20.

Table 24: GUSTO Bleeding Events by Severity and Provocation, Safety Population

Bleeding Parameter	Ticagrelor n = 5508	Placebo n = 5468
GUSTO mild bleeding	266 (4.8%)	51 (0.9%)
Spontaneous	244 (4.4%)	42 (0.8%)
Procedural	9 (0.2%)	3 (0.1%)
Trauma	13 (0.2%)	6 (0.1%)

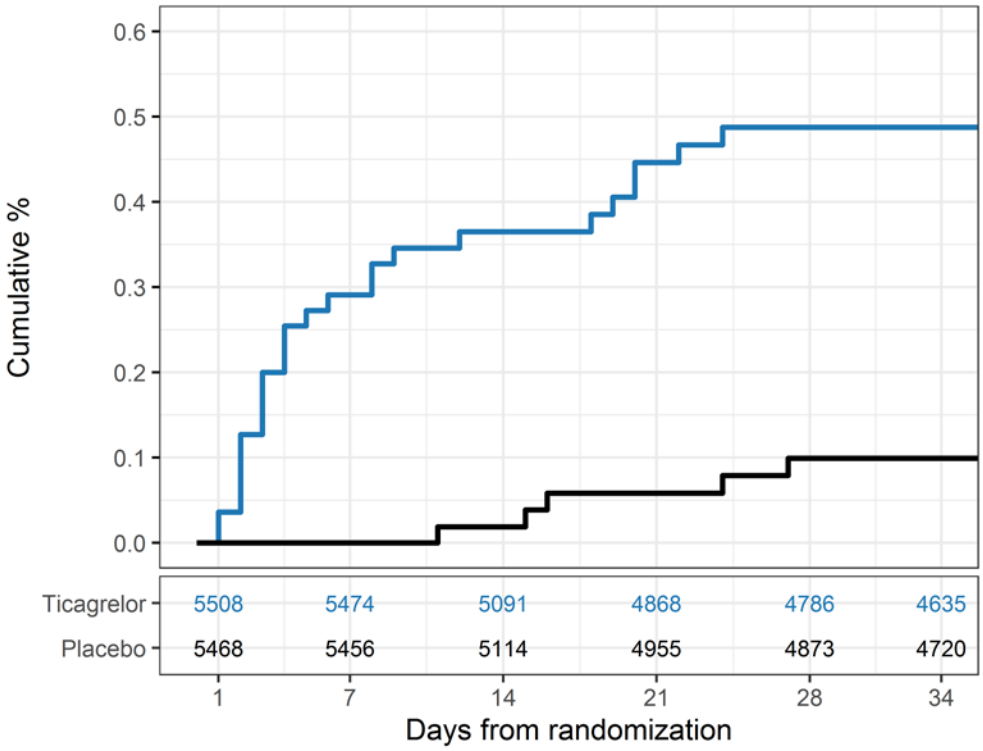
Bleeding Parameter	Ticagrelor n = 5508	Placebo n = 5468
GUSTO moderate bleeding	10 (0.2%)	2 (<0.1%)
Spontaneous	9 (0.2%)	1 (<0.1%)
Trauma	1 (<0.1%)	1 (<0.1%)
GUSTO severe bleeding	26 (0.5%)	6 (0.1%)
Spontaneous	24 (0.4%)	3 (0.1%)
Procedural	1 (<0.1%)	1 (<0.1%)
Trauma	1 (<0.1%)	2 (<0.1%)

Source: adae (MedDRA version 22.1), fa**; Software:** R

Abbreviations: GUSTO, Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries (see Appendix 14.1)

The Kaplan-Meier curves for GUSTO severe bleeding in the safety dataset (Figure 7) show bleeding events accumulating at the onset of therapy and the difference was maintained throughout the study.

Figure 7: Kaplan-Meier Curve for treatment emergent GUSTO severe bleeding events by treatment, Safety Population



Source: adtte.xpt; **Software:** R
Abbreviations: GUSTO, Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries (see Appendix 14.1)
[1]Treatment emergent AE defined as including up to last day of treatment plus 7 days.

9.4. Integrated Assessment of Safety

This sNDA was based on a single clinical trial. Therefore, an integrated safety assessment was not conducted. The data from THALES did not show any new safety signal for serious adverse events and the bleeding risk of ticagrelor is expected based on the mechanism of action.

10. Advisory Committee Meeting and Other External Consultations

There is no plan for an advisory committee meeting.

Reference ID: 4689224

During the review of the sNDA a consult review request was submitted to the Office of Neurology (DARRTS 08/04/2020), which requested input on the interpretation on the mRS score (see appendix 14.2), whether there were other stroke types that should be considered and applicability of the findings of THALES to US practice.

The consult review from the Office of Neurology (DARRTS 10/05/2020) noted that mRS is typically assessed at day 90, but that mRS at day 30 is expected to correlate with day 90. The consult concluded that the lack of difference between the treatment groups at day 30 in mRS is likely due to too few events to detect a difference and that the study was not powered to detect a difference in mRS based on previously reported trials. The consult also noted that the mRS score is not used as a measure of stroke severity, which is usually of interest during the acute stage and measured using the NIHSS score. Instead the mRS score on day 30 is a reasonable assessment of the severity of the index stroke and that the results, at a minimum, suggest that strokes in the ticagrelor group were not worse than those in the placebo group and, in fact, trended to have less disabling status on day 30.

The consult noted that hemorrhagic transformation presumably in the territory of the index stroke might be considered a new stroke for the purposes of the efficacy analysis, but that the addition of these events would not impact the results. It was also noted that it would not be unreasonable to include other hemorrhagic events, such as intracerebral hemorrhage or subarachnoid hemorrhage, as adverse events attributable to treatment.

Concerning the applicability of THALES to the US practice, the consult stated that the characteristics of a TIA or minor stroke is not expected to differ from that of the US (see Table 4 in applicant's justification for foreign data) and that the treatment guidelines are generally the same, including carotid endarterectomy and use of endovascular thrombectomy. Lastly, the consult concluded that the population selected do not appear to differ significantly by previous medical or neurological history or by risk factors from a comparable population in the US (see Table 7 in applicant's justification for foreign data).

11. Labeling Recommendations

11.1. Prescription Drug Labeling

The initially proposed indication and usage language in the label states:

The following modification to the current language is suggested:

"BRILINTA is indicated to reduce the risk of stroke in patients with acute ischemic stroke (NIH Stroke Scale score ≤ 5) or transient ischemic attack (TIA) [see Clinical Studies (14.3)*].*

For the management of acute ischemic stroke or TIA, initiate BRILINTA treatment with a 180 mg loading dose and then continue with 90 mg twice daily. Although patients in the trial received BRILINTA for 30 days, the treatment effect was observed early in the course of therapy [see Clinical Studies (14)]. "

The study only included patients with milder strokes (NIHSS ≤ 5). The protocol specified that patients meeting this cutoff have a substantial short-term risk for new ischemic events and a limited risk for ICH (CSP). The NIHSS is a 42-point scale and most patients were enrolled with an acute ischemic stroke (91%) and a NIHSS score of ≤ 3 (61%) and while there appears to be a similar reduction in strokes for the subgroup with elevated NIHSS it is not possible to do a similar analysis for bleeding due to limited number of bleeding events. While the study supports a positive benefit-risk it is unclear if the results can be extrapolated to patients with more severe strokes, who might be a greater risk for ICH.

The study was not designed to evaluate the optimal duration; however, the findings do indicate that the benefit in reduction of stroke is observed early on and that the benefit is maintained throughout the study.

The label should also describe the loading dose of aspirin that was included in THALES in the section that describes the aspirin dose for the new stroke indication.

There are now three studies (PEGASUS [Figure 13 in current label], THEMIS [Figure 15 in current label] and THALES [Figure 5]). While, each of the figures referenced describe the results of a univariate subgroup analysis it might be appropriate to revisit the statement in section 8.5 of the proposed label that assert that there are no overall differences between age groups. Of note, when adjusting for other covariates the interaction between age and treatment remained prominent in THEMIS (DARRTS 04/20/2020).

11.2. Nonprescription Drug Labeling

Not applicable.

12. Risk Evaluation and Mitigation Strategies (REMS)

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

13. Postmarketing Requirements and Commitments

There are no postmarketing requirements or commitments.

14. Appendices

14.1. GUSTO bleeding definition

Classification	Definition
GUSTO Severe Bleeding	Any one of the following: • Fatal • Intracranial[a] • Bleeding that caused haemodynamic compromise requiring intervention (eg, systolic blood pressure < 90 mm Hg that required blood or fluid replacement, or vasopressor/inotropic support, or surgical intervention).
GUSTO Moderate Bleeding	Bleeding requiring transfusion of whole blood or packed red blood cells without haemodynamic compromise (as defined above)
GUSTO Mild Bleeding	Bleeding without blood transfusion or haemodynamic compromise
No GUSTO Bleeding Event	Asymptomatic haemorrhagic transformations and microhaemorrhages

[a] Excluding asymptomatic haemorrhagic transformations of ischaemic brain infarctions and excluding microhaemorrhages < 10 mm evident only on gradient-echo magnetic resonance imaging. This is an adaptation of the standard GUSTO definition to better distinguish clinically relevant events in the acute stroke population (Easton et al 2017).

Source: THALES study report, Table 6

14.2. modified Rankin Scale score

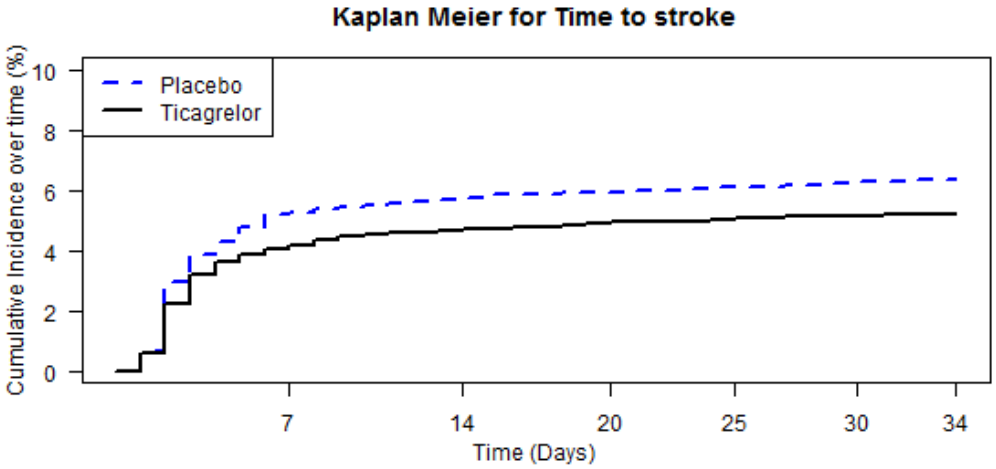
Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

Derived from: the Internet Stroke Center at www.strokecenter.org

Source: THALES study report, Table 7

14.3. Additional Statistical Analyses

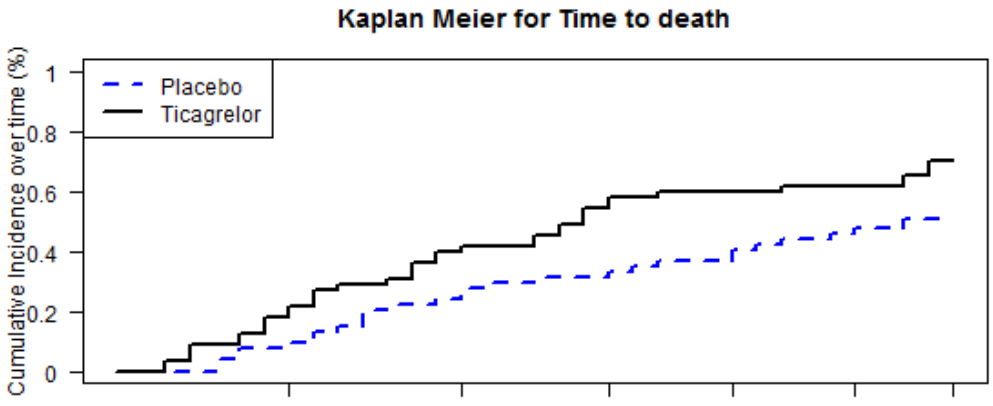
Figure 8: Kaplan Meier Curve for Time to Any Stroke Endpoint



Number of Events						
Placebo	287	316	326	333	343	347
Ticagrelor	228	258	271	280	282	284
Number at Risk						
Placebo	5201	5160	5143	5134	5125	1135
Ticagrelor	5287	5236	5223	5213	5208	1091
Cumulative Incidence (%)						
$\hat{F}_{Placebo}$	5.23	5.76	5.94	6.07	6.25	6.42
$\hat{F}_{Ticagrelor}$	4.13	4.68	4.92	5.08	5.12	5.16

[Source: Statistical Reviewer]

Figure 9: Kaplan Meier Curve for Time to Death Endpoint

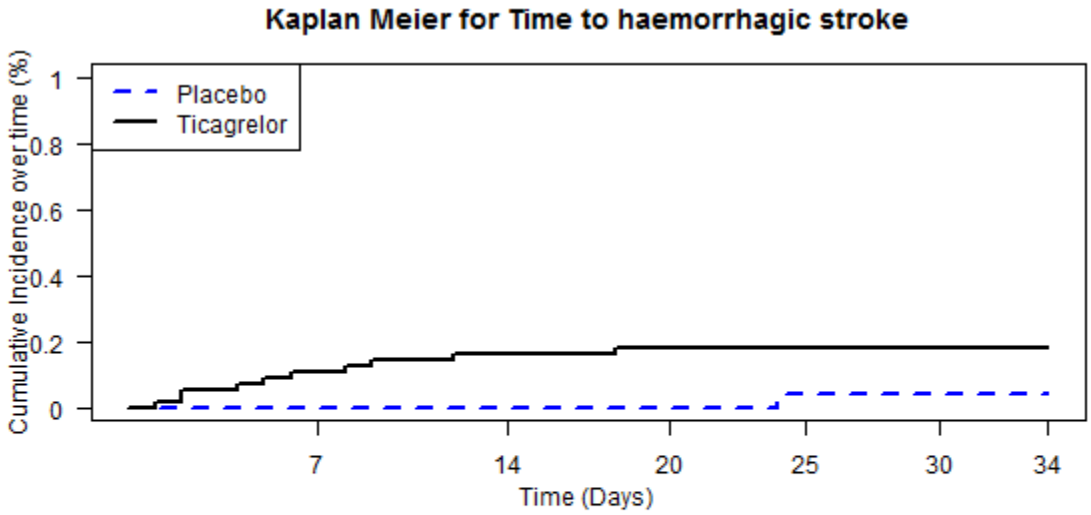


Number of Events						
Placebo	5	15	18	22	26	27
Ticagrelor	12	23	32	33	34	36
Number at Risk						
Placebo	5486	5470	5463	5460	5455	1218
Ticagrelor	5502	5487	5479	5475	5474	1153
Cumulative Incidence (%)						
$\hat{F}_{Placebo}$	0.09	0.27	0.33	0.40	0.47	0.51
$\hat{F}_{Ticagrelor}$	0.22	0.42	0.58	0.60	0.62	0.70

[Source: Statistical Reviewer]

