

TICAGRELOR**BRILINTA®**

60 mg and 90 mg Film-Coated Tablet

Antithrombotic Agent (Platelet Aggregation Inhibitor excl. heparin)

**1. NAME OF MEDICINAL PRODUCT**

Ticagrelor (BRILINTA) 90 mg Film-Coated Tablet

Ticagrelor (BRILINTA) 60 mg Film-Coated Tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

90 mg: Each tablet contains 90 mg of Ticagrelor.

60 mg: Each tablet contains 60 mg of Ticagrelor.

For excipients, see section 6.1

3. PHARMACEUTICAL FORM

90 mg - Round, biconvex, yellow, film-coated tablets. The tablets are marked with "90" above "T" on one side and plain on the other.

60 mg - Round, biconvex, pink, film-coated tablets. The tablets are marked with "60" above "T" on one side and plain on the other.

4. CLINICAL PARTICULARS**4.1 Therapeutic indications****Ticagrelor (BRILINTA) 90 mg**

- Ticagrelor (BRILINTA) 90 mg is indicated for the prevention of thrombotic events (cardiovascular death, myocardial infarction and stroke) in patients with Acute Coronary Syndromes (ACS) (unstable angina, non-ST elevation Myocardial Infarction [NSTEMI] or ST elevation Myocardial Infarction [STEMI]) including patients managed medically, and those who are managed with percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG).
- Ticagrelor (BRILINTA) 90 mg is indicated for the prevention of stroke in patients with Acute Ischaemic Stroke or Transient Ischaemic Attack (TIA).

Ticagrelor (BRILINTA) 60 mg

- Ticagrelor (BRILINTA) 60 mg is indicated for the prevention of thrombotic events (cardiovascular death, myocardial infarction and stroke) in patients with a history of myocardial infarction (MI occurred at least one year ago) and a high risk of developing a thrombotic event.
- Ticagrelor (BRILINTA) 60 mg is indicated for the prevention of thrombotic events (cardiovascular death, myocardial infarction and stroke) in patients with Coronary Artery Disease (CAD) and Type 2 Diabetes Mellitus (T2DM) who have undergone percutaneous coronary intervention (PCI).

4.2 Posology and method of administration

Ticagrelor (BRILINTA) 90 mg

In patients with **Acute Coronary Syndromes**, Ticagrelor (BRILINTA) treatment should be initiated with a single 180 mg loading dose (two tablets of 90 mg) and then continued at 90 mg twice daily. Treatment is recommended for at least 12 months unless discontinuation of Ticagrelor (BRILINTA) is clinically indicated (see section 5.1). After one year, patients initiated on 90 mg twice daily may continue treatment with 60 mg twice daily without interruption.

In patients with **Acute Ischaemic Stroke** or **Transient Ischaemic Attack**, initiate Ticagrelor (BRILINTA) with a single 180 mg loading dose (two tablets of 90 mg) and then continue with 90 mg twice daily for 30 days (see section 5.1).

Patients taking Ticagrelor (BRILINTA) should also take a daily low maintenance dose of acetylsalicylic acid (ASA) of 75-150 mg, unless specifically contraindicated. An initial loading dose of ASA is recommended for patients with ACS, acute ischaemic stroke or TIA (see section 5.1).

Ticagrelor (BRILINTA) 60 mg

In patients with a history of **Myocardial Infarction** (MI occurred at least one year ago) and in patients with **Coronary Artery Disease and Type 2 Diabetes Mellitus** who have undergone percutaneous coronary intervention (for all patients with ACS see **Ticagrelor (BRILINTA) 90 mg**), no loading dose of Ticagrelor (BRILINTA) is required and the recommended dose is 60 mg twice daily. Long-term treatment is recommended unless discontinuation of Ticagrelor (BRILINTA) is clinically indicated (see section 5.1).

Patients taking Ticagrelor (BRILINTA) should also take a daily low maintenance dose of acetylsalicylic acid (ASA) of 75-150 mg, unless specifically contraindicated.

Patients may start treatment with Ticagrelor (BRILINTA) 60 mg twice daily, regardless of their previous antiplatelet regimen, and irrespective if there has been a lapse in therapy or not.

Patients should discontinue their current antiplatelet therapy before initiating Ticagrelor (BRILINTA) with low dose ASA at the next scheduled dose.

Patients initiated on Ticagrelor (BRILINTA) 90 mg twice daily at the time of an ACS event, after one year, may continue treatment with 60 mg twice daily without interruption.

Ticagrelor (BRILINTA) 60 and 90 mg

Missed dose

Lapses in therapy should be avoided. A patient who misses a dose of Ticagrelor (BRILINTA) should take their next dose at its scheduled time.

Premature discontinuation

Premature discontinuation with any antiplatelet therapy, including Ticagrelor (BRILINTA), could result in an increased risk of cardiovascular (CV) death, MI, or stroke due to the patient's underlying disease (see section 4.4)

Switching

In patients having an ACS event, the loading dose of 180 mg should be given as soon as possible regardless of any previous antiplatelet treatment.