Reference ID: 4689224

Figure 10: Kaplan Meier Curve for Time to Hemorrhagic Stroke

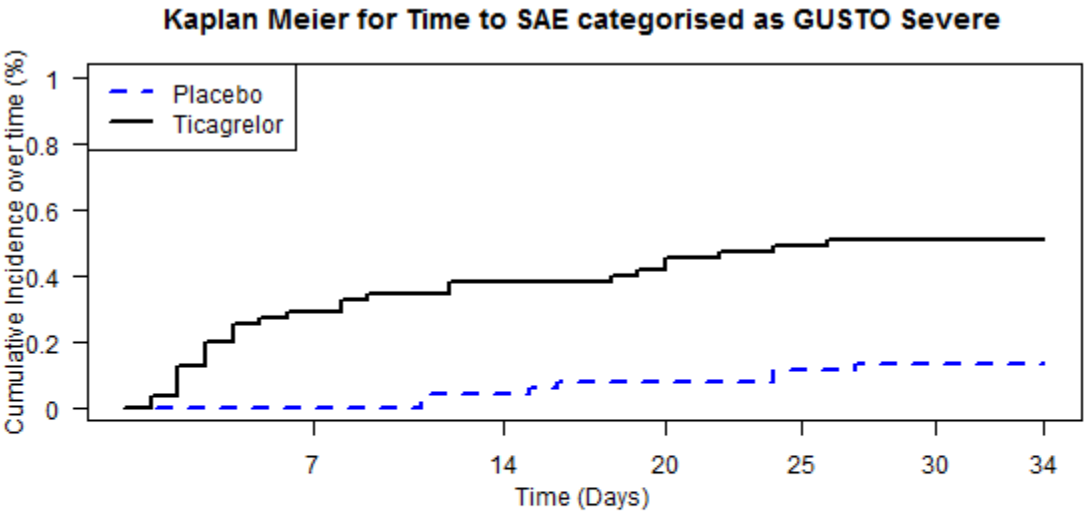


Number of Events						
Placebo	0	0	0	2	2	2
Ticagrelor	6	9	10	10	10	10
Number at Risk						
Placebo	5481	5462	5457	5454	5453	1217
Ticagrelor	5497	5476	5472	5470	5470	1153
Cumulative Incidence (%)						
$\hat{F}_{Placebo}$	0.00	0.00	0.00	0.04	0.04	0.04
$\hat{F}_{Ticagrelor}$	0.11	0.16	0.18	0.18	0.18	0.18

[Source: Statistical Reviewer]

Reference ID: 4689224

Figure 11: Kaplan Meier Curve for Time to GUSTO Severe



Number of Events						
Placebo	0	2	4	6	7	7
Ticagrelor	16	21	25	27	28	28
Number at Risk						
Placebo	5481	5461	5454	5451	5450	1216
Ticagrelor	5487	5468	5463	5457	5456	1146
Cumulative Incidence (%)						
$\hat{F}_{Placebo}$	0.00	0.04	0.07	0.11	0.13	0.13
$\hat{F}_{Ticagrelor}$	0.29	0.38	0.45	0.49	0.51	0.51

[Source: Statistical Reviewer]

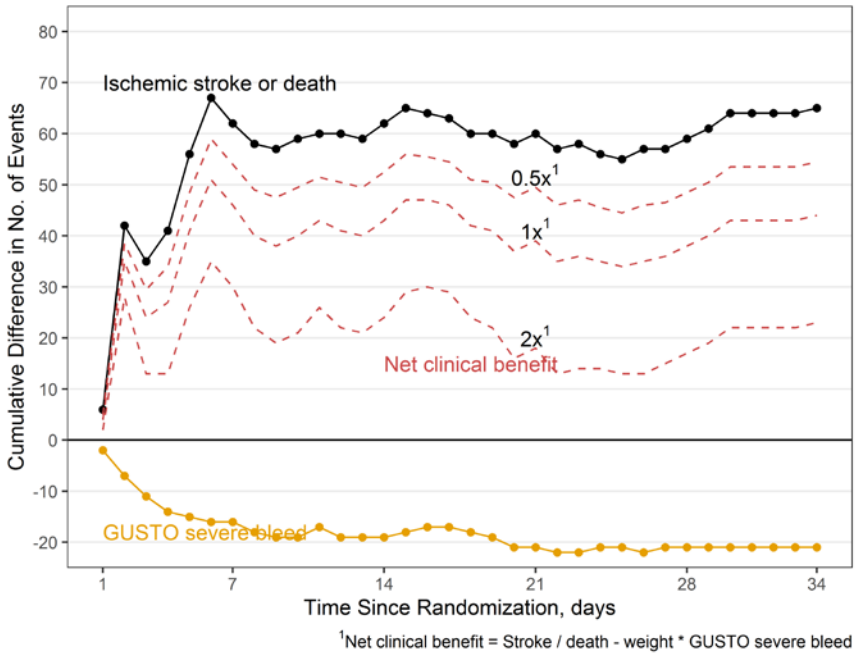
14.4. Post-hoc benefit-risk analysis

Weighted benefit-risk analysis was conducted by comparing the difference between cumulative efficacy events (ischemic stroke or death not due to bleeding) compared to GUSTO severe bleeding (Figure 12) with weights varying from 0.5 to 2, i.e., weighting increase in bleeding less (50%) or weighting increase in bleeding more (200%). A similar analysis was performed using all disabling ischemic strokes (Figure 13). It should be noted that this is a post-hoc analysis and that it is assumed that the mRS score on day 30 reflects the severity of the subsequent stroke. The results of these analysis suggest that there is a positive net clinical benefit.

Sensitivity analysis to different benefit-risk comparisons were also performed including and the results are shown in Figure 14 based on number needed to treat (NNT) and number needed to harm (NNH) analysis. The results of this analysis suggest a positive net clinical benefit except for

when benefit/risk was based on prevention of any stroke or bleeding related death compared to discontinuation due to bleeding.

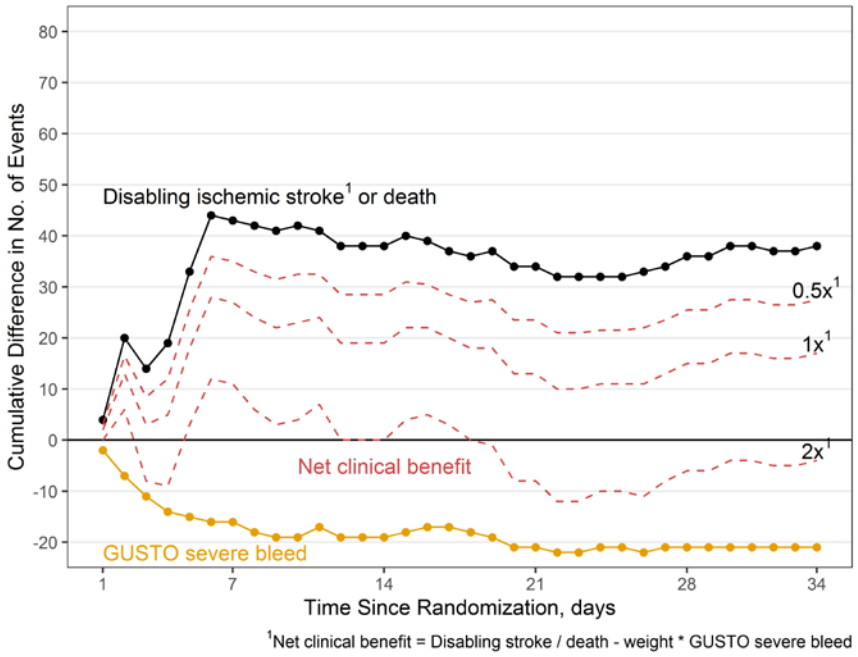
Figure 12: Weighted benefit-risk analysis for all ischemic strokes in full analysis population



Source: adtte.xpt and R

Abbreviations: GUSTO, Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries (see Appendix 14.1)

Figure 13: Weighted benefit-risk analysis for disabling ischemic strokes in full analysis population

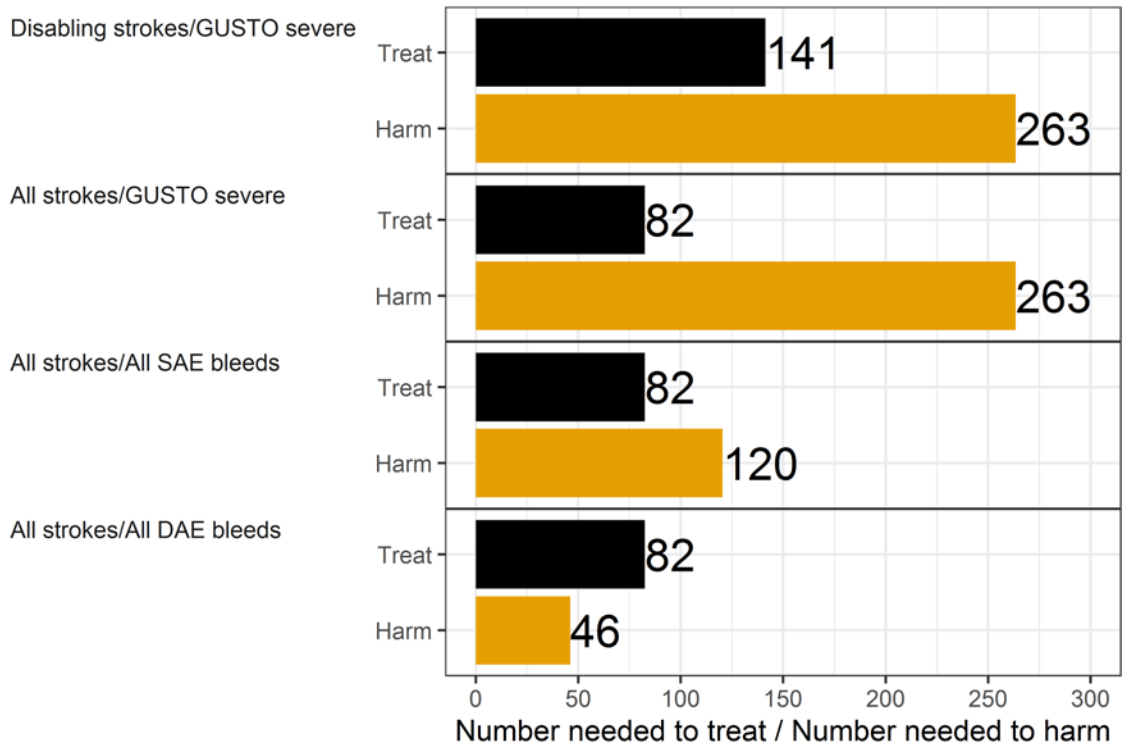


Source: adtte.xpt; adqs.xpt and R

Abbreviations: GUSTO, Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries (see Appendix 14.1)

[1] Disabling strokes were defined based on modified Ranking scale (see Appendix 14.2) greater than 2 on day 30. If value was assessed before the stroke it was assigned as missing. Missing mRS values were imputed as 6 if the patient died and otherwise as 0.

Figure 14: Sensitivity analysis for benefit-risk, full analysis set



Source: adtte.xpt; adqs.xpt; adae.xpt; adce.xpt and R

Abbreviations: DAE, Premature permanent discontinuation of investigational product due to adverse event; GUSTO, Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries (see Appendix 14.1); SAE, Serious Adverse Event

[1]All strokes refer to the same definition as for the primary endpoint. Disabling strokes were defined based on modified Ranking scale (see Appendix 14.2) greater than 2 on day 30. If value was assessed before the stroke it was assigned as missing. Missing mRS values were imputed as 6 if the patient died and otherwise as 0.

[2]SAE bleeds were defined using the narrow FMQ for hemorrhage (version 01/29/2020) or GUSTO severe bleeding.

[3]DAE bleeds were bleeds that resulted in permanent discontinuation of study drug.

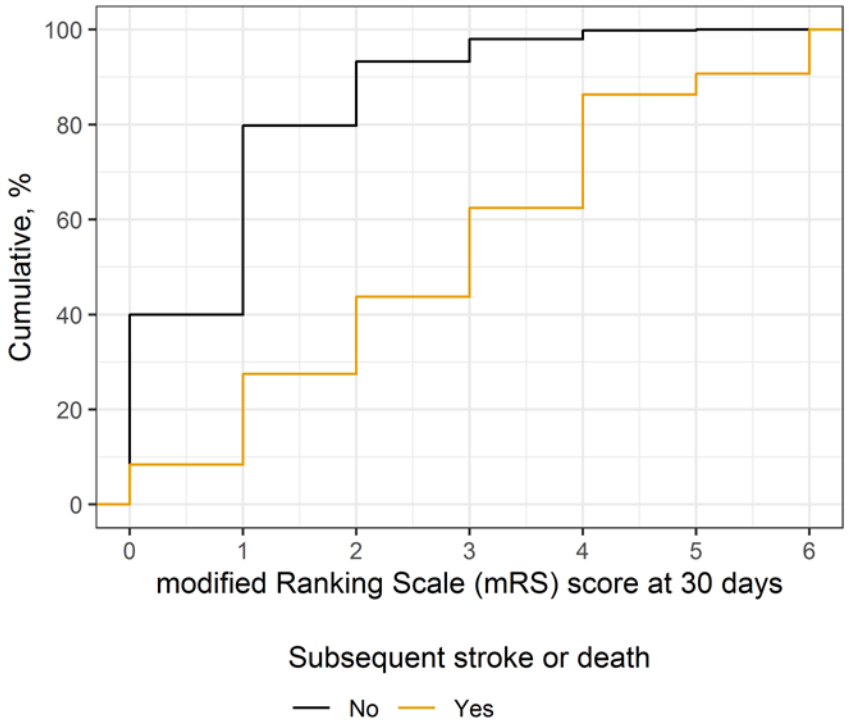
14.5. Post-hoc analysis of stroke by modified Ranking scale score

Post-hoc analysis of patients with and without a subsequent stroke revealed a higher mRS score on day 30 (Figure 15). This is a pooled analysis across treatment arms and similar results were observed by treatment.

Further analysis of the primary endpoint events based on mRS score on day 30 was also conducted (Figure 16). This post-hoc analysis suggests that for patients with a mRS score of less

than or equal to 5 that there was a numerical reduction in primary endpoint events for ticagrelor vs placebo and an increase in events for patients with a mRS score of 6. Of note, one patient in the placebo group who died had a mRS score of 5 and was therefore placed in that mRS category.

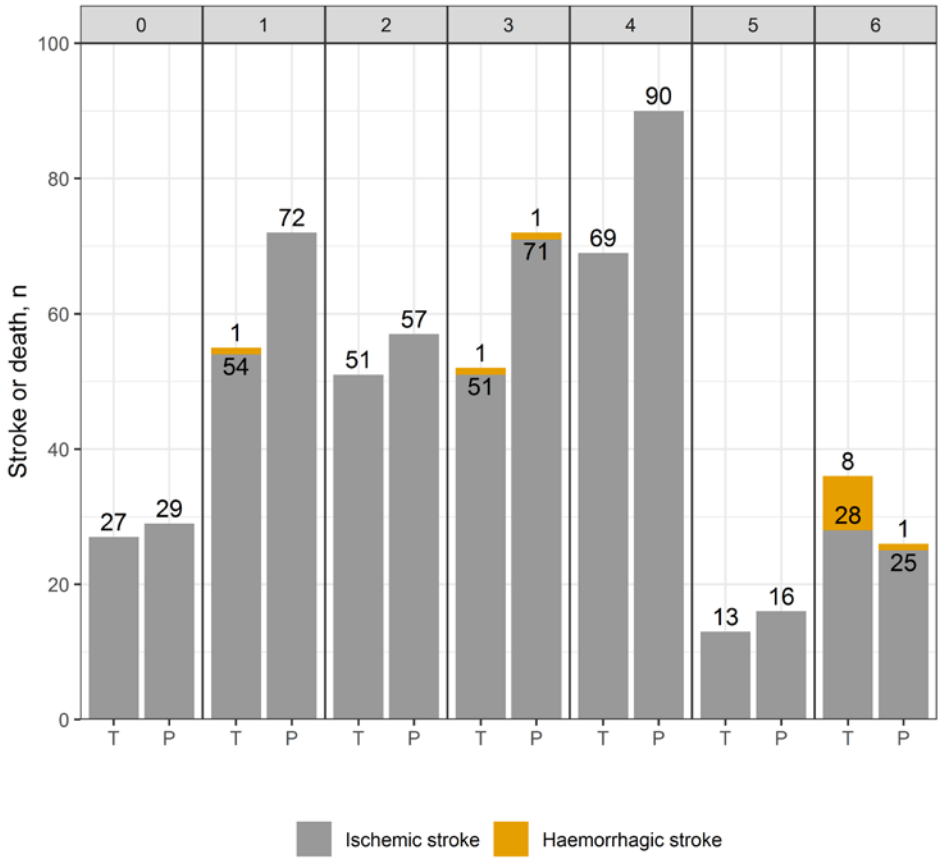
Figure 15: Cumulative distribution of modified Ranking scale scores, full analysis set



Source: adqs.xpt; adtte.xpt and R

Reference ID: 4689224

Figure 16: Analysis of primary endpoint events by modified Rankin scale score on day 30, full analysis set



Source: adqs.xpt; adtte.xpt and R

Abbreviations: T, Ticagrelor; P, Placebo.

[1]Missing modified Rankin scale (see Appendix 14.2) scores were imputed as 6 if the patient died and otherwise as 0. If value was assessed before the stroke it was assigned as missing and subsequently imputed using the imputation strategy.

[2]The numbers in the plot refers to the number of patients with ischemic strokes (bottom) and number of patients with any hemorrhagic stroke (top).

14.6. References

Bansal, S., Sangha, K.S. and Khatri, P., 2013. Drug treatment of acute ischemic stroke. American Journal of Cardiovascular Drugs, 13(1), pp.57-69.

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Jonasson, J., Minematsu, K., Molina, C.A. and Wang, Y., 2016. Ticagrelor versus aspirin in acute stroke or transient ischemic attack. New England Journal of Medicine, 375(1), pp.35-43.

Johnston, S.C., Easton, J.D., Farrant, M., Barsan, W., Conwit, R.A., Elm, J.J., Kim, A.S., Lindblad, A.S. and Palesch, Y.Y., 2018. Clopidogrel and aspirin in acute ischemic stroke and high-risk TIA. New England Journal of Medicine, 379(3), pp.215-225.

Powers, W.J., Rabinstein, A.A., Ackerson, T., Adeoye, O.M., Bambakidis, N.C., Becker, K., Biller, J., Brown, M., Demaerschalk, B.M., Hoh, B. and Jauch, E.C., 2019. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke, 50(12), pp.e344-e418.

Wang, Y., Wang, Y., Zhao, X., Liu, L., Wang, D., Wang, C., Wang, C., Li, H., Meng, X., Cui, L. and Jia, J., 2013. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. N Engl J Med, 369, pp.11-19.

14.7. Financial Disclosure

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

Covered Clinical Study (Name and/or Number): THALES (D5134C00003)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 2508		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 1		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
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: 0 Significant payments of other sorts: 0		

Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
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) 4		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

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/

LARS JOHANNESEN
10/21/2020 01:37:36 PM

WILLIAM J KOH
10/21/2020 01:38:52 PM

JIALU ZHANG
10/21/2020 02:02:03 PM

CHRISTINE E GARNETT
10/21/2020 02:04:24 PM

FORTUNATO F SENATORE
10/21/2020 02:55:46 PM

Review and Evaluation of Clinical Data
Consultation Review of sNDA

sNDA	022433, Suppl 29
Supporting Document Number	e565
Sponsor	AstraZeneca
Drug	Ticagrelor
Proposed Indication	To reduce the risk of stroke in patients with acute ischemic stroke or transient ischemic attack (TIA)
Correspondence Date	5/5/2020
Consultation Due Date	9/14/20
Date Review Completed	9/4/20
Reviewer	Lawrence Rodichok MD, ON, DN2
Materials Reviewed	NDA 022433 S29

FDA text, ***reviewer comment***, extracted from sponsor documents

1. Introduction

1.1. Executive Summary

The Division of Cardiology and Nephrology has requested that DN2 provide an opinion on selected trial results submitted in support of an sNDA for Brilinta for a proposed indication to reduce the risk of stroke in patients with an acute "minor" stroke or a TIA. The trial compared treatment with aspirin alone to aspirin plus ticagrelor for 30 days following the index minor stroke/TIA. The primary endpoint was stroke or death from any cause during the 30-day treatment period. Secondary endpoints were the time to new stroke and the mRS at day 30. Specifically, our opinion is requested regarding the absence of a statistically significant reduction in the 30-day mRS score. We were also asked to review the types of strokes counted towards the primary endpoint. Because the population studied does not include patients from the US, we were asked to comment on the applicability of the trial results to the U.S. population.

1.2. Scientific and Regulatory Background

1.2.1 Scientific Background

Ticagrelor (BRILINTA™) is an oral, direct-acting, selective, and reversibly binding $P2Y_{12}$ receptor antagonist that prevents adenosine diphosphate-mediated platelet activation and aggregation.

1.2.2 Regulatory Background

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

BRILINTA is a P2Y12 platelet inhibitor indicated

Reference ID: 4680885

- 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.
- 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).

2. Review of Selected Aspects of the Clinical Protocol

(Note that British spellings have been retained below, as the text has been reproduced from the clinical protocol.)

2.1. Design/objectives of study

3.1.1 Objectives

3.1.1.1 Primary objective

To demonstrate superior efficacy of ticagrelor and ASA compared with placebo and ASA in AIS/TIA patients in the prevention of the composite of stroke and death at 30 Days

3.1.1.2 Secondary objective(s)

To demonstrate superior efficacy of ticagrelor and ASA compared with placebo and ASA in AIS/TIA patients in the prevention of ischaemic stroke at 30 days

To demonstrate superior efficacy of ticagrelor and ASA compared with placebo and ASA in AIS/TIA patients in reducing overall disability at 30 days

2.2. Dosing regimen

At randomisation (Visit 1/Day 1), eligible patients will be randomly assigned to 1 of 2 treatments: ticagrelor or placebo. Treatments will be given orally with loading doses on Day 1 followed by maintenance treatment until Visit 3/Day 30. Patients will be treated with:

- A loading dose of ticagrelor (2 tablets ticagrelor 90 mg) on Day 1, followed by ticagrelor 90 mg twice daily, OR
- A loading dose of placebo (2 tablets matching ticagrelor 90 mg) on Day 1, followed by placebo (matching ticagrelor 90 mg) twice daily.

Concomitant ASA treatment

In addition to the IP, all patients should be treated with ASA. Patients should receive an ASA loading dose on Day 1. The recommended loading dose is 300 to 325 mg ASA. Any dose of ASA given after symptom onset but before randomisation should be taken into account (for instance, if a patient has received 300 mg ASA just prior to randomisation, the patient does not need to receive a second loading dose after randomisation). Thereafter, patients should be treated with ASA 75 to 100 mg once daily.

Reference ID: 4680885

2.3. Study conduct/schedule

2.3.1.1. Assessments

Reviewer Comment: Key assessments of interest for this consultation were:

- ***NIHSS at baseline only***
- ***mRS at day 30 only***
- ***SAEs, DAEs, and endpoints at day 1, 7, 30 and 60.***

Endpoints (death, stroke), bleedings fulfilling SAE/DAE criteria and classified according to the GUSTO bleeding scale. SAEs will be recorded from the time of informed consent. Endpoints will be collected from the time of randomisation. DAEs will be collected from the first intake of investigational product until the end of study treatment.

5.1 Efficacy assessments
5.1.1 Stroke
The definition for stroke is based on the standardised definitions for endpoints (Hicks et al 2015). All strokes occurring post-enrolment will be recorded as SAEs. All strokes occurring post-randomisation will be considered endpoints. Stroke is defined as an acute episode of focal or global neurological dysfunction caused by cerebral vascular injury as a result of infarction or haemorrhage not caused by trauma. Investigators will classify strokes into 1 of 3 mutually exclusive categories: ischaemic, haemorrhagic, or undetermined. Whenever possible, stroke diagnoses should be confirmed using neuroimaging (CT or MRI) to minimise the number of strokes classified as "undetermined".

5.1.1.1 Ischaemic stroke

An acute episode of focal cerebral dysfunction caused by cerebral infarction. Either of the following is considered to be an ischaemic stroke:

1. Rapid onset (or existence on awakening) of a new focal neurological deficit with clinical or imaging evidence of infarction and not attributable to a non-ischaemic aetiology (not associated with brain infection, trauma, tumour, seizure, severe metabolic disease, or degenerative neurological disease)

2. Rapid worsening of an existing focal neurological deficit (e.g., the index stroke event) that is judged by the Investigator to be attributable to a new infarction or extension of a previous infarction in the same vascular bed, based on persisting symptoms or imaging evidence of infarction and no evidence of a non-ischaemic aetiology. In case imaging is inconclusive, persistent symptoms is defined as duration of ≥24 hours or until death

Haemorrhagic transformation of an ischaemic stroke (not an efficacy endpoint)

Haemorrhage may be a consequence of an ischaemic stroke (the index event or a subsequent stroke), i.e., a haemorrhagic transformation. Haemorrhagic transformations are not considered to be haemorrhagic strokes nor to be stroke endpoints.

Haemorrhagic transformations may be either symptomatic or asymptomatic. Symptomatic

Reference ID: 4680885

haemorrhagic transformation of an ischaemic stroke must have imaging evidence of extravascular blood within an area of known acute/subacute infarction that is judged to be nontraumatic and at least partially responsible for the patient's clinical neurological deterioration with neurological symptoms out of proportion to what would be expected for the size and location of the infarction. These should be reported as SAEs and be GUSTO-classified as an ICH.

Asymptomatic haemorrhagic transformation of an ischaemic stroke must have imaging evidence of any extravascular blood within an area of known acute/subacute infarct, judged to be nontraumatic, with no detected worsening of neurological symptoms related to the haemorrhage. These should not be recorded as SAEs. However, if the Investigator chooses to discontinue IP permanently and prematurely due to an asymptomatic haemorrhagic transformation, the event should be recorded as DAE and be GUSTO-classified as "No GUSTO Bleeding Event."

5.1.1.2 Haemorrhagic stroke

An acute episode of focal or global cerebral dysfunction caused by intraparenchymal, intraventricular, or subarachnoid haemorrhage not caused by trauma. Subdural haematomas are ICH events but not strokes.

5.1.1.3 Undetermined category of stroke

An acute episode of focal or global neurological dysfunction caused by presumed brain vascular injury as a result of haemorrhage or infarction but with insufficient information to allow categorisation as either ischaemic or haemorrhagic. Strokes of undetermined category will be analysed as ischaemic strokes.

2.3.2. Blinding

The blinding is ensured by using double-blind technique. The ticagrelor tablets and the placebo tablets for ticagrelor will be identical in size, colour, smell, and taste. Each bottle will be labelled with a unique kit ID number that will be used to assign the treatment to the patient but will not indicate treatment allocation to the Investigator or patient.

2.3.3. Discontinuation

3.9.1 Management of IP in case of dyspnoea or bleeding
Dyspnoea, usually mild to moderate intensity, is an identified adverse drug reaction to ticagrelor and a common reason for discontinuing IP. However, if the dyspnoea is tolerable to the patient, IP can be continued without interruption. For further details, see the Investigator's Brochure.

IP does not need to be discontinued in case of minimal or minor bleeding. IP must be stopped immediately in case of a bleed judged by the Investigator to be clinically significant (e.g., a significant fall in haemoglobin, need for transfusion, haemodynamically significant, or in a critical location such as intracranial, intraspinal, intraocular, or pericardial bleeds), but may be reinstated when the risk of bleeding is judged by the Investigator to be low. All bleedings should be treated and followed up according to standard clinical practice and treatment guidelines.

Reference ID: 4680885

2.4. Eligibility criteria

The study population is defined as patients ≥40 years of age who have experienced a non-cardioembolic AIS (NIHSS score ≤5) OR high-risk TIA (defined as ABCD2 score2 ≥6 or ipsilateral atherosclerotic stenosis ≥50% in an extra/intracranial artery) who could be randomised within 24 hours of symptom onset.

3.4.1 Key Inclusion Criteria

3. Acute onset of cerebral ischaemia due to

(a) AIS with NIHSS ≤5. AIS is defined as acute onset of neurological deficit attributed to focal brain ischaemia, and either of the following:
- Persistent signs or symptoms of the ischaemic event at the time of randomisation, OR
- Acute ischaemic brain lesion documented before randomisation by computed tomography (CT) scan or magnetic resonance imaging (MRI) (diffusion-weighted imaging) and that could account for the clinical presentation

(b) High-risk TIA, defined as neurological deficit of acute onset attributed to focal ischaemia of the brain by history or examination with complete resolution of the deficit, and at least one of the following:
- ABCD^2 score ≥6 and TIA symptoms not limited to isolated numbness, isolated visual changes, or isolated dizziness/vertigo
- Symptomatic intracranial arterial occlusive disease that could account for the clinical presentation, documented by transcranial Doppler or vascular imaging and defined as at least 50% narrowing in the diameter of the vessel lumen
- Internal carotid arterial occlusive disease that could account for the clinical presentation, documented by Doppler, ultrasound, or vascular imaging and defined as at least 50% narrowing in diameter of the vessel lumen

4. Randomisation occurring within 24 hours after onset of symptoms; for wake-up strokes (when the time of symptom onset is not known), within 24 hours from the time point at which the patient was reported to be in their normal condition

Reviewer Comment: Because randomization was required within 24 hours of stroke symptom onset, there may not have been adequate time for the persistence of symptoms to be confirmed at 24 hours.

5. CT or MRI performed after symptom onset ruling out intracranial haemorrhage or other pathology, such as vascular malformation, tumour, or abscess that according to the Investigator could explain symptoms or contraindicate study treatment

3.4.2 Key Exclusion Criteria

3. Patients who should receive or have received any intravenous or intra-arterial thrombolysis or mechanical thrombectomy within 24 hours prior to randomisation

Reference ID: 4680885

Reviewer Comment: It appears that patients were eligible if treated with thrombolysis or EVT as long as the treatment was administered within 24 hours of randomization.

4. Planned carotid endarterectomy that requires halting investigational product within 3 days of randomisation or is expected to require unblinding of investigational product (planned carotid endarterectomy is in itself not an exclusion criterion)

Reviewer Comment: It is not likely that CTE would occur within 3 days of randomization due to the increased risk, but it is likely that unblinding would be necessary because DAPT would likely increase the risk of the procedure. Therefore, potential patients for whom CTE was planned were probably excluded.

2.5. Safety measures and considerations

5.2 Safety assessments
The safety objective of the study is to assess safety particularly with respect to major bleeding events. Bleeding events that fulfil SAE or DAE criteria will be classified by the Investigator according to GUSTO bleeding definitions and by provocation (Table 2).

Reviewer Comment: GUSTO = Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries

Table 2 GUSTO definitions

Classification	Definition
GUSTO Severe Bleeding	Any one of the following: - Fatal - Intracranial[a] - Bleeding that caused haemodynamic compromise requiring intervention (eg, systolic blood pressure <90 mm Hg that required blood or fluid replacement, or vasopressor/inotropic support, or surgical intervention).
GUSTO Moderate Bleeding	Bleeding requiring transfusion of whole blood or packed red blood cells without haemodynamic compromise (as defined above)
GUSTO Mild Bleeding	Bleeding without blood transfusion or haemodynamic compromise
No GUSTO Bleeding Event	Asymptomatic haemorrhagic transformations and microhaemorrhages

[a] Excluding asymptomatic haemorrhagic transformations of ischaemic brain infarctions and excluding microhaemorrhages <10 mm evident only on gradient-echo MRI. This is an adaptation of the standard GUSTO definition to better distinguish clinically relevant events in the acute stroke population.