Physicians who desire to switch patients, with a prior ACS event to Ticagrelor (BRILINTA), should administer the first dose of Ticagrelor (BRILINTA) 24 hours following the last dose of the other antiplatelet medication.

Special Populations

Paediatric patients:

Safety and efficacy in children below the age of 18 have not been established (see section 5.1).

Elderly patients:

No dose adjustment is required.

Patients with renal impairment:

No dose adjustment is necessary for patients with renal impairment (see section 5.2).

Patients with hepatic impairment:

No dose adjustment is necessary for patients with mild hepatic impairment. Ticagrelor (BRILINTA) has not been studied in patients with severe hepatic impairment and there is limited information on treatment of patients with moderate hepatic impairment (see sections 4.3, 4.4 and 5.2).

Administration

For oral use. Ticagrelor (BRILINTA) can be taken with or without food.

For patients who are unable to swallow the tablet(s) whole, Ticagrelor (BRILINTA) tablets can be crushed to a fine powder and mixed in half a glass of water and drunk immediately. The glass should be rinsed with a further half glass of water and the contents drunk. The mixture can also be administered via a nasogastric tube (CH8 or greater). It is important to flush the nasogastric tube through with water after administration of the mixture.

4.3 Contraindications

Hypersensitivity to Ticagrelor or any of the excipients listed in section 6.1 (see section 4.8).

Active pathological bleeding.

History of intracranial haemorrhage (see section 4.8).

Severe hepatic impairment (see sections 4.2, 4.4 and 5.2).

4.4 Special warnings and special precautions for use

Bleeding risk

As with other antiplatelet agents, the use of Ticagrelor (BRILINTA) in patients at known increased risk for bleeding should be balanced against the benefit in terms of prevention of thrombotic events. If clinically indicated, Ticagrelor (BRILINTA) should be used with caution in the following patient groups:

- Patients with a propensity to bleed (e.g. due to recent trauma, recent surgery, active or recent gastrointestinal bleeding, or moderate hepatic impairment) or who are at increased risk of trauma. The use of Ticagrelor (BRILINTA) is contraindicated in patients with active pathological bleeding and in those with a history of intracranial haemorrhage and severe hepatic impairment (see section 4.3).
- Patients with concomitant administration of medicinal products that may increase the risk of bleeding (e.g. non-steroidal anti-inflammatory drugs (NSAIDs), oral anticoagulants, and/or fibrinolytics within 24 hours of Ticagrelor (BRILINTA) dosing).

Platelet transfusion did not reverse the antiplatelet effect of Ticagrelor (BRILINTA) in healthy volunteers and is unlikely to be of clinical benefit in patients with bleeding. Since co-administration of Ticagrelor (BRILINTA) with desmopressin did not decrease template bleeding time, desmopressin is unlikely to be effective in managing clinical bleeding events.

Antifibrinolytic therapy (aminocaproic acid or tranexamic acid) and/or recombinant factor VIIa therapy may augment haemostasis. Ticagrelor (BRILINTA) may be resumed after the cause of bleeding has been identified and controlled.

Surgery

- If a patient requires surgery, physicians should consider each patient's clinical profile as well as the benefits and risks of continued antiplatelet therapy when

determining when discontinuation of Ticagrelor (BRILINTA) treatment should occur.

- Because of the reversible binding of Ticagrelor (BRILINTA), restoration of platelet aggregation occurs faster with Ticagrelor (BRILINTA) compared to clopidogrel. In the OFFSET Study, mean Inhibition of Platelet Aggregation (IPA) for Ticagrelor (BRILINTA) at 72 hours post-dose was comparable to mean IPA for clopidogrel at 120 hours post-dose. The more rapid offset of effect may predict a reduced risk of bleeding complications, e.g. in settings where antiplatelet therapy must be temporarily discontinued due to surgery or trauma.
- In PLATO, patients undergoing CABG, Ticagrelor (BRILINTA) had a similar rate of major bleeds compared to clopidogrel at all days after stopping therapy except Day 1 where Ticagrelor (BRILINTA) had a higher rate of major bleeding.
- If a patient is to undergo elective surgery and antiplatelet effect is not desired, Ticagrelor (BRILINTA) should be discontinued 5 days prior to surgery (see section 5.1).

Patients with prior ischaemic stroke

ACS patients with prior ischaemic stroke can be treated with Ticagrelor (BRILINTA) for up to 12 months (PLATO).

In PEGASUS (history of MI) and THEMIS (CAD and T2DM), patients with prior ischaemic stroke were not included. Therefore, in the absence of data, caution is advised for treatment beyond one year.

Patients with moderate hepatic impairment

There is limited experience with Ticagrelor (BRILINTA) in patients with moderate hepatic impairment, therefore, caution is advised in these patients. Use of Ticagrelor (BRILINTA) is contraindicated in patients with severe hepatic impairment (see sections 4.2, 4.3 and 5.2).