5.3.3 Vessel imaging for assessment of symptomatic ipsilateral stenosis
For TIA patients, the presence of symptomatic ipsilateral stenosis is a potential eligibility criterion. Presence of known symptomatic ipsilateral stenosis should be recorded for all patients at randomisation.

Reference ID: 4680885

5.3.4 Cerebrovascular atherosclerosis phenotyping
For all patients, the Investigator should record in the eCRF whether or not imaging (as part of clinical practice) of intra- or extracranial arteries following the index event was performed. If performed, data should be collected for extra- and intracranial arteries supplying the ischaemic field (ipsilateral) as well as for other arteries, and the results of the examination should be documented in the eCRF. The documentation of the cerebrovascular atherosclerosis phenotyping should comprise data supporting a diagnosis of atherosclerosis as well as negative findings (Figure 2).

In addition, the presence or absence of aortic atheroma and any history of coronary artery bypass grafting, MI, percutaneous coronary intervention, and peripheral artery disease should be recorded. Thereby, the cerebrovascular as well as the generalised atherosclerosis phenotypes can be described for all patients.

6.5 Recording of cerebrovascular interventions
Invasive cerebrovascular procedures or surgery following the index event (ie, carotid endarterectomy) or a subsequent stroke event (ie, carotid endarterectomy, carotid angioplasty/stenting, thrombectomy, or thrombolysis) should be recorded in the eCRF.

2.6. Study endpoint

9.4.1 Primary variable
The primary variable is the time from randomisation to first subsequent stroke or death. Patients who have not experienced either of these events will be censored at Visit 3, Day 34, or the date of the last event assessment, whichever occurs earlier.
9.4.2 Secondary variables

The secondary variables, presented in the hierarchical order in which they will be tested, are:
1. Time from randomisation to first subsequent ischaemic stroke
2. mRS score >1 at Visit 3

For the time-to-event variable, patients who have not experienced the event will be censored at Visit 3, Day 34, or the date of the last event assessment, whichever occurs earlier. The mRS score for patients who have died prior to Visit 3 will by definition be 6. No other imputation for missing data will be made.

2.7. Statistical considerations/analyses

The sample size was based on the assumption that there would be a primary endpoint event rate of 6.7% in the placebo group. If at least 770 events occurred, there would be 85% power to detect a Hazard ratio of 0.805.

3. Efficacy Results

There was a statistically significant reduction in the number of subjects who met the primary endpoint of stroke or death at day 30. There was also a significant reduction of the stroke component of the composite primary endpoint, but deaths were numerically greater, 36/0.7% in the ticagrelor group vs. 27/0.5% in the placebo group.

Reference ID: 4680885

Sponsor Table 2 Analysis of the Composite of Stroke and Death (Primary Endpoint) and its Components up to Visit 3 (Full Analysis Set)

	Ticagrelor 90 mg bd (N=5523)		Placebo (N=5493)				
Variable	Patients with events (%)	KM%	Patients with events (%)	KM%	Hazard ratio	95% CI	p-value
Composite of stroke/death	303 (5.5)	5.4	362 (6.6)	6.5	0.83	(0.71, 0.96)	0.015
Stroke	284 (5.1)	5.1	347 (6.3)	6.3	0.81	(0.69, 0.95)	0.008
Death	36 (0.7)	0.6	27 (0.5)	0.5	1.33	(0.81, 2.19)	0.264

Source: Table 2, Clinical Overview

However, there was no statistically significant reduction in the percentage of patients with disability at Day 30 in the ticagrelor group compared with the placebo group, as defined by patients with an mRS score > 1 at Visit 3 (OR 0.98 [95% CI 0.89, 1.07], p = 0.613).

Sponsor Table 21 Analysis of Overall Disability at 30 Days, Using mRS Score at Visit 3 (Secondary Endpoint) (Full Analysis Set)

			Comparison between groups	
Group	n	Number (%) of patients with mRS score > 1	Odds ratio (95% CI)	p-value
Ticagrelor 90 mg bd (N=5523)	5386	1282 (23.8)	0.98 (0.89, 1.07)	0.613
Placebo (N=5493)	5333	1284 (24.1)		

Source: Table 21, CSR

Because the incidence of a primary endpoint event was relatively infrequent, the mRS was assessed for the subgroup that did have a primary endpoint event. For those subjects who did have a primary endpoint event, there was no difference in the mean or median 30-day mRS.

Table 1: Reviewer analysis of 30-day mRS for those with a primary endpoint event

TRTP of ADTTE	N with a primary event	N with a value	mRS at day 30 (AVAL)					
			Mean	Std Dev	Min	Max	Median	Missing
Placebo	362	348	2.87	1.58	0	6	3	14
Ticagrelor 90 mg bd	303	291	2.99	1.71	0	6	3	12

Source: CNSR_0 Subset of PARAM_TTSD Subset of Join ADTTE c PARAM_mRS of ADQS incl NM AVAL By (TRTP of ADTTE).jmp
*: Unpaired t test: Mean difference Ticagrelor minus Placebo = 0.1200; 95%CI: -0.1360 to 0.3760; p=0.3575

For the full analysis population, there were similar numbers of patients in the ticagrelor and placebo groups across individual mRS categories.

Sponsor Table 14.2.3.4 Summary statistics for mRS score at visit 3 (full analysis set)

mRS score	Number (%) of patients	
	Ticagrelor 90 mg bd (N=5523)	Placebo (N=5493)
0	2020 (36.6)	1964 (35.8)

mRS score	Number (%) of patients	
	Ticagrelor 90 mg bd (N=5523)	Placebo (N=5493)
1	2116 (38.3)	2126 (38.7)
2	755 (13.7)	755 (13.7)
3	307 (5.6)	302 (5.5)
4	168 (3.0)	182 (3.3)
5	21 (0.4)	24 (0.4)
6	36 (0.7)	27 (0.5)
missing	100 (1.8)	113 (2.1)

Source: Table 14.2.3.4, CSR

For the population that did have a primary endpoint event, the distribution of mRS scores was also similar by treatment group.

Reviewer Table 2: Reviewer analysis of the distribution of 30-day mRS scores for those with a primary endpoint event

30-day mRS score	Placebo N=362		Ticagrelor N=303	
	N	%	N	%
Missing	14	3.87	12	3.96
0	15	4.14	15	4.95
1	72	19.9	55	18.2
2	57	15.7	51	16.8
3	72	19.9	52	17.2
4	90	24.9	69	22.8
5	16	4.42	13	4.29
6	26	7.18	36	11.9

Source: CNSR_0 Subset of PARAM_TTSD Subset of Join ADTTE c PARAM_mRS of ADQS incl NM By (USUBJID of ADTTE, TRTP of ADTTE, AVAL of PARAM_mRS Subset of ADQS) NUSUBJID By TRTP By (AVAL).jmp

For those with a primary endpoint event, the mRS dichotomized at 1, 2, or 3 still shows no differences by treatment group.

Reviewer Table 3: Reviewer analysis of mRS >1 for those with a primary endpoint event

AVAL >1	N Rows	Placebo		Ticagrelor	
		N	%	N	%
Missing	26	14	3.87	12	3.96
N	157	87	24	70	23.1
Y	482	261	72.1	221	72.9

Source: CNSR_0 Subset of PARAM_TTSD Subset of Join ADTTE c PARAM_mRS of ADQS incl NM By (AVAL >1).jmp

Reviewer Table 4: Reviewer analysis of mRS >2 for those with a primary endpoint event

AVAL >2		Placebo		Ticagrelor	
	Total	N	%	N	%
missing	26	14	3.87	12	3.96
N	265	144	39.8	121	39.9
Y	374	204	56.4	170	56.1

Source: CNSR_0 Subset of PARAM_TTSD Subset of Join ADTTE c PARAM_mRS of ADQS incl NM By (AVAL >2).jmp

Reference ID: 4680885

Reviewer Table 5: Reviewer analysis of mRS >3 for those with a primary endpoint event

AVAL >3		Placebo		Ticagrelor	
	Total	N	%	N	%
	26	14	3.87	12	3.96
N	389	216	59.7	173	57.1
Y	250	132	36.5	118	38.9

Source: CNSR_0 Subset of PARAM_TTSD Subset of Join ADTTE c PARAM_mRS of ADQS incl NM By (AVAL >3).jmp

Reviewer Table 6: Summary of dichotomized mRS for those with a primary endpoint event – reviewer analysis

	Ticagrelor 90 mg bd (N=291*)		Placebo (N=348*)				
Variable	n	(%)	n	(%)	Odds ratio	95% CI	p-value
Subsequent stroke and mRS score > 2 at visit 3	170	58.4%	204	58.6%	0.9952	(0.7465, 1.3267)	0.9736
Subsequent stroke and mRS score > 1 at visit 3	221	76%	261	75%	1.0393	(0.7316,1.4765)	0.8297
Subsequent stroke and mRS score > 3 at visit 3	118	40.6%	132	37.9%	1.0441	(0.8103,1.3452)	0.7388

*: missing not included

Reviewer Comment: Even when limited to those who did have an event, there does not appear to be a difference in 30-day mRS between treatment groups, no matter how the endpoint is analyzed.

There was, however, a clear increase in mRS for those who had a primary endpoint event compared to those who did not.

Table 7: Reviewer analysis of the 30-day mRS for those who did and did not have a primary endpoint event (0 = event)

TRTP of ADTTE	Total	mRS at day 30 (AVAL)													
		N with a value		Mean		Std Dev		Min		Max		Median		Missing	
		CNSR													
		0	1	0	1	0	1	0	1	0	1	0	1	0	1
Placebo	5493	348	5032	2.87	0.91	1.58	0.95	0	0	6	6	3	1	14	99
Ticagrelor 90 mg bd	5523	291	5132	2.99	0.91	1.71	0.96	0	0	6	5	3	1	12	88

Source: PARAM_TTSD Subset of Join ADTTE c PARAM_mRS of ADQS incl NM AVAL by CNSR By (TRTP of ADTTE).jmp

Reference ID: 4680885

Reviewer Comment: One potential explanation for the absence of a difference between treatment groups would be that the stroke events that did occur were relatively minor. The above analysis does not support that possibility.

The time in days to the primary endpoint event in shown in the table below. Because the mRS was assessed on day 30, on average, the mRS was assessed approximately 24 days (median 27 days) after the primary endpoint event.

Table 8: Reviewer analysis of time in days to a primary endpoint event

TRTP of ADTTE	N with event	Time in days to primary endpoint event (ADY)					
		Mean	Std Dev	Min	Max	Median	Missing
Placebo	362	5.8	6.99	1	34	3	0
Ticagrelor 90 mg bd	303	5.79	6.43	1	32	3	0

Source: Reviewer analysis: CNSR_0 Subset of PARAM_TTSD Subset of Join ADTTE c PARAM_mRS of ADQS incl NM ADY By (TRTP of ADTTE).jmp

All endpoint strokes

An endpoint stroke occurred in 6.32% of placebo subjects compared to 5.14% of those treated with ticagrelor.

Table 9: Subjects with an endpoint stroke (CNSR = 0)

CNSR	Total	Placebo		Ticagrelor 90 mg bd	
		N	%	n	%
0	631	347	6.32	284	5.14
1	10385	5146	93.7	5239	94.9

Source: PARAMCD_TTS Subset of Join ADTTE c PARAM_mRS of ADQS incl NM CNSR By (CNSR).jmp

For this population, i.e. with deaths excluded, there is no difference between treatment groups in the 30-day mRS.

Table 10: Reviewer analysis of 30-day mRS, all endpoint strokes

TRTP		Day-30 mRS (AVAL)					
	N with a value	Mean	Std Dev	Min	Max	Median	Missing
Placebo	347	2.73	1.46	0	6	3	14
Ticagrelor 90 mg bd	284	2.78	1.57	0	6	3	12

Source: CNSR_0 Subset of PARAMCD_TTS Subset of Join ADTTE c PARAM_mRS of ADQS incl NM AVAL By (TRTP of ADTTE).jmp

The time to the new stroke was just over 5 days. Therefore the 30-day mRS was collected, on average, 25 days after the event.

Table 11: Time to primary endpoint event – all endpoint strokes

TRTP	Study day of event (ADY)						
	N with an event	Mean	Std Dev	Min	Max	Median	Missing
Placebo	347	5.38	6.57	1	34	3	0
Ticagrelor 90 mg bd	284	5.22	5.94	1	31	3	0

Reference ID: 4680885

Source: CNSR_0 Subset of PARAMCD_TTS Subset of Join ADTTE c PARAM_mRS of ADQS incl NM ADY By (TRTP of ADTTE).jmp

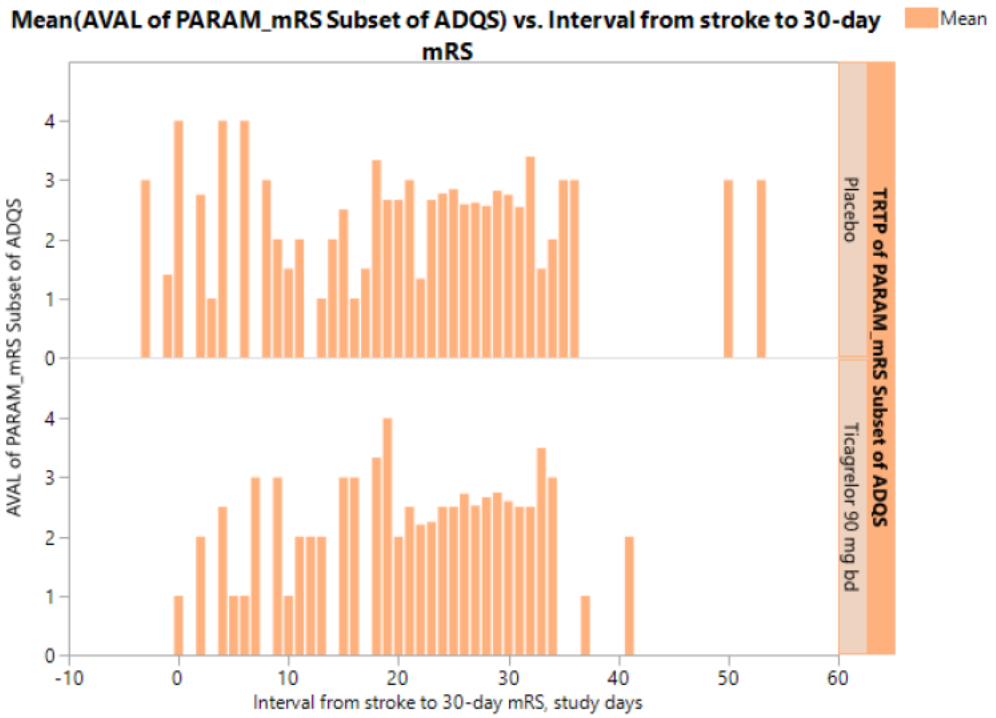
Table 12: Interval from event to 30-day mRS - all endpoint strokes

TRTP	N with an event	Interval from stroke to 30-day mRS					
		Mean	Std Dev	Min	Max	Median	Missing
Placebo	347	25.6	7.24	-3	53	27	25
Ticagrelor 90 mg bd	284	25.9	6.3	0	41	28	29

CNSR_0 Subset of PARAMCD_TTS Subset of Join ADTTE c PARAM_mRS of ADQS incl NM Interval By (TRTP of ADTTE).jmp

Reviewer Comment: Because there is some relationship between the 30-day mRS and the more accepted outcome at 90 days, the 30-day mRS in this trial suggests that there may be no difference between the treatment groups even if the outcome was measured at 90 days, even if the analysis was limited to those with an event. The graph below does not show a major change in the mRS scores in either group over the 25 days between the new stroke and the 30-day mRS. The study was not powered to show a difference between the treatment groups for this endpoint.