Bradycardia

Holter ECG monitoring has shown an increased frequency of mostly asymptomatic ventricular pauses during treatment with ticagrelor compared with clopidogrel. In phase 3 studies evaluating the safety and efficacy of Ticagrelor (BRILINTA), bradycardic events were reported in a similar frequency for ticagrelor and comparators (placebo, clopidogrel and ASA). Patients with an increased risk of bradycardic events (e.g. patients without a pacemaker who have sick sinus syndrome, 2nd or 3rd degree atrioventricular (AV) block, or bradycardic-related syncope) have been excluded from Ticagrelor (BRILINTA) outcome studies. Therefore, due to the limited clinical experience in these patients, caution is advised (see also section 5.1).

Bradycardic events and AV blocks have been reported in the post-marketing setting in patients taking Ticagrelor (BRILINTA) (see section 4.8), primarily in patients with ACS, where cardiac ischemia and concomitant drugs reducing the heart rate or affecting cardiac conduction are potential confounders. The patient's clinical condition and concomitant medication should be assessed as potential causes prior to adjusting treatment.

Dyspnoea

Dyspnoea, usually mild to moderate in intensity and often resolving without need for treatment discontinuation, is reported in patients treated with Ticagrelor (BRILINTA) (see section 4.8). The mechanism has not yet been elucidated. If a patient reports new, prolonged, or worsened dyspnoea this should be investigated fully, and if not tolerated, treatment with Ticagrelor (BRILINTA) should be stopped.

Central Sleep Apnoea

Central sleep apnoea including Cheyne-Stokes respiration has been reported in the post-marketing setting in patients taking Ticagrelor (BRILINTA). If central sleep apnoea is suspected, further clinical assessment may be considered.

Thrombotic Thrombocytopenic Purpura (TTP)

Thrombotic Thrombocytopenic Purpura has been reported very rarely with the use of Ticagrelor (BRILINTA). TTP is a serious condition and requires prompt treatment.

Interference with laboratory tests

Platelet function tests to diagnose Heparin induced thrombocytopenia (HIT)

False negative results in platelet function test for heparin induced thrombocytopenia (HIT) have been reported in patients administered ticagrelor. This is related to inhibition of the P2Y₁₂-receptor on the healthy donor platelets in the test by ticagrelor in the patient's sera/plasma. Information on concomitant treatment with ticagrelor is required for interpretation of HIT platelet function tests.

Before considering discontinuation of ticagrelor, the benefit and risk of continued treatment should be assessed, taking both the prothrombotic state of HIT and the increased risk of bleeding with concomitant anticoagulant and ticagrelor treatment into consideration.

Other

Based on a relationship observed in the PLATO Study between maintenance ASA dose and relative efficacy of Ticagrelor compared to clopidogrel, co-administration of Ticagrelor and high maintenance dose ASA (>300 mg) is not recommended (see section 5.1).

Co-administration of Ticagrelor (BRILINTA) with strong CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin, nefazodone, ritonavir, and atazanavir) should be avoided as co-administration may lead to a substantial increase in exposure to Ticagrelor (BRILINTA) (see section 4.5).

Discontinuations

Patients who require discontinuation of Ticagrelor (BRILINTA) are at increased risk for cardiac events or stroke. Premature discontinuation of treatment should be avoided. If Ticagrelor (BRILINTA) must be temporarily stopped due to an adverse event(s), it should be re-initiated as soon as possible when the benefits outweigh the risks of the adverse event or when the adverse event has come to resolution (see section 4.2).

4.5 Interaction with other medicinal products and other forms of interaction

Drug-Drug Interactions

Effects of Other Drugs on Ticagrelor (BRILINTA)

Medicinal Products metabolised by CYP3A4

Ketoconazole (Strong CYP3A4 Inhibitors)

Co-administration of ketoconazole with Ticagrelor increased Ticagrelor C_{max} and AUC equal to 2.4-fold and 7.3-fold, respectively. The C_{max} and AUC of the active metabolite were reduced by 89% and 56%, respectively. Other strong inhibitors of CYP3A4 (clarithromycin, nefazodone, ritonavir, and atazanavir) would be expected to have similar effects and should not be given concomitantly with Ticagrelor (BRILINTA) (see section 4.4).

Diltiazem (Moderate CYP3A4 inhibitors)

Co-administration of Ticagrelor and diltiazem increased the C_{max} of Ticagrelor by 69% and AUC by 174%, and decreased the active metabolite C_{max} by 38% and AUC was unchanged. There was no effect of Ticagrelor on diltiazem plasma levels. Other moderate CYP3A4 inhibitors (e.g. amprenavir, aprepitant, erythromycin, fluconazole, and verapamil) can as well be co-administered with Ticagrelor (BRILINTA).

Rifampin and Other CYP3A Inducers

Co-administration of rifampin with Ticagrelor decreased Ticagrelor C_{max} and AUC by 73% and 86%, respectively. The C_{max} of the active metabolite was unchanged and the AUC was decreased by 46%, respectively. Other CYP3A4 inducers (e.g. phenytoin, carbamazepine, and phenobarbital) would be expected to decrease the exposure to Ticagrelor as well and may result in reduced efficacy of Ticagrelor (BRILINTA).