For the population with any stroke, the change in mRS with increasing time interval from the event is shown in the graph below.



Source: 30day mRS by interval from stroke event.jrp; CNSR_0 Subset of PARAMCD_TTS Subset of Join ADTTE c PARAM_mRS of ADQS incl NM.jmp

As mentioned above, one possible explanation for the absence of a difference between the treatment groups would be that the stroke events that did occur were minor. An analysis of the severity of the new strokes that did occur is shown in sponsor table 23 below.

Sponsor Table 23 Analysis of Disabling Stroke Using mRS Scores in Patients with Subsequent Stroke Events (Full Analysis Set)

	Ticagrelor 90 mg bd (N=5523)		Placebo (N=5493)				
Variable	n	Patients with events (%)	n	Patients with events (%)	Odds ratio	95% CI	p-value
Subsequent stroke and mRS score > 2 at visit 3	5472	150 (2.7)	5430	188 (3.5)	0.78	(0.62, 0.97)	0.024
Subsequent stroke and mRS score > 1 at visit 3	5472	201 (3.7)	5430	245 (4.5)	0.80	(0.66, 0.97)	0.021
Subsequent stroke and mRS score > 3 at visit 3	5472	98 (1.8)	5430	117 (2.2)	0.82	(0.63, 1.08)	0.154

Source: Table 23, CSR

Reviewer Comment: an mRS score of over 2 indicates an inability to manage ADLs but retention of the ability to walk. An mRS of over 1 indicates a retention of ADLs. These two dichotomies suggest a lower stroke severity in those treated with ticagrelor. An mRS over 3 indicates loss of the ability to walk independently. The odds ratio is just below the level of nominal statistical significance in favor of tricagrelor.

Ischemic stroke

If only ischemic strokes are considered, there is still no difference in the 30-day mRS between the treatment groups, although it is clear that those who did have an event had a worse 30-day mRS compared to those who did not have an event (Reviewer Table 13 below).

Sponsor Table 3 Analysis of Ischaemic Stroke (Secondary Endpoint) up to Visit 3 (Full Analysis Set)

	Ticagrelor 90 mg bd (N=5523)		Placebo (N=5493)				
Variable	Patients with events (%)	KM%	Patients with events (%)	KM%	Hazard ratio	95% CI	p-value
Ischaemic stroke	276 (5.0)	5.0	345 (6.3)	6.2	0.79	(0.68, 0.93)	0.004

Source: Table 3, Clinical Overview

Reference ID: 4680885

Table 13: Reviewer analysis of 30-day mRS for subjects who did vs. those who did not have an endpoint ischemic stroke

TRTP of ADTTE	Total	mRS at day 30 (AVAL)													
		N with a value		Mean		Std Dev		Min		Max		Median		Missing	
		CNSR													
		0	1	0	1	0	1	0	1	0	1	0	1	0	1
Placebo	5493	331	5049	2.72	0.92	1.45	0.99	0	0	6	6	3	1	14	99
Ticagrelor 90 mg bd	5523	264	5159	2.71	0.94	1.51	1.02	0	0	6	6	3	1	12	88

Source: PARAMCD_TTIS Subset of Join ADTTE c PARAM_mRS of ADQS incl NM AVAL by CNSR By (TRTP of ADTTE).jmp

30-day mRS for those with an ischemic stroke

TRTP	N with an event	30-day mRS (AVAL)					
		Mean	Std Dev	Min	Max	Median	Missing
Placebo	345	2.72	1.45	0	6	3	14
Ticagrelor 90 mg bd	276	2.71	1.51	0	6	3	12

Source: CNSR_0 Subset of PARAMCD_TTIS Subset of Join ADTTE c PARAM_mRS of ADQS incl NM AVAL By (TRTP of ADTTE).jmp

Intracranial hemorrhage

For those with an endpoint hemorrhagic event, the 30-day mRS is worse compared to those who did not have such an event, but there is no significant difference by treatment group.

Table 14: Reviewer analysis of the 30-day mRS for subjects who did and who did not have an endpoint hemorrhagic stroke

TRTP of ADTTE	Total	mRS at day 30 (AVAL)													
		N with an event		Mean		Std Dev		Min		Max		Median		Missing	
		CNSR													
		0	1	0	1	0	1	0	1	0	1	0	1	0	1
Placebo	5493	6	5374	4.67*	1.03	1.37	1.1	3	0	6	6	5	1	0	113
Ticagrelor 90 mg bd	5523	19	5404	3.89*	1.01	2.16	1.1	0	0	6	6	4	1	1	99

Source: PARAMCD_GUSTH Subset of Join ADTTE c PARAM_mRS of ADQS incl NM AVAL by CNSR By (TRTP of ADTTE).jmp
*: p = 0.1142, 2-tailed t-test (mean difference 0.78, -0.21, 1.76)

4. Safety Results

All strokes

If all adverse events that represented any type of stroke were included, the incidence of stroke remains lower in the ticagrelor group. The difference of 8 more events in the placebo group and 10 more events in the ticagrelor group, compared to the primary endpoint analysis, is accounted for primarily by the addition of the hemorrhagic transformations, which were not included as primary endpoint events.

Reference ID: 4680885

Reviewer Comment: There is no indication of a significant change in the reduction of the number of strokes due to the omission of hemorrhagic transformations or any other events that might be considered stroke from the primary endpoint analysis.

Table 15: All adverse events of stroke

AEDECOD	Placebo		Ticagrelor	
	N	%	N	%
Ischaemic stroke	325	5.92	251	4.54
Cerebrovascular accident	7	0.13	6	0.11
Haemorrhagic transformation stroke	5	0.09	8	0.14
Cerebral infarction	7	0.13	5	0.09
Ischaemic cerebral infarction	6	0.11	4	0.07
Haemorrhagic stroke	1	0.02	7	0.13
Cerebral haemorrhage	2	0.04	3	0.05
Haemorrhage intracranial	0	0	2	0.04
Lacunar stroke	2	0.04	0	0
Subarachnoid haemorrhage	0	0	2	0.04
Thalamic infarction	0	0	2	0.04
Basal ganglia haemorrhage	0	0	1	0.02
Brain stem stroke	0	0	1	0.02
Cerebellar infarction	0	0	1	0.02
Lacunar infarction	0	0	1	0.02
Total	355	6.46	294	5.32
Primary endpoint stroke events*	347	6.3	284	5.1

Source: Stroke Subset of TRTEMFL_Y Subset of AESER_Y Subset of ADAE By (USUBJID, TRTA, AEDECOD, AEBODSYS) By (AEBODSYS, AEDECOD).jmp
*: Table 2, Clinical Overview

Asymptomatic CNS hemorrhagic events that caused discontinuation of study drug were not included as primary endpoint events and were not considered SAEs. These events were categorized as No GUSTO bleeding events. There were 4 such hemorrhagic transformations that were not SAEs in each treatment group and one microhemorrhage in the ticagrelor group. These events would not have affected the overall efficacy result.

Table 16: Reviewer analysis, non-serious hemorrhagic CNS adverse events

AEDECOD	N(USUBJID, Placebo)	N(USUBJID, Ticagrelor 90 mg bd)
Cerebral microhaemorrhage	0	1
Haemorrhagic transformation stroke	4	4

Source: AESER_N Subset of CNS hem Subset of AEACN_WD Subset of TRTEMFL_Y Subset of ADAE By (USUBJID, TRTA, AEDECOD) By (AEDECOD).jmp

5. Reviewer responses to questions

1) Despite the statistically significant reduction in the number of ischemic strokes in the ticagrelor arm compared to placebo at the 30-day timepoint in the THALES trial, there was no difference in the distribution of the mRS between the arms of the trial at that timepoint.

a) Given that the THALES trial was not designed to assess changes in a mRS shift, please provide us your opinion on the clinical significance of a statistically significant reduction in ischemic stroke with no apparent favorable difference in the distribution in mRS scores between the treatment arms.

DN2: The mRS Score is considered a valid assessment of patient functional status following a stroke. The mRS is typically measured 90 days after the event, because at that point the score tends to plateau. However, there is a reasonable correlation of an earlier mRS score, such as at 30 days, with the outcome at 90 days[1]. In the THALES trial, the mRS was measured at study day 30, which was, on average, about 25 days after a new stroke. Although a baseline mRS following the index minor stroke/TIA was not established, if one assumes that randomization balanced the treatment groups for the baseline mRS, then the absence of a difference in the 30-day mRS would most likely correlate with no difference at 90 days compared to placebo. Although hemorrhages were more common with ticagrelor, there was also no significant difference by treatment group in the 30-day mRS after these events.

Although there was no difference at 90 days in the mRS scores, in the ticagrelor group as compared to placebo, this was not the case in the patients that had a stroke during the trial. For those subjects who did have a stroke, there was a mean and median 2-point higher mRS at day 30 compared to those who did not have a stroke. Therefore, the lack of a difference in the 30-day mRS between treatment groups does not appear to be due to a predominance of minor new strokes. The most likely explanation for the absence of a difference in the 30-day mRS between treatment groups is that too few events occurred to detect a difference if there was one. The study was not powered to detect a difference in the 30-day mRS. It was powered to detect 770 primary endpoint events which would yield 85% power to show an HR of 0.805 assuming an event rate of 6.7% in the placebo group. This would not be adequate to detect a difference in the mRS based on the sample size estimated to be necessary to detect a significant difference in previously reported neuroprotectant trials[2,3].

In a trial adequately powered to evaluate functional status, the lack of any observed benefit on the mRS would call into question the clinical meaningfulness of any numerical reduction in stroke incidence; however, as the current trial was not designed or powered to assess function, the absence of a difference between the treatment arms in mRS scores at Day 30 is of uncertain clinical significance (and would not a priori undermine the observed results). We defer the interpretation of the mRS results in THALES in the context of the overall trial findings to DCN.

b) Please comment if the mRS scores at 30 days is an appropriate measure of stroke severity.

Reference ID: 4680885

DN2: The mRS is not generally used as a measure of stroke severity because severity is usually of interest in the acute stage of a trial. Assessment of some aspects of the mRS is limited in the acute period. The National Institutes of Health Stroke Scale (NIHSS) score, which measures neurologic deficit, is typically used to assess acute severity. However, an analysis based on the mRS during the recovery period, e.g. at day 30, would be a reasonable assessment of the severity of the original stroke. The mRS is often dichotomized at various levels to assess outcome. The analysis in Table 23 of the CSR suggests, at a minimum, that the strokes that occurred in the ticagrelor population were not worse that those in the placebo group, and, in fact, trended to have less disabling status at 30 days.

c) Please comment whether there are other stroke types (e.g., hemorrhagic strokes) that should be considered when assessing the benefit of ticagrelor.

DN2: Hemorrhagic transformation, presumably in the territory of the index stroke, might be considered a new stroke for purposes of analysis of efficacy endpoint. However, addition of these events to the primary endpoint analysis does not affect the primary endpoint result. It is not unreasonable to include these and other hemorrhagic events, such as intracerebral hemorrhage or subarachnoid hemorrhage, as adverse events attributable to aspirin or aspirin/ticagrelor.

2) THALES was conducted entirely ex-USA. Most of the subjects were enrolled in Eastern Europe or Asia. We are concerned about regional differences in the practice paradigm concerning stroke management and secondary prevention. Please provide us with your opinion on the applicability of the trial information to American practice.

DN2: The characteristics of a TIA or minor stroke in the population selected would not be expected to differ from that of the US population because the clinical criteria for these events are the same. The underlying risk factors for these events vary somewhat even within the regions included in the study population. The guidelines for treatment of TIA and stroke are generally the same outside the US as well. That includes the guidelines for carotid endarterectomy and the guidelines for the use of endovascular thrombectomy. The population selected for this trial, i.e. those with a new minor stroke or TIA, who might or might not have been treated with thrombolysis or endovascular thrombectomy, does not appear to differ significantly by previous medical or neurologic history or by risk factors, from a comparable population in the US. (The sponsor provides an analysis of the applicability of the outside U.S. data in Appendix 20200505 in module 1.)

References

1. Ovbiagele B, Lyden PD, Saver JL. Disability status at 1 month is a reliable proxy for final ischemic stroke outcome. Neurology 2010;75:688-92.
2. Diener HC, Lees KR, Lyden P, et al. NXY-059 for the treatment of acute stroke: pooled analysis of the SAINT I and II Trials. Stroke 2008;39:1751-8.

Reference ID: 4680885

3. Lees KR, Zivin JA, Ashwood T, et al. NXY-059 for acute ischemic stroke. N Engl J Med 2006;354:588-600.

Lawrence Rodichok MD, Clinical Reviewer

Heather Fitter MD, Team Leader

Nicholas Kozauer, Division Director (Acting)

Reference ID: 4680885

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/s/

LAWRENCE D RODICHOK
10/05/2020 12:11:02 PM

HEATHER D FITTER
10/05/2020 01:44:56 PM

NICHOLAS A KOZAUER
10/05/2020 01:50:58 PM

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: September 30, 2020

From: Stephen M. Grant, M.D.
Clinical reviewer
Division of Cardiology and Nephrology /CDER

To: File

Subject: NDA #22433/S029 ticagrelor

Astra-Zeneca has submitted an efficacy supplement to NDA #22-433 seeking approval to market their dug ticagrelor "to reduce the risk of stroke in patients with acute ischemic stroke or transient ischemic attack." Ticagrelor is a reversible P2Y12 platelet inhibitor first approved in 2011. The current approved indications for ticagrelor are:

- to reduce the risk of CV death, MI, and stroke in patients with acute coronary syndrome or a history of MI.
- to reduce the risk of a first MI or stroke in patients with coronary artery disease at high risk for such events.

The principal support for the efficacy of ticagrelor for treatment of stroke and TIA is the THALES study, a randomized, double-blind, placebo-controlled, event-driven study in which 11016 patients within 24 hours of onset of mild noncardioembolic ischemic stroke or high-risk transient ischemic attack (TIA) were randomized to ticagrelor 90 mg bid or placebo on a background of low dose aspirin to for 30 days to reduce the occurrence of death and subsequent stoke.

I was assigned the clinical review and made a mid-cycle presentation on 12 August. Everything in this memo including the recommendation to present this application to an Advisory Committee was either presented during that mid-cycle or sent in clarifying emails shortly thereafter. It is based on my review of the documents submitted by the applicant; I did not perform any independent analyses. I am retiring so will not be completing the final clinical review. Nonetheless, I have identified some important issues that need to be resolved prior to a decision about approvability. And I have concluded that this application should be presented to an advisory committee for their input prior to the final decision about approval for reasons discussed below.

Background

Patients who present with nondisabling ischemic stroke ("mild stroke") and TIA are at a

significant risk for subsequent disabling stroke and death in the days to few weeks after presentation. This risk is diminished but not eliminated by administration of the antiplatelet drug aspirin to patients who do not require anticoagulant (such as patients with cardioembolic stroke associated with atrial fibrillation).