Cyclosporine (P-gP and CYP3A inhibitor)

Co-administration of cyclosporine (600 mg) with ticagrelor increased ticagrelor C_{max} and AUC equal to 2.3-fold and 2.8-fold, respectively. The AUC of the active metabolite was increased by 32% and C_{max} was decreased by 15% in the presence of cyclosporine. There was no effect of ticagrelor on cyclosporine blood levels.

Others

Clinical pharmacology interaction studies showed that co-administration of Ticagrelor with heparin, enoxaparin, and ASA did not have any effect on Ticagrelor or the active metabolite plasma levels. Co-administration of Ticagrelor and heparin had no effect on heparin based on activated partial thromboplastin time (aPTT) and activated coagulation time (ACT) assays. Co-administration of Ticagrelor and enoxaparin had no effect on enoxaparin based on factor Xa assay.

Delayed and decreased exposure to oral P2Y₁₂ inhibitors, including ticagrelor and its active metabolite, has been reported in patients treated with morphine (approximately 35% reduction in ticagrelor). This interaction may be related to reduced gastrointestinal motility, and therefore apply to other opioids. The clinical relevance is unknown.

Effects of Ticagrelor (BRILINTA) on Other Drugs

Medicinal Products metabolised by CYP3A4

Simvastatin

Co-administration of Ticagrelor with simvastatin increased simvastatin C_{max} by 81% and AUC by 56% and increased simvastatin acid C_{max} by 64% and AUC by 52% with some individual increases equal to 2 to 3-fold. Consideration of the clinical significance should be given to the magnitude and range of changes on the exposure to patients requiring greater than 40 mg of simvastatin. There was no effect of simvastatin on Ticagrelor plasma levels. Ticagrelor (BRILINTA) may have similar effect on lovastatin, but is not expected to have a clinically meaningful effect on other statins.

Atorvastatin

Co-administration of atorvastatin and Ticagrelor increased atorvastatin acid C_{max} by 23% and AUC by 36%. Similar increases in AUC and C_{max} were observed for all atorvastatin acid metabolites. These increases are not considered clinically significant.

Medicinal products metabolised by CYP2C9

Tolbutamide

Co-administration of Ticagrelor with tolbutamide resulted in no change in the plasma levels of either drug, which suggest that Ticagrelor is not a CYP2C9 inhibitor and unlikely to alter the CYP2C9 mediated metabolism of drugs like warfarin and tolbutamide.

Oral Contraceptives

Co-administration of Ticagrelor and levonorgestrel and ethinyl estradiol increased ethinyl estradiol exposure by approximately 20% but did not alter the PK of levonorgestrel. No clinically relevant effect on oral contraceptive efficacy is expected when levonorgestrel and ethinyl estradiol are co-administered with Ticagrelor (BRILINTA).

Digoxin (P-gP substrate)

Concomitant administration of Ticagrelor increased the digoxin C_{max} by 75% and AUC by 28%. Therefore, appropriate clinical and/or laboratory monitoring is recommended when giving narrow therapeutic index P-gp dependent drugs like digoxin concomitantly with Ticagrelor (BRILINTA).

Other Concomitant Therapy

In clinical studies, Ticagrelor (BRILINTA) was commonly administered with ASA, heparin, low molecular weight heparin, intravenous GpIIb/IIIa inhibitors, proton pump inhibitors, statins, beta-blockers, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers as needed for concomitant conditions. These studies did not produce any evidence of clinically significant adverse interactions.

4.6 Fertility, pregnancy and lactation

Fertility

Ticagrelor had no effect on male or female fertility in animals (see section 5.3).

Pregnancy

No clinical study has been conducted in pregnant or lactating women.

Limited clinical data on exposure to Ticagrelor (BRILINTA) during pregnancy are available.

Animal studies do not indicate direct harmful effects with respect to pregnancy, embryonal/foetal development, parturition, or postnatal development.

Because animal reproduction studies are not always predictive of a human response, Ticagrelor should be used during pregnancy only if the potential benefit to the mother justifies any potential risks to the foetus.

Lactation

It is not known whether this medicinal product is excreted in human milk. Studies in rats have shown that Ticagrelor and active metabolites are excreted in the milk. The use of Ticagrelor (BRILINTA) during breastfeeding is not recommended.

4.7 Effects on ability to drive and use machines

No studies on the effects of Ticagrelor (BRILINTA) on the ability to drive and use machines have been performed. Ticagrelor (BRILINTA) is expected to have no or negligible influence on the ability to drive and use machines. During treatment with Ticagrelor (BRILINTA) dizziness and confusion have been reported. Therefore, patients who experience these symptoms should be cautious while driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

The safety profile of Ticagrelor (BRILINTA) has been evaluated in a large development programme where more than 58,000 patients and healthy volunteers have received ticagrelor. Data on adverse drug reactions identified in clinical studies or from post-marketing experience with ticagrelor are presented below including information from clinical studies specific to the approved indications (PLATO, PEGASUS, THEMIS and THALES). For information on those studies see section 5.1.

In PLATO, patients on Ticagrelor (BRILINTA) had a higher incidence of discontinuation of study drug due to adverse events than patients on clopidogrel (7.4% for ticagrelor 90 mg twice daily vs. 5.4% for clopidogrel 75 mg once daily).