Two previous studies have been reported that tested the hypothesis that addition of a second antiplatelet drug to aspirin would further reduce the risk of subsequent stroke in patients with nondisabling ischemic stroke or high-risk TIA. The first study was the CHANCE study, which was reported in the New England Journal of Medicine (NEJM) on 26 June 2013 (the study has not been submitted to FDA for review) and was sponsored by the Ministry of Science and Technology of the People's Republic of China. CHANCE was a randomized, double-blind, placebo-controlled study conducted at 114 Chinese sites between October 2009 and July 2012. 5170 patients within 24 hours after onset of minor ischemic stroke or high-risk TIA were randomized to either clopidogrel 75 mg qd or placebo on a background of aspirin for 90 days. The primary outcome, occurrence of stroke at 90 days, was observed in 8.2% of clopidogrel vs 11.7% of placebo (HR, 0.68; 95% CI, 0.57 to 0.81). The rates of bleeding and death were similar between both groups. Functional disability was not reported in the NEJM although the protocol indicates a measure of functional status, modified Rankin Scale score (mRS), in which a score ≥ 2 indicates some disability (highest score is 6), was collected at various times. An 18 August 2015 publication in the journal Neurology reported that 254 (9.9%) clopidogrel subjects vs 299 (11.6%) placebo subjects mRS ≥ 2 at 90 days (absolute difference in poor outcome, 1.70%; 95% CI 0.03%–3.42%). The statistic analytic plan published in NEJM indicates mRS was a secondary endpoint, but no particular analysis plan is specified so it is not known whether the analysis published in Neurology was designed after the results were known.

The second study was the POINT study, which was reported in the New England Journal of Medicine (NEJM) on 19 July 2018 (the study has not been submitted to FDA for review) and was sponsored by the National Institute of Neurological Disorders and Stroke. POINT was a randomized, double-blind, placebo-controlled study conducted at between May 2010, to December 2017 at 269 sites in 10 countries. 83% of subjects were Americans and 20% were black. 4881 patients within 12 hours after onset of minor ischemic stroke or high-risk TIA were randomized to either clopidogrel 75 mg qd or placebo on a background of aspirin for 90 days. The primary outcome, occurrence of ischemic stroke, MI, or death from ischemic vascular causes at 90 days, was observed in in 5.0 % of clopidogrel vs 6.5% of placebo (HR, 0.75; 95% CI 0.59 to 0.95). Deaths trended adversely; 18 clopidogrel patients died vs 12 placebo. Major hemorrhage (defined as bleeding resulting in death, intracranial hemorrhage, transfusion of 2 units of red blood cells, or need for or prolongation of hospitalization) also trended adversely 23 (0.9%) ticagrelor vs 10 (0.4%) placebo. Functional disability measured as mRS at day 90 was a prespecified secondary endpoint with a prespecified analytic plan. mRS ≥ 2 at day 90 occurred in 13.3% of ticagrelor subjects vs 13.7% placebo; HR 0.97 (95% CI 0.82-1.14). It should be noted that S. Claiborne Johnston is the first author on the NEJM report of POINT and is the senior author on the NEJM report of CHANCE. He was also the principal investigator for the THALES study.

Based on the results of POINT and CHANCE, the 2019 update to the American Stroke Association/ American Heart Association "Guidelines for the Early Management of Patients With Acute Ischemic Stroke" states that "In patients presenting with minor noncardioembolic ischemic…treatment with dual antiplatelet therapy (aspirin and clopidogrel) started within 24

hours after symptom onset and continued for 21 days is effective in reducing recurrent ischemic stroke for a period of up to 90 days from symptom onset.

Description and Outcomes of the THALES Study

The THALES ("Acute Stroke or Transient Ischaemic Attack Treated with Ticagrelor and ASA for Prevention of Stroke and Death") study a randomized, double-blind, placebo-controlled, event-driven study of administering ticagrelor 90 mg vs placebo on a background of low dose aspirin to patients within 24 hours of onset of mild noncardioembolic ischemic stroke or high-risk TIA for 30 days. After 30 days subjects reverted to "usual care" with a final visit at 60 days. The primary endpoint was time to a composite of all-cause death and stroke through day 30. Two secondary endpoints were stipulated within the plan to conserve alpha: 1) Time to ischemic stroke through day 30 and 2) Functional disability at 30 days as measured by modified Rankin Scale stroke > 1. The principal eligibility criteria were:

1. 40 years of age within 24 hours of onset of
   - Acute ischemic stroke with NIH Stroke Scale/Score (NIHSS) ≤ 5

   OR
   - High-risk TIA or ≥ 50% narrowing of an artery that could account for the TIA
2. CT or MRI performed after symptom onset ruling out intracranial hemorrhage or other nonischemic pathology
3. No thrombolysis or mechanical thrombectomy
4. No planned carotid endarterectomy within 3 days of randomization

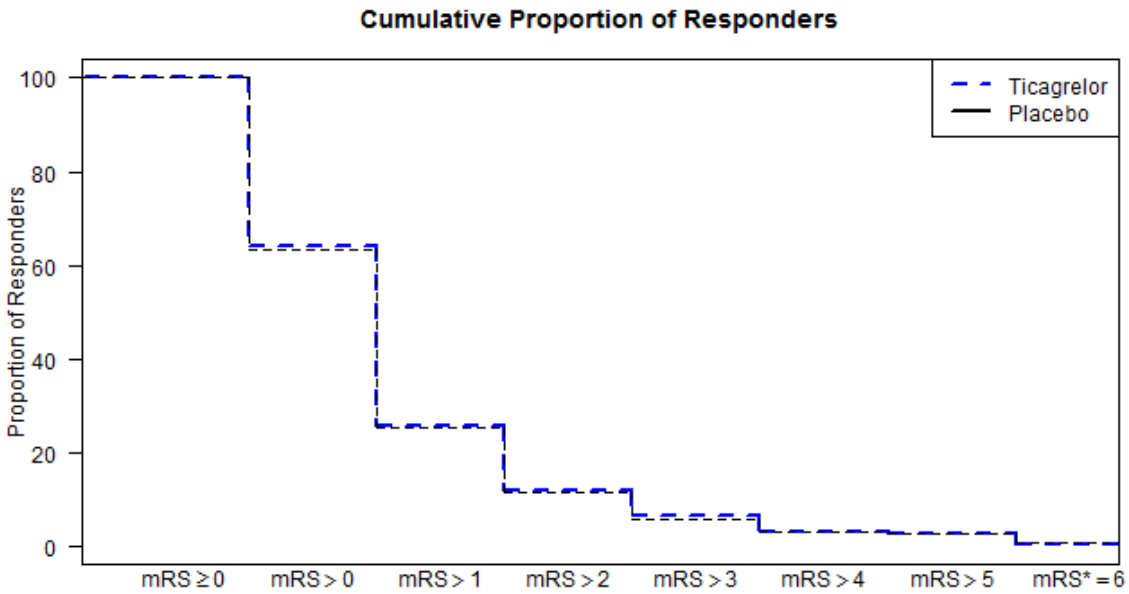
NIHSS is a well-validated quantitative measure of stroke-related neurologic deficit and has been shown to be a predictor of both short- and long-term outcome. It is widely used in both clinical practice and clinical studies. For example, it is used to decide whether a stroke is likely to be disabling if untreated and so justifies the risks of thrombolysis. The score ranges from 0 to 42 with a score below 5 indicating a mild stroke, i.e. low likelihood of disabling stoke if untreated.

11073 patients with the following characteristics were enrolled at 414 sites in 28 countries from January 2018 to October 2019:

- Most patients were enrolled in Asia (45%) or Eastern Europe (33%). Essentially no North Americans were enrolled.
- Mostly White or Asian, 0.5% Black
- Male: female 60%: 40%
- 50% < 65 years of age
- Mean BMI 26 kg/m^2
- 80% hypertensive; 30% diabetic; 10-15% history of coronary disease
- 16% previous stroke
- 60% NIHSS ≤3, 30% NIHSS 4-5, 10% TIA
- Imaging of "intracranial or extracranial" arteries performed in 80% (not required by protocol)
- 4% occluded ipsilateral artery
- 10 % ≥ 50% stenosis ipsilateral artery
- ~ 100 had carotid or vertebral revascularization
- No categorization of ischemic stroke subtype based on CT/MRI & vascular imaging

Reference ID: 4678836

The primary outcome occurred in occurred in 362 ticagrelor subjects (5.4%) vs 303 placebo (6.5%) – HR 0.83 [95% CI 0.71, 0.96], p = 0.02. The result was driven entirely by stroke; deaths through day 30 trended adversely: 36 ticagrelor (0.7%) vs 27 placebo (0.5%) (19 vs 15 as first events). No effect on functional disability as measured by Modified Rankin Scale score at day 30 - mRS > 1: 1282 (23.8) ticagrelor vs 1284 (24.1) placebo OR 0.98 (0.89, 1.07). This outcome is demonstrated graphically in the figure below taken from Dr. William Koh's mid-cycle presentation:



Number (%)								
Ticagrelor	5523 (100.0%)	3503 (63.4%)	1387 (25.1%)	632 (11.4%)	325 (5.9%)	157 (2.8%)	136 (2.5%)	36 (0.7%)
Placebo	5493 (100.0%)	3529 (64.2%)	1403 (25.5%)	648 (11.8%)	346 (6.3%)	164 (3.0%)	140 (2.5%)	27 (0.5%)

The primary safety outcome, GUSTO severe bleeding (defined as death, intracerebral hemorrhage, bleeding resulting in hemodynamic compromise requiring surgery or vasopressors), occurred in 28 ticagrelor patients vs 7 placebo with ICH or fatal bleeding occurred in 22 ticagrelor subjects vs 6 placebo. Discontinuation of investigational product was attributed to bleeding in 152 (2.9%) ticagrelor subjects vs 32 (0.6%) placebo.

Conclusions:

1. Approval of ticagrelor for the indication sought would not meet an unmet medical need. In fact, the evidence for the utility of clopidogrel in this clinical situation is stronger. There are two adequate and well-controlled studies of clopidogrel supporting its efficacy as opposed to only one for ticagrelor. One of the clopidogrel studies appears to demonstrate that administration reduces disability whereas THALES does not demonstrate such a reduction. Patients in both CHANCE and POINT were followed longer allowing assessment for a longer period of time. Clopidogrel caused less serious bleeding in CHANCE and POINT than did ticagrelor in THALES and so clopidogrel appears to be safer. The pharmacology of clopidogrel as well as the results of previous clinical trials directly comparing clopidogrel to

Reference ID: 4678836

ticagrelor also demonstrate clopidogrel cause less bleeding than ticagrelor. Finally, approximately 20% of the patients enrolled in the POINT study were black allowing an assessment of clopidogrel's safety and efficacy in that group of patients.

2. THALES demonstrates that the administration of ticagrelor for 30 days to patients with recent minor stroke or high-risk TIA poses serious risks to patients. Patients administered ticagrelor had a significantly increased risk of serious bleeding, including intracranial hemorrhage, and a trend toward increased mortality.
3. THALES demonstrates that the administration of ticagrelor for 30 days to patients with recent minor stroke or high-risk TIA reduces the risk of recurrent stroke during that time period. However, it does not demonstrate that ticagrelor reduces disability, one of the two major adverse outcomes of stroke. That most, or even all, of the strokes prevented by ticagrelor were mild nondisabling strokes cannot be ruled out.
4. THALES demonstrates that the administration of ticagrelor for 30 days to patients with recent minor stroke or high-risk TIA does not reduce the risk of death, the other major adverse outcome of stroke. In fact, there was a trend toward increased mortality in patients administered ticagrelor.
5. Very few blacks were enrolled in THALES; too few to make a reasonable assessment of outcomes. Making such an assessment is important because the risk of having a first stroke is nearly twice as high for blacks as for whites, and blacks have a higher rate of death due to stroke (CDC-"Underlying Cause of Death, 1999–2018" and "Heart disease and stroke statistics—2020 update: a report from the American Heart Association").
6. NIHSS is a well-validated quantitative measure of stroke-related neurologic deficit and has been shown to be a predictor of both short and long term outcome. To eligible to enroll in THALES patients were supposed to have had an NIHSS of ≤ 5, which predicts a mild stroke. Nonetheless, 729 of the 10408 patients without strokes subsequent to enrollment were disabled as assessed by mRS > 2 at day 30. It may be that subjects with baseline deficits more severe than NIHSS of 5 were enrolled. The final review will need to consider whether an approximately 7% rate of disabling stroke in patients with NIHSS of ≤ 5 is so high it impugns the conduct of the study.
7. The final clinical review should determine whether the rate of extracranial revascularization is lower than would be expected in the USA, as it seems to be. If so, the effect on outcomes needs to be assessed. At a minimum, the rate should be disclosed in section 14 of any resulting PI and potentially be disclosed in section 1 as a limitation of use.
8. In the final clinical review baseline ischemic stroke subtype should be categorized based on CT/MRI & vascular imaging to 1) explore whether the effects of ticagrelor significantly vary among the subtypes and 2) for disclosure in the PI, should the application be approved.

Recommendation

I recommend that this application be reviewed by an Advisory Committee for the following reasons:

1. To get external input into the approvability of the application. The risk-benefit relationship for ticagrelor for reducing the risk of stroke in the 30 days following nondisabling ischemic

Reference ID: 4678836

stroke or high-risk TIA does not appear to support approval. Ticagrelor increases the risk of serious bleeding and likely increases the risk of death. Although it does reduce the risk of stroke, no reduction in disability was demonstrated. A reduction in the risk of minor mild nondisabling stroke may not be a significant enough benefit to outweigh the increased risk of serious bleeding and probably death.

2. To discuss the significance of the low enrollment of blacks in THALES. The FDA guidance "Collection of Race and Ethnicity Data in Clinical Trials" states "This guidance does not address the level of participation of racial and ethnic groups in clinical trials. For questions related to the level of participation or the size of a trial, sponsors should consult with the review division of the appropriate centers and office for guidance on clinical trial design and demographic sub-groups prior to the start of a trial." The Division of Cardiology and Nephrology has consistently not required any particular level of participation of racial and ethnic groups in clinical trials intended to support a marketing application (although the level required appears to vary significantly among other review Divisions and Centers). It appears to this reviewer that DCN's reasons for not requiring any particular level have been as follows:

    i. Enrolling certain subgroups is difficult and so demanding their inclusion may unreasonably delay the conduct of studies that could provide useful therapy.
    ii. There often is no information to suggest that the effect of the drug expressed as a relative risk reduction is different in the subgroup. The baseline risk and competing risks may be different but that can be accounted for if the relative risk reduction is known without a direct demonstration.
    iii. The benefit of some drugs is so obvious and large that variation in relative risk reduction is likely inconsequential.

    None of these concerns are applicable to this application. The principal investigator of THALES had just conducted a similar study with clopidogrel in which 20% of the subjects were black so the information needed to identify sites that could enroll blacks was available. Stroke is an important and disproportionate cause of mortality and serious morbidity in blacks but it is unclear if stroke in the Black population is different or responds differently to treatment. Here a lack of evidence should not be construed as lack of effect. Finally, the benefit provided by ticagrelor is clearly not large in relationship to the risk. If the effect of ticagrelor in Blacks is different, it may be important in assessing the benefit-risk in this population.

    Finally, this reviewer believes DCN's approach to the inclusion of blacks and other important demographic subgroups in clinical trials intended to support marketing applications should be transparent and receive external input. It is a topic that has been frequently discussed in the clinical literature for quite a while and a discussion by an advisory committee is likely to informative and of great interest.

Reference ID: 4678836

APPEARS THIS WAY ON ORIGINAL

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/s/

STEPHEN M GRANT
09/30/2020 04:30:36 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022433Orig1s029

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION
FILING REVIEW OF AN NDA/BLA

NDA #:	NDA022433
Sequence #:	0565
Supplement #:	029
Related IND #:	IND 115807
Product Name:	Brilinta (ticagrelor)
Indication(s):	Reduce the risk of stroke in patients with acute ischemic stroke or transient ischemic attack
Applicant:	Astra Zeneca
Dates:	Submission date: May 05, 2020
	PDUFA date: March 05, 2021
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II
Statistical Reviewer:	William Koh, PhD, Statistical Reviewer
Concurring Reviewers:	Jialu Zhang, PhD, Team Leader
Medical Division:	Division of Cardiovascular and Nephrology
Clinical Team:	Stephen Grant, MD, Clinical Reviewer
	Fred Senatore, MD, Team Leader
Project Manager:	Bridget Kane

1. Summary of Efficacy/Safety Clinical Trials to be Reviewed

The applicant submitted a supplemental New Drug Application (sNDA) for the approval of ticagrelor to reduce the risk of stroke in patients with acute ischemic stroke or transient ischemic attack based on a single study, THALES (D5135C00003, NCT03354429). The proposed dosing regimen for this indication is a loading dose of 180 mg subcutaneous injection, followed by 90 mg twice daily for 30 days.

THALES was a randomized, parallel-group, placebo-controlled, multi-center, double-blind clinical trial (Table 1). The primary objective of the study was to determine the efficacy and safety of ticagrelor compared to placebo in the prevention of stroke and or death in patients with acute ischemic stroke or transient ischemic attack. The primary efficacy endpoint is time to composite stroke or death through Day 30 (Visit 3).

Reference ID: 4619605

Table 1 Summary of Trials to be Assessed in the Statistical Review

Trial ID	Design/ Patient Population	Treatment/ Sample Size	Primary Endpoint/ Analysis	Preliminary Findings
THALES	MC, R, DB, PG, PC Patients ≥ 40 years of age with acute ischemic stroke or TIA, randomized within 24 hours after onset of symptoms	PBO (n=5493) Ticagrelor (n=5523) FPFV: January 22, 2018 LPLV: December 13, 2019	<u>Primary Endpoint</u> Time to composite of stroke and death through Day 30 <u>Analysis Method</u> Cox PH regression with factor for treatment and Efron method for handling ties.	<u>Events</u> Ticagrelor: 303 Placebo: 362 Hazard Ratio: 0.83 95% CI: 0.71, 0.96 p=0.015

Abbreviations: MC=multi-center; R=randomized; DB=double-blind; PG=parallel group; PC=placebo-controlled; PBO=placebo; PH=proportional hazards; CI=confidence interval; FPFV=first patient first visit; LPLV=last patient last visit
[Source: Clinical study report; Protocol D5134C00003]

A total of 11016 screened patients from 414 sites in 28 countries were randomized in a 1:1 ratio to ticagrelor (n=5523) or placebo (n=5493). A total of 86.6% of the patients completed randomized treatment (Table 2). There were no numerical differences between the number of patients who discontinued randomized treatment across treatment arms. All but one patient's vital status was ascertained at Visit 3, the primary efficacy time-point, Day 30. There appears to be minimal missing data for the primary efficacy endpoint.

Table 2 Summary of Patient Disposition for THALES

	Ticagrelor (N=5523)	Placebo (N=5493)	Total (N=11073)
Patients randomized who did not receive treatment	17 (0.3)	23 (0.4)	40 (0.4)
Patients randomized who received treatment	5506 (99.7)	5470 (99.6)	10976 (99.6)
Patients who completed treatment	4715 (85.4)	4825 (87.8)	9540 (86.6)
Patients who discontinued treatment	791 (14.3)	645 (11.7)	1436 (13.0)
Patients who withdraw consent before Visit 3	7 (0.1)	6 (0.1)	13 (0.1)
Alive	7 (0.1)	6 (0.1)	13 (0.1)
Dead	0 (0.0)	0 (0.0)	0 (0.0)
Vital Status unknown	0 (0.0)	0 (0.0)	0 (0.0)
Patients in the study at Visit 3	5516 (99.9)	5487 (99.9)	11003 (99.9)
Alive	5479 (99.2)	5460 (99.4)	10939 (99.3)
Dead	36 (0.7)	27 (0.5)	63 (0.6)
Vital status unknown	1 (0.0)	0 (0.0)	1 (0.0)

[Source: Statistical reviewer adapted Table 14.1.1.1 from the clinical study report]

A summary of the key clinical findings is presented in Table 3.

Table 3 Summary of Primary and Key Secondary Endpoints

	Ticagrelor (N=5523) [1]	Placebo (N=5493) [1]	Total (N=11073) [2]
Time to first Stroke or Death	303; (5.4%)	362 (6.5%)	0.83 (0.71, 0.96); 0.015
Time to first Stroke	284; (5.1%)	347 (6.3%)	0.81 (0.69, 0.95); 0.008
Time to death	36; (0.6%)	27 (0.5%)	1.33 (0.81, 2.19); 0.264
Time to first Ischemic Stroke	276; (5.0%)	345 (6.2%)	0.79 (0.68, 0.93); 0.004

1: Number of events and the estimate from the Kaplan Meier curves are presented in parenthesis
2: Hazard ratio, respective 95% CI, and p-values are presented.
Abbreviations: CI=confidence intervals
[Source: Statistical reviewer compiled results from Table 18 and 20 from the clinical study report]

2. Assessment of Protocols and Study Reports

Table 4 Summary of Information Based Upon Review of the Protocol and the Study Report

Content Parameter	**Response/Comments**
Designs utilized are appropriate for the indications requested.	The study design was randomized, double-blind, parallel group. The study appears to be adequate to address the proposed indication.
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	The primary endpoint and method of statistical analysis were pre-specified.
Interim analyses (if present) were pre-specified in the protocol with appropriate adjustments in significance level. DSMB meeting minutes and data are available.	There was an interim analysis planned. The SAP had specified an efficacy stopping boundary based on a Haybittle-Peto procedure. The DSMB meeting minutes were submitted for review.
Appropriate details and/or references for novel statistical methodology (if present) are included (e.g., codes for simulations).	The SAS macros and codes were submitted for various analysis. Will be determined later if the codes were enough.
Investigation of effect of missing data and discontinued follow-up on statistical analyses appears to be adequate.	The applicant specified a tipping point analysis may be performed by adding events to the ticagrelor group at time of censoring until a non-significant result is obtained. The appropriateness of their methodology will be a review issue.

Abbreviations: DSMB=data safety monitoring board; SAP=statistical analysis plan

3. Electronic Data Assessment

Table 5 Information Regarding the Data

Content Parameter	Response/Comments
Dataset location	NDA022433\0565\m5\datasets\ d5134c00003\analysis\adam\datasets NDA022433\0565\m5\datasets\ d5134c00003\tabulations\sdtm
Were analysis datasets provided?	Yes.
Dataset structure (e.g., SDTM or ADaM)	The datasets were submitted in ADaM format under CDISC ADaM Conformance Rules v2.0
Are the define files sufficiently detailed?	The define files for both the tabulation and analysis data had sufficient description.
List the dataset(s) that contains the primary endpoint(s)	Under analysis datasets: adtte (where PARAMCD=``TTSD")
Are the *analysis datasets* sufficiently structured and defined to permit analysis of the primary endpoint(s) without excess data manipulation?	Yes.
Are there any initial concerns about site(s) that could lead to inspection? If so, list the site(s) that you request to be inspected and the rationale.	Clinical decided that there would not be any site inspection.
Safety data are organized to permit analyses across clinical trials in the NDA.	This was a single study. Therefore, there is no integrated safety review.

Abbreviations: NDA=new drug application; SDTM=study data tabulation model; ADaM=analysis data model; ISS=integrated summary of safety; SAP=statistical analysis plan; CDISC=clinical data interchange standards consortium

4. Filing Issues

Table 6 Initial Overview of the NDA/BLA for Refuse-to-file (RTF):

Content Parameter	Yes	No	NA	Comments
Index is sufficient to locate necessary reports, tables, data, etc..	√			
ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.).			√	This is a single study and therefore ISS and ISE are not required.
Safety and efficacy were investigated for gender, racial, and geriatric subgroups.	√			

Reference ID: 4619605

Content Parameter	Yes	No	NA	Comments
Data sets are accessible, sufficiently documented, and of sufficient quality (e.g., no meaningful data errors).	√			
Application appears to be free from any other deficiencies that render the application unreviewable, administratively incomplete, or inconsistent with regulatory requirements.	√			

Abbreviations: ISS=integrated summary of safety; ISE=integrated summary of efficacy; AEs=adverse events

IS THE APPLICATION FILEABLE FROM A STATISTICAL PERSPECTIVE?

Yes

5. Comments to be Conveyed to the Applicant

NA

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/s/

WILLIAM J KOH
06/04/2020 12:15:37 PM

JIALU ZHANG
06/04/2020 03:07:51 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022433Orig1s029

OTHER REVIEW(S)

DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Regulatory Project Manager Review

NDA:	22433/S-029
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 #Study #D5134C00003, entitled: "A Randomized, Double-Blind, Placebo-Controlled, International, Multicenter, Phase III Study to Investigate the Efficacy and Safety of Ticagrelor and ASA Compared with ASA in the Prevention of Stroke and Death in Patients with Acute Ischemic Stroke or Transient Ischemic Attack" (THALES).
Proposed Indication:	BRILINTA is indicated to reduce the risk of stroke in patients with acute ischemic stroke or transient ischemic attack (TIA).
Approved Indication:	BRILINTA is indicated to reduce the risk of stroke in patients with acute ischemic stroke (NIH Stroke Scale score ≤5) or high-risk transient ischemic attack (TIA).
Date of Submission:	5 May 2020
Approval date:	5 November 2020
PDUFA date:	5 November 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
      - Fred Senatore, MD, PhD – Cross Disciplinary Team Leader (CDTL)
      - Stephen Grant, MD – Clinical Reviewer (through midcycle)
      - Christine Garnett, PharmD – Team Leader (post-midcycle)
      - Lars Johannesen, PharmD – Clinical Reviewer/Analyst (post-midcycle)
      - Bridget Kane, MS – Sr. Regulatory Health Project Manager
  - Office of Biometrics, Division of Biometrics II
    - Jialu Zhang, PhD – Team Leader
    - William Koh, PhD - Reviewer

❖ BACKGROUND

BRILINTA (ticagrelor), developed by Astra Zeneca (AZ), is a P2Y12 platelet inhibitor approved in 2011 for reduction of the rate of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) (unstable angina, non-ST elevation myocardial infarction, or ST elevation myocardial infarction) based on the results of the PLATO trial. In 2015, the indication was expanded to include treatment of patients with a history of myocardial infarction based on the results of the PEGASUS trial. Most recently, on 28 May 2020, the Division approved Supplement-028, based on the THEMIS trial, 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).*

In 2016, under IND 115807, the Sponsor completed SOCRATES (#D5134C00001), a large randomized, double-blind trial comparing treatment with ticagrelor monotherapy (90 mg bid) to acetylsalicylic acid (ASA) monotherapy (81 mg qd) in patients with acute minor ischemic stroke or high-risk transient ischemic attack stroke (TIA). The study was not successful on its primary endpoint: time from randomization to the first occurrence of the composite of stroke (ischemic or hemorrhagic), myocardial infarction, or death. During the SOCRATES topline meeting with the Division on 19 April 2016, the Sponsor noted that the results of SOCRATES suggest that early dual antiplatelet therapy with ticagrelor and ASA after an acute stroke or TIA may prevent subsequent strokes. The Division suggested that the Sponsor conduct a large simple trial to evaluate the use of ticagrelor plus ASA versus ASA alone to test this hypothesis (Meeting Minutes dated 5 May 2016).

In September 2016, the Sponsor requested a pre-phase 3 meeting (Preliminary Comments dated 27 October 2016) to discuss the design of a study to further explore ticagrelor for the prevention of stroke and death in patients with acute ischemic stroke or TIA. In January 2018, study #D5134C00003, titled "Acute S**T**roke or Transient Isc**H**aemic Attack Treated with Tic**A**gre**L**or and ASA for Pr**E**vention of **S**troke and Death (THALES)" was initiated. THALES was a phase 3, multi-national, randomized, placebo-controlled, double-blind, parallel-group, event-driven study designed to evaluate whether ticagrelor in combination with aspirin (ASA) is superior to ASA alone in preventing the composite of stroke and death at 30 days in patients with acute ischemic stroke or TIA. The Sponsor randomized 11,016 subjects to accrue 665 primary events. The last patient visit was conducted in December 2019 and the database was locked in January 2020.

A topline meeting was held on 25 February 2020 (Meeting Minutes dated 6 March 2020) to discuss the results of THALES. THALES met its primary endpoint at p=0.015 indicating treatment for 30 days with ticagrelor + aspirin reduced the rate of stroke and death in patients with acute ischemic stroke or TIA when compared to aspirin alone. A numerical benefit/risk analysis favored ticagrelor.

On 5 May 2020, AZ submitted a S-029 to add a new indication based on the results of the THALES trial; a priority review was requested. The application was filed on 4 July 2020 and granted a priority review. The Division consulted the Division of Neurology-2 with questions related to the severity of stroke in each arm as measured by the modified Rankin Score as well as stroke management / secondary prevention.

After the mid-cycle meeting, the clinical reviewer (Grant) retired; Lars Johannesen and Christine Garnett completed the clinical review. At the request of Dr. Ellis Unger, the Division brought the application to a Medical Policy and Program Review Committee (MPPRC) meeting (12 October 2020) to discuss the benefit/risk profile. The MPPRC agreed with the Division that the benefit/risk profile was favorable.

See Discipline Review Section for recommendations.

❖ REGULATORY TIMELINE

- Pre-NDA Meeting (WRO): 25 July 2019
- Topline Meeting: 25 February 2020
- Stamp Date: 5 May 2020
- Site Selection Meeting: 26 May 2020
- Filing Meeting: 3 June 2020
- Filing Letter Sent: 2 July 2020
- Filing Date (Day 60): 4 July 2020
- Team Meeting: 6 July 2020
- Team Meeting: 30 July 2020
- Mid-Cycle Meeting: 12 August 2020
- Team Meeting: 18 August 2020
- Post-Midcycle Meeting: 19 August 2020
- Team Meeting: 3 September 2020
- PeRC Review: 15 September 2020
- Labeling Meeting #1: 16 September 2020
- MPPRC Meeting: 21 October 2020
- Labeling Meeting #2: 22 October 2020
- PDUFA Date: 5 November 2020

❖ ADMINISTRATIVE ITEMS

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

Facilities
N/A

Site Inspections
A site selection meeting was held on 26 May 2020; the review team determined site inspections were not needed.

Pediatric Review Committee (PeRC)
This supplement triggered PREA and the applicant submitted a request for full waiver (Agreed iPSP obtained 19 September 2019). The application/request was reviewed by the PeRC on 15 September 2020. 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 Priority Review.

❖ LABELING REVIEW

Labeling negotiations began on 1 October 2020 and concluded on 3 November 2020. Attached is a tracked changes version of the label that includes all changes made to Full Package Insert during this review cycle.

❖ DISCIPLINE REVIEWS

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

Clinical/Statistics Review (21 October 2020 – Johannesen, Koh, Zhang, Garnett, Senatore)
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 stroke in patients with acute ischemic stroke (NIH Stroke Scale score ≤5) or high-risk transient ischemic attack (TIA).*

The reviewers stated that the "… efficacy analysis showed a statistically significant absolute reduction of -1.1% in the risk of the composite endpoint favoring ticagrelor over placebo. This corresponded to a relative risk reduction of 20% (hazard ratio 0.8; 95% confidence interval 0.71 – 0.96). The results were driven by a reduction in any stroke, with consistent significant findings in key secondary endpoint for ischemic stroke, and prespecified subgroups. Based on the Kaplan Meier curves, the benefit in reducing recurrent ischemic stokes occurred early during the trial."

The observed risks (severe bleeding and dyspnea) in THALES are consistent with the known and labeled risks for ticagrelor. Several benefit/risks analyses were performed by the team and they concluded that the benefit/risk ratio was favorable for ticagrelor treatment in this population.