In PEGASUS, patients on Ticagrelor (BRILINTA) had a higher incidence of discontinuation of study drug due to adverse events compared to ASA therapy alone (16.1% for ticagrelor 60 mg twice daily with ASA vs. 8.5% for ASA therapy alone).

In THEMIS patients who had undergone PCI, discontinuation of study drug due to adverse events was 21.3% for Ticagrelor (BRILINTA) in combination with ASA vs. 13.0% for ASA alone.

In THALES, patients on Ticagrelor (BRILINTA) in combination with ASA had a higher incidence of discontinuation of study drug due to adverse events compared to ASA

therapy alone (9.7% for ticagrelor 90 mg twice daily in combination with ASA vs. 7.6% for ASA therapy alone)

The most commonly reported adverse drug reactions in patients treated with ticagrelor were bleeding and dyspnoea (see also section 4.4).

Tabulated list of adverse drug reactions

Adverse drug reactions determined from clinical studies with Ticagrelor (BRILINTA) are listed by MedDRA System Organ Class (SOC) and frequency category in Table 1. Within each SOC and frequency category, adverse drug reactions are presented in order of decreasing seriousness. Frequency categories are defined according to the following conventions: Very common ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1,000$ to $< 1/100$), Rare ($\geq 1/10,000$ to $< 1/1,000$), Very rare ($< 1/10,000$), Not known (cannot be estimated from the available data).

Table 1 - Adverse Drug Reactions observed in clinical studies

System Organ Classification	Very Common	Common	Uncommon
<i>Neoplasms benign, malignant and unspecified (including cysts and polyps)</i>			Tumour bleedings ^b
<i>Blood and lymphatic system disorders</i>	Blood disorder bleedings ^c		
<i>Metabolism and nutrition disorders</i>	Hyperuricaemia ^a	Gout	
<i>Psychiatric disorders</i>			Confusion
<i>Nervous system disorders</i>		Dizziness Syncope	Intracranial haemorrhage ^l
<i>Eye disorders</i>			Eye haemorrhage ^d
<i>Ear and labyrinth disorders</i>		Vertigo	Ear haemorrhage
<i>Vascular disorders</i>		Hypotension	
<i>Respiratory, thoracic, and mediastinal disorders</i>	Dyspnoea	Respiratory system bleedings ^e	

System Organ Classification	Very Common	Common	Uncommon
<i>Gastrointestinal Disorders</i>		Gastrointestinal haemorrhage ^f , Diarrhoea, Nausea	Retroperitoneal haemorrhage
<i>Skin and subcutaneous tissue disorders</i>		Subcutaneous or dermal bleeding ^g , Pruritus	
<i>Musculoskeletal connective tissue and bone</i>			Muscular bleedings ^h
<i>Renal and urinary disorders</i>		Urinary tract bleeding ⁱ	
<i>Reproductive system and breast disorders</i>			Reproductive system bleedings ^j
<i>Investigations</i>		Blood creatinine increased ^a	
<i>Injury, poisoning and procedural complications</i>		Post procedural haemorrhage, Traumatic bleedings ^k	

^a Frequencies derived from lab observations (Uric acid increases to >ULN from baseline below or within reference range. Creatinine increases of >50% from baseline) and not crude adverse event report frequency.

^b e.g. bleeding from bladder cancer, gastric cancer, colon cancer.

^c e.g. increased tendency to bruise, spontaneous haematoma, haemorrhagic diathesis.

^d e.g. conjunctival, retinal, intraocular bleeding.

^e e.g. epistaxis, haemoptysis.

^f e.g. gingival bleeding, rectal haemorrhage, gastric ulcer haemorrhage.

^g e.g. ecchymosis, skin haemorrhage, petechiae.

^h e.g. haemarthrosis, muscle haemorrhage.

ⁱ e.g. haematuria, cystitis haemorrhagic.

^j e.g. vaginal haemorrhage, haematospermia, postmenopausal haemorrhage.

^k e.g. contusion, traumatic haematoma, traumatic haemorrhage.

^l i.e. spontaneous, procedure related or traumatic intracranial haemorrhage.

Postmarketing experience

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

Blood disorders: Thrombotic Thrombocytopenic Purpura (see section 4.4)

Cardiac disorders: Bradyarrhythmia, AV block (see section 4.4)

Immune system disorders: Hypersensitivity reactions including angioedema (see section 4.3).

Nervous system disorders: Central sleep apnoea including Cheyne-Stokes respiration (see section 4.4)

Skin and subcutaneous tissue disorders: Rash

Description of selected adverse drug reactions

Bleeding findings in PLATO

Overall outcome of bleeding events in the PLATO Study are shown in Table 2.