CDTL Memo (26 October 2020 – Senatore, Stockbridge)
Recommended Action: Approval
The CDTL & Division Director agreed with the team's recommendation for approval and concluded that the benefit of preventing a recurrent stroke that may result in disability outweighed the potential risk of a severe bleed following treatment with ticagrelor in patients with high risk TIA or acute ischemic stroke. Because the benefit occurred early in the trial and the risk for bleeding continued, the Division labeled ticagrelor administration for 'up to 30 days' to allow discretion to limit duration based on clinical judgement.

The CDTL memo also addressed the uncertainties raised by Dr. Grant in his review dated 30 September 2020.

❖ CONSULT REVIEWS

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

- Division of Neurology 2 – Rodichok, 5 October 2020
- DMEPA (labeling) – Mehta, 6 October 2020
- OPDP (labeling) – Patel, 8 October 2020
- Patient Labeling – Walker, 13 October 2020

❖ CONCLUSION

After taking into consideration the primary and consult reviews, the Division issued an approval letter for NDA 22433/S-029 on 5 November 2020. This approval letter was signed by Norman Stockbridge, MD, PhD – Division Director.

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/s/

BRIDGET E KANE
11/05/2020 10:36:36 AM

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

PATIENT LABELING REVIEW

Date:	October 13, 2020
To:	Bridget Kane, MS Senior Regulatory Health Project Manager **Division of Cardiology and Nephrology (DCN)**
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-029
Applicant:	AstraZeneca

1 INTRODUCTION

On May 5, 2020, AstraZeneca submitted for the Agency's review an efficacy supplement to their New Drug Application (NDA) 22433/S-029 for BRILINTA (ticagrelor) tablets. This supplement includes a proposed new indication to reduce the risk of stroke in patients with acute ischemic stroke or transient ischemic attack.

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 Cardiology and Nephrology (DCN) on June 17, 2020 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 May 5, 2020, and received by DMPP and OPDP on October 1, 2020.
- Draft BRILINTA (ticagrelor) tablets Prescribing Information (PI) received on May 5, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 1, 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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10/13/2020 02:15:26 PM

ZARNA PATEL
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LASHAWN M GRIFFITHS
10/13/2020 03:02:36 PM

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

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

Memorandum

Date: October 8, 2020

To: Bridget Kane, Regulatory Project Manager
Division of Cardiology and Nephrology (DCN)

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 29

In response to DCN's consult request dated June 17, 2020, OPDP has reviewed the proposed product labeling (PI) and the Medication Guide for BRILINTA (ticagrelor) tablets, for oral use (Brilinta). This supplement (S29) pertains to the indication for acute ischemic stroke or transient ischemic attack.

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 October 1, 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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/s/

ZARNA PATEL
10/08/2020 11:42:44 AM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

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

Date of This Review:	October 06, 2020
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 22433/S-029
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
FDA Received Date:	May 5, 2020 and June 10, 2020
OSE RCM #:	2020-923
DMEPA Team Leader:	Hina Mehta, PharmD

Reference ID: 4681995

1 REASON FOR REVIEW

AstraZeneca submitted supplemental NDA 22433/S-029 for Brilinta (ticagrelor) tablets to propose a new indication to reduce the risk of stroke in patients with acute ischemic stroke or transient ischemic attack (TIA). The indication is based on the results of a single, Phase III study, D5134C00003, entitled: "*A Randomized, Double-Blind, Placebo-Controlled, International, Multicenter, Phase III study to Investigate the Efficacy and Safety of Ticagrelor and ASA Compared with ASA in the Prevention of Stroke and Death in Patients with Acute Ischaemic Stroke or Transient Ischaemic Attack (THALES)*." We reviewed the proposed Brilinta Prescribing Information (PI) and Medication Guide (MG) for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

Brilinta (ticagrelor) is a $P2Y_{12}$ platelet inhibitor approved July 20, 2011. It 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. It is available in 60 mg and 90 mg tablets.

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 Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F
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

AstraZeneca proposed a new indication for Brilinta (ticagrelor) to reduce the risk of stroke in patients with acute ischemic stroke or transient ischemic attack. We performed a risk assessment of the proposed PI and Medication Guide to determine if they are acceptable from a medication error perspective.

Reference ID: 4681995

We note the dosing for the proposed indication will be a loading dose of 180 mg and then 90 mg twice daily. This dosing scheme is the same as the currently approved dosing for ACS or history of MI.

Our review of the proposed PI identified areas that can be improved to increase readability. We provide recommendations for the Division in Section 4.1. We find the proposed Medication Guide acceptable from a medication error perspective.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed PI are unacceptable from a medication error perspective and can be improved to promote the safe use of the product. We provide recommendations for the PI to the Division in Section 4.1 below.

4.1 RECOMMENDATIONS FOR DIVISION OF CARDIOLOGY AND NEPHROLOGY (DCN)

A. Highlights and Full Prescribing Information

1. Dosage and Administration Section

a. We recommend the unit of measure be included after each value to prevent confusion. Revise ’75-100 mg’ to ’75 mg – 100 mg’.

APPEARS THIS WAY ON ORIGINAL

Reference ID: 4681995

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Brilinta received on June 10, 2020 from AstraZeneca.

Table 2. Relevant Product Information for Brilinta	
Initial Approval Date	July 20, 2011
Active Ingredient	ticagrelor
Indication	Reduce the risk of cardiovascular death, myocardial infarction (MI), and stroke in patients with acute coronary syndrome (ACS) or a history of MI. Reduce the risk of stent thrombosis in patients who have been stented for treatment of ACS. Reduce the risk of MI of a first MI or stroke in patients with coronary artery disease (CAD) at high risk for such events. *Proposed: Reduce the risk of stroke in patients with acute ischemic stroke or transient ischemic attack (TIA).*
Route of Administration	Oral
Dosage Form	Tablets
Strength	60 mg and 90 mg
Dose and Frequency	ACS or History of MI – 180 mg loading dose them 90 mg twice daily during the first year. After one year, administer 60 mg twice daily CAD and No Prior Stroke or MI – 60 mg twice daily *Acute Ischemic Stroke – 180 mg loading dose then continue with 90 mg twice daily for 30 days.*
How Supplied	90 mg – bottle of 60 and 100 count Hospital Unit Dose 60 mg – bottle of 60
Storage	Store at 25˚C (77˚F); excursions permitted to 15˚ to 30˚C (59˚ to 86˚F) [see USP controlled room temperature]

Reference ID: 4681995

APPENDIX B. PREVIOUS DMEPA REVIEWS

On October 6, 2020, we searched for previous DMEPA reviews relevant to this current review using the terms, Brilinta and ticagrelor. Our search identified one previous reviews[a] and we considered our previous recommendations to see if they are applicable for this current review.

APPEARS THIS WAY ON ORIGINAL

[a] Jone, G. Label and Labeling Review for Brilinta (NDA 022433/S-028). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 DEC 20. RCM No.: 2019-1635.

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,[b] along with postmarket medication error data, we reviewed the following Brilinta labels and labeling submitted by AstraZeneca.

- Prescribing Information and Medication Guide (Image not shown) received on June 10, 2020 available from \\CDSESUB1\evsprod\nda022433\0605\m1\us\annotated-draft-label-thales-new-indication.pdf

APPEARS THIS WAY ON ORIGINAL

[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

HINA S MEHTA
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022433Orig1s029

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 115807

MEETING REQUEST-
WRITTEN RESPONSES

Astra Zeneca LP
Attention: Craig Zecher
US Regulatory Affairs Director
One MedImmune Way
Gaithersburg, MD 20878

Dear Mr. Zecher:

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

We also refer to your submission dated 31 May 2019, containing a meeting request. The purpose of the requested meeting was to discuss the format and content of an sNDA based on the THALES trial - "A Randomised, Double-Blind, Placebo-Controlled, International, Multicentre, Phase III Study to Investigate the Efficacy and Safety of Ticagrelor and ASA Compared with ASA in the Prevention of Stroke and Death in Patients with Acute Ischaemic Stroke or Transient Ischaemic Attack".

Further reference is made to our Meeting Granted letter dated 5 June 2019, wherein we agreed that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your 21 June 2019 background package.

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 Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:

- Written Responses

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

WRITTEN RESPONSES

Meeting Type:	B
Meeting Category:	Pre-sNDA
Application Number:	115807
Product Name:	Brilinta (ticagrelor)
Proposed Indication:	Ticagrelor 90 mg is indicated for the prevention of stroke and death in patients with acute ischemic stroke or transient ischemic attack.
Sponsor Name:	Astra Zeneca
Regulatory Pathway:	505(b)(1)

1.0 BACKGROUND

BRILINTA (ticagrelor), developed by Astra Zeneca, is a P2Y12 platelet inhibitor approved in 2011 for reduction of the rate of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) (unstable angina, non-ST elevation myocardial infarction, or ST elevation myocardial infarction) based on the results of the PLATO trial. In 2015, based on the results of the PEGASUS trial, the indication was expanded to include treatment of patients with a history of myocardial infarction.

In 2016, the sponsor completed SOCRATES (#D5134C00001), a large randomized, double-blind trial comparing treatment with ticagrelor monotherapy (90 mg bid) to acetylsalicylic acid (ASA) monotherapy (81 mg qd) in patients with acute minor ischemic stroke or high-risk transient ischemic attack stroke (TIA). The study was not successful on its primary analysis, time from randomization to the first occurrence of the composite of stroke (ischemic or hemorrhagic), myocardial infarction, or death. During the SOCRATES topline meeting with the Division on 19 April 2016, the sponsor noted that the results of SOCRATES suggest that early dual antiplatelet therapy with ticagrelor and ASA after an acute stroke or TIA may prevent subsequent strokes. The Division suggested that the sponsor conduct a large simple trial to evaluate the use of ticagrelor plus ASA versus ASA alone to test this hypothesis.

In September 2016, the sponsor requested a pre-phase 3 meeting (Preliminary Comments dated 27 October 2016) to discuss the design of a study (THALES) to further explore ticagrelor for the prevention of stroke and death in patients with acute ischemic stroke or TIA. In January 2018, THALES was initiated. THALES (#D5134C00003) is a phase 3, multi-national, randomized, placebo-controlled, double-blind, parallel-group, event-driven study designed to evaluate whether ticagrelor in combination with aspirin (ASA) is superior to ASA alone in preventing the composite of stroke and death at 30 days in patients with acute ischemic stroke or TIA. To date the sponsor has randomized ~9552 subjects and ~539 events have occurred. The sponsor plans to enroll approximately 11,000 subjects.

The purpose of this meeting was to discuss the proposed format and content of a supplemental NDA based on the results of THALES.

2.0 QUESTIONS AND RESPONSES

1. Does the Agency agree with the proposed documentation and reporting of efficacy in the planned THALES sNDA?

   FDA Response:
   Yes.

2. Does the Agency agree with the proposed documentation and reporting of safety in the planned THALES sNDA?

   FDA Response:
   Yes.

3. Does the Agency agree with the proposed approach for addressing the requirement to demonstrate the applicability of foreign data to the US population?

   FDA Response:
   Yes.

4. Does the Agency agree with the proposal for provision of the Case Report Tabulations and Summary Level Clinical Site datasets?

   FDA Response:
   Yes.

5. Does the Agency agree with the proposal for provision of the Case Report Form (CRF) information in the suggested format?

   FDA Response:
   Yes.

6. Does the Agency agree with the proposal for the 4-month safety update?

   FDA Response:
   Yes.

2.1. Additional Comments for the Sponsor

Please submit the following information at the time of NDA submission:

a. Protocol and Statistical Analysis Plan (SAP)

   1) all versions of the protocol for THALES and the date when changes were implemented and the number of subjects enrolled in the trial and the total number of

primary events collected at the time the change was made. Include a Summary of Changes for each version.

2) all versions of the SAP for THALES. Include a summary of changes for each version and the number of subjects enrolled in the trial and the total number of primary events collected at the time the change was made.

b. Clinical Trial Materials

3) sample clinical trial kits, from both treatment arms, identical to those used during THALES. Ship them to Bridget Kane's desk address in the same packaging as will be used for shipping to investigative sites.

4) all data management plans for THALES. Cite all amendments for each data management plan, including all manual and programmatical checks.

5) all site monitoring plans for THALES. If changes to your site monitoring plans were not documented contemporaneously by formal signed amendments, explain the amendment process.

6) a description of the responsibilities of each academic research organization (ARO) or clinical research organization (CRO) used in THALES.

7) all charters for committees involved in conducting THALES (e.g., Data Safety Monitoring Board [DSMB], Steering Committee, etc.)

8) all meeting minutes of all groups with any responsibility for the management of the trial, e.g., Executive Committee, Clinical Endpoint Committee, Steering Committee and DSMB. Include agendas and all data/slides presented to the Committee. Indicate whether the meeting was open or closed. For those meetings that were cancelled or meetings where no minutes were taken, include a place holder for that meeting noting such and signed by a member of the clinical team. Ensure that these packages include a table of contents and are bookmarked by date.

9) all newsletters and all other communications to investigational sites and national coordinators from the group(s) responsible for the conduct of THALES. Please bookmark the communication by date.

c. General Data and Analyses

10) all scripts and datasets used to create your analyses found in the main sections of your Summary of Clinical Efficacy, Summary of Clinical Safety, and Phase 3 trial clinical study report. If script contains a macro, include the macro script.

11) Footnote the tables and figures featured in the main clinical efficacy and safety sections of the NDA with the name of the script used to create the table or figure.

12) list of datasets that you assert are of high quality for review. Explain how you assessed the quality of your datasets and what you did to ensure your datasets are suitable for an NDA review. Submit script that was used to create or clean up your analyses datasets.

13) Kaplan-Meier time to event analysis datasets and script (both safety and efficacy) censoring subjects without an event at the date of last known information about the event of interest (not vital status check at the end of the study). Indicate how censoring was determined (e.g., by a patient visit or by telephone call). This dataset should allow one to analyze by intent-to-treat (ITT) as well as on-treatment. The events should include all important endpoints, important adverse events, and laboratory parameter changes of interest.

14) dataset that contains all subjects that were unblinded. Include the unique subject ID, the treatment received, who requested unblinding, date of unblinding, and the reason for unblinding.

15) dataset that contains a list of all subjects for whom you submitted a CRF or narrative. The dataset should contain three variables: (usubjid, CRF, and narrative. CRF and narrative are variables that indicate) with an indicator for whether each item was submitted.

16) a table that contains a list of all subjects for whom you submitted a CRF or narrative. The table should hyperlink to the subject's CRF and/or narrative.

17) one table which includes the following information for the THALES:
- Dates of first patient and last patient visits
- Dates of data lock
- Dates for each interim analysis
- Dates of all versions of the SAP (with a hyperlink to each SAP)
- Dates of the initial protocol and all revisions. (with a hyperlink to the protocol and each revision).

d. Important Endpoints

18) a comprehensive description of the algorithm used to identify potential endpoint events in your final clinical study report. If your algorithm changed, you should also provide detailed information on its evolution, including when and why changes were made.

e. Other

19) statement of Good Clinical Practice confirming that all clinical studies were conducted under the supervision of an Institutional Review Board and with adequate informed consent procedures. If you were granted an IRB Waiver during this trial because a specific site or country operated under a Central Ethics Committee (CEC) and/or Local Ethics Committees (EC) which we agreed maintain the same oversight responsibilities as IRBs, please reference the waiver and include the date.

20) an annotated version of the pre-NDA meeting minutes that include a hyperlink, when applicable, to the analysis and/or documents requested. This document is usually placed in Module 1.

3.0 OTHER IMPORTANT INFORMATION

PREA REQUIREMENTS

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(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.[1] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[2]

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[3] and Pregnancy and Lactation Labeling Final Rule[4] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.

- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.

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[1] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[2] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[3] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[4] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

- Regulations and related guidance documents.

- A sample tool illustrating the format for Highlights and Contents, and

- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

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

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

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

MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[5]

[5] https://www.fda.gov/media/85061/download

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/

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