Table 2 Analysis of overall bleeding events, Kaplan-Meier estimate of bleeding rates by treatment at 12 months (PLATO)

Safety Endpoints	Ticagrelor (BRILINTA) 90 mg twice daily N=9235		Clopidogrel 75 mg once daily N=9186	
	KM%	Hazard Ratio (95% CI)	KM%	p-value
PLATO-defined bleeding categories				
Primary Safety Endpoint PLATO-defined Total Major	11.6	1.04 (0.95, 1.13)	11.2	0.4336
Secondary Endpoints PLATO Fatal/Life-Threatening	5.8	1.03 (0.90, 1.16)	5.8	0.6988
PLATO Total Major or Minor	16.1	1.11 (1.03, 1.20)	14.6	0.0084
PLATO Non-CABG Major	4.5	1.19 (1.02, 1.38)	3.8	0.0264
PLATO Non-Procedural Major	3.1	1.31 (1.08, 1.60)	2.3	0.0058
PLATO Non-Procedural Major or Minor	5.9	1.39 (1.21, 1.60)	4.3	<0.0001
TIMI-defined bleeding categories				
TIMI Major	7.9	1.03 (0.93, 1.15)	7.7	0.5669
TIMI Major or Minor	11.4	1.05 (0.96, 1.15)	10.9	0.3272

Bleeding category definitions:

PLATO Major Fatal/life-threatening: Fatal bleeding, OR any intracranial bleeding, OR intrapericardial with cardiac tamponade, OR with hypovolaemic shock or severe hypotension requiring pressors/inotropes or surgery OR clinically apparent with >50 g/L decrease in haemoglobin, OR ≥ 4 red cell units transfused.

PLATO Major Other: Significantly disabling, OR clinically apparent with 30-50 g/L decrease in haemoglobin, OR 2-3 red cell units transfused.

PLATO Minor: Requires medical intervention to stop or treat bleeding.

TIMI Major: Fatal bleeding, OR any intracranial bleeding, OR clinically overt signs of haemorrhage associated with a drop in haemoglobin (Hgb) of ≥ 50 g/L, or when Hgb is not available, a fall in haematocrit (Hct) of $\geq 15\%$.

TIMI Minor: Clinically apparent with 30-50 g/L decrease in haemoglobin.

In PLATO, time to first PLATO-defined Total Major bleeding for Ticagrelor (BRILINTA) did not differ significantly from that of clopidogrel. There were few fatal bleeding events in the study, 20 (0.2%) for Ticagrelor (BRILINTA) 90 mg twice daily and 23 (0.3%) for clopidogrel 75 mg once daily. When minor bleeding was included, combined PLATO-defined Major and Minor bleeding events were significantly higher on Ticagrelor (BRILINTA) than on clopidogrel. Overall rates of TIMI-defined bleeding events did not differ significantly between Ticagrelor (BRILINTA) and clopidogrel.

CABG-related bleeding: In PLATO, 42% of the 1584 patients (12% of cohort) who underwent CABG surgery had a PLATO-defined Major Fatal/Life-threatening bleeding with no difference between the treatment groups. Fatal CABG bleeding occurred in 6 patients in each treatment group (see section 4.4).

Non-CABG related bleeding and non-procedural related bleeding: Ticagrelor (BRILINTA) and clopidogrel did not differ in non-CABG PLATO-defined Major Fatal/Life-threatening bleeding, but PLATO-defined Total Major, TIMI Major, and TIMI Major + Minor bleeding were more common with ticagrelor. Similarly, when removing all procedure related bleeding, more bleeding occurred with ticagrelor than with clopidogrel (Table 2). Discontinuation of treatment due to non-procedural bleeding was more common for ticagrelor (2.9%) than for clopidogrel (1.2%; $p < 0.001$).

Age, gender, weight, ethnicity, geographic region, concurrent conditions, concomitant therapy, and medical history, including a previous stroke or transient ischaemic attack, all did not predict either overall or non-procedural PLATO-defined Major bleeding. Thus, no particular group was identified at risk for any subset of bleeding.

Intracranial bleeding: There were more intracranial non-procedural bleeds with ticagrelor (n=27 bleeds in 26 patients, 0.3%) than with clopidogrel (n=14 bleeds, 0.2%), of which 11 bleeds with ticagrelor and 1 with clopidogrel were fatal. There was no difference in overall fatal bleeds. The percentage of intracranial bleeding was low in both treatment groups given the significant comorbidity and cardiovascular risk factors of the population under study.

Bleeding findings in PEGASUS

Overall outcome of bleeding events in the PEGASUS Study are shown in Table 3.

Table 3 Analysis of overall bleeding events, Kaplan-Meier estimate of bleeding rates by treatment at 36 months (PEGASUS)

	Ticagrelor (BRILINTA) 60 mg twice daily with ASA N=6958		ASA alone N=6996	
Safety Endpoints	KM%	Hazard Ratio (95% CI)	KM%	p-value
TIMI-defined bleeding categories				
TIMI Major	2.3	2.32 (1.68, 3.21)	1.1	<0.0001
Fatal	0.3	1.00 (0.44, 2.27)	0.3	1.0000
ICH	0.6	1.33 (0.77, 2.31)	0.5	0.3130
Other TIMI Major	1.6	3.61 (2.31, 5.65)	0.5	<0.0001
TIMI Major or Minor	3.4	2.54 (1.93, 3.35)	1.4	<0.0001
TIMI Major or Minor or Requiring medical attention	16.6	2.64 (2.35, 2.97)	7.0	<0.0001
PLATO-defined bleeding categories				
PLATO Major	3.5	2.57 (1.95, 3.37)	1.4	<0.0001
Fatal/Life-threatening	2.4	2.38 (1.73, 3.26)	1.1	<0.0001
Other PLATO Major	1.1	3.37 (1.95, 5.83)	0.3	<0.0001
PLATO Major or Minor	15.2	2.71 (2.40, 3.08)	6.2	<0.0001

Bleeding category definitions:

TIMI Major: Fatal bleeding, OR any intracranial bleeding, OR clinically overt signs of haemorrhage associated with a drop in haemoglobin (Hgb) of ≥ 50 g/L, or when Hgb is not available, a fall in haematocrit (Hct) of $\geq 15\%$.

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

ICH: Intracranial haemorrhage.

Other TIMI Major: Non-fatal non-ICH TIMI Major bleeding.

TIMI Minor: Clinically apparent with 30-50 g/L decrease in haemoglobin.

TIMI Requiring medical attention: Requiring intervention, OR leading to hospitalisation, OR prompting evaluation.

PLATO Major Fatal/life-threatening: Fatal bleeding, OR any intracranial bleeding, OR intrapericardial with cardiac tamponade, OR with hypovolaemic shock or severe hypotension requiring pressors/inotropes or surgery OR clinically apparent with >50 g/L decrease in haemoglobin OR ≥ 4 red cell units transfused.

PLATO Major Other: Significantly disabling, OR clinically apparent with 30-50 g/L decrease in haemoglobin, OR 2-3 red cell units transfused.

PLATO Minor: Requires medical intervention to stop or treat bleeding.

In PEGASUS, TIMI Major bleeding for Ticagrelor (BRILINTA) 60 mg twice daily was higher than for ASA alone. No increased bleeding risk was seen for fatal bleeding and only a minor increase was observed in intracranial haemorrhages, as compared to ASA

therapy alone. There were few fatal bleeding events in the study, 11 (0.3%) for Ticagrelor (BRILINTA) 60 mg and 12 (0.3%) for ASA therapy alone. The observed increased risk of TIMI Major bleeding with Ticagrelor (BRILINTA) 60 mg was primarily due to a higher frequency of Other TIMI Major bleeding driven by events in the gastrointestinal SOC.

Increased bleeding patterns similar to TIMI Major were seen for TIMI Major or Minor and PLATO-defined Major and PLATO-defined Major or Minor bleeding categories (see Table 3). Discontinuation of treatment due to bleeding was more common with Ticagrelor (BRILINTA) 60 mg compared to ASA therapy alone (6.2% and 1.5%, respectively). The majority of these bleedings were of less severity (classified as TIMI Requiring medical attention), e.g. epistaxis, bruising, and haematomas.

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

Intracranial bleeding: Spontaneous ICHs were reported in similar rates for Ticagrelor (BRILINTA) 60 mg and ASA therapy alone (n=13, 0.2% in both treatment groups). Traumatic and procedural ICHs showed a minor increase with Ticagrelor (BRILINTA) 60 mg treatment, (n=15, 0.2%) compared with ASA therapy alone (n=10, 0.1%). There were 6 fatal ICHs with Ticagrelor (BRILINTA) 60 mg and 5 fatal ICHs with ASA therapy alone. The incidence of intracranial bleeding was low in both treatment groups given the significant comorbidity and cardiovascular risk factors of the population under study.

Bleeding findings in THEMIS patients who had undergone PCI

The bleeding events in THEMIS patients who had undergone PCI are shown in Table 4.

Table 4 Analysis of bleeding events, Kaplan-Meier estimate of bleeding rates by treatment at 36 months (THEMIS PCI patients)

	Ticagrelor (BRILINTA) twice daily with ASA N=5536		ASA alone N=5564	
Safety Endpoints	KM%	Hazard Ratio (95% CI)	KM%	p-value
TIMI-defined bleeding categories				
TIMI Major	2.4%	2.03 (1.48, 2.76)	1.3%	<.0001
TIMI Major or Minor	3.4%	2.23 (1.70, 2.92)	1.7%	<.0001
TIMI Major or Minor or Requiring medical attention	13.1%	2.28 (1.99, 2.62)	6.3%	<.0001
PLATO-defined bleeding categories				
PLATO Major	3.8%	2.22 (1.72, 2.86)	1.9%	<.0001
Fatal/Life-threatening	2.5%	2.10 (1.54, 2.86)	1.3%	<.0001
Other PLATO Major	1.5%	2.53 (1.64, 3.93)	0.6%	<.0001

Bleeding category definitions:

TIMI Major: Fatal bleeding, OR any intracranial bleeding, OR clinically overt signs of haemorrhage associated with a drop in haemoglobin (Hgb) of ≥ 50 g/L, or when Hgb is not available, a fall in haematocrit (Hct) of 15%. If CABG related bleeding: fatal bleeding or perioperative intracranial bleeding or reoperation following closure of the sternotomy incision for the purpose of controlling bleeding or transfusion of ≥ 5 units of whole blood or PRBCs within a 48 hour period (cell saver transfusion will not be counted in calculations of blood products) or chest tube output > 2 L within a 24 hour period.

TIMI Minor: Clinically apparent with 30-50 g/L decrease in Hgb or $\geq 10\%$ to $< 15\%$ decrease in Hct, OR if no observed blood loss; ≥ 40 g/L decrease in Hgb concentration or $\geq 12\%$ decrease in Hct.

TIMI Requiring medical attention: Requiring intervention, OR leading to hospitalization, OR prompting evaluation.

PLATO Major Fatal/life-threatening: Fatal bleeding, OR any intracranial bleeding, OR intrapericardial with cardiac tamponade, OR with hypovolaemic shock or severe hypotension requiring pressors/inotropes or surgery OR clinically apparent with > 50 g/L decrease in Hgb OR ≥ 4 red cell units transfused.

If CABG related bleeding: fatal bleeding or perioperative intracranial bleeding or reoperation following closure of the sternotomy incision for the purpose of controlling bleeding or transfusion of ≥ 5 units of whole blood or PRBCs within a 48 hour period (cell saver transfusion will not be counted in calculations of blood products) or chest tube output > 2 L within a 24 hour period.

PLATO Major Other: Significantly disabling, OR clinically apparent with 30-50 g/L decrease in Hgb, OR 2-3 red cell units transfused.

There were few fatal bleeding events, 6 for Ticagrelor (BRILINTA) in combination with ASA and 6 for ASA therapy alone. The number of patients with intracranial haemorrhages was 33 for Ticagrelor (BRILINTA) in combination with ASA and 31 for ASA alone.

Discontinuation of study drug due to bleeding in patients who had undergone PCI was more common with Ticagrelor (BRILINTA) in combination with ASA compared to ASA alone (4.7% and 1.3%, respectively). Epistaxis and increased tendency to bruise

were the most common bleeding events resulting in the discontinuation of Ticagrelor (BRILINTA).

Bleeding findings in THALES

Overall outcome of bleeding events in the THALES study are shown in Table 5.

Table 5 Analysis of bleeding events, Kaplan-Meier estimate of bleeding rates by treatment at 30 days (THALES)^a

	Ticagrelor (BRILINTA) 90 mg twice daily with ASA N=5523			ASA alone N=5493		
Safety Endpoints	Patients with events	KM%	Hazard Ratio (95% CI)	Patients with events	KM%	p-value
GUSTO-defined bleeding categories						
GUSTO Severe	28 (0.5%)	0.5%	3.99 (1.74, 9.14)	7 (0.1%)	0.1%	0.001
GUSTO Severe or Moderate	36 (0.7%)	0.6%	3.27 (1.67, 6.43)	11 (0.2%)	0.2%	<.001

Bleeding category definitions:

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

GUSTO Moderate: Bleeding requiring transfusion of whole blood or packed red blood cells without haemodynamic compromise (as defined above).

^a Full analysis set – intention-to-treat analysis: included all patients randomised irrespective of their protocol adherence and continued participation in the study.

In THALES, the rate of GUSTO Severe bleeding for Ticagrelor (BRILINTA) 90 mg twice daily in combination with ASA was higher than for ASA alone. A similar bleeding pattern was observed for the GUSTO Severe or Moderate bleeding category (see Table 5). Due to the low number of GUSTO Severe bleeding events, no conclusion can be drawn regarding bleeding risk across subgroups. Discontinuation of treatment due to bleeding was more common with Ticagrelor (BRILINTA) 90 mg with ASA compared to ASA therapy alone (2.9% and 0.6%, respectively).

Intracranial bleeding and fatal bleeding: In total, there were 21 intracranial haemorrhages (ICHs) (19 spontaneous, 1 traumatic, 1 procedural) for Ticagrelor (BRILINTA) 90 mg with ASA and 6 ICHs (3 spontaneous, 2 traumatic, 1 procedural) for ASA alone. Fatal bleedings occurred in 11 patients (10 fatal ICHs, 1 fatal gastro-

intestinal bleed) for Ticagrelor (BRILINTA) 90 mg with ASA and in 2 patients (2 fatal ICHs) for ASA alone.

Dyspnoea

In PLATO, dyspnoea adverse events were reported in 13.8% of patients taking ticagrelor 90 mg twice daily and in 7.8% of patients taking clopidogrel 75 mg once daily. Most reported dyspnoea adverse events were mild to moderate in intensity and often resolved without the need of treatment discontinuation. Dyspnoea was usually reported in the initial phase of treatment and 87% of the patients who reported dyspnoea experienced a single episode. Dyspnoea serious adverse events were reported in 0.7% taking ticagrelor and 0.4% taking clopidogrel. Patients who reported dyspnoea tended to be older and more frequently had dyspnoea, congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), or asthma at baseline. PLATO data do not suggest that the higher frequency with Ticagrelor (BRILINTA) is due to new or worsening heart or lung disease. There was no indication of an adverse effect of Ticagrelor (BRILINTA) on pulmonary function (see section 4.4).

In PEGASUS, dyspnoea was reported in 14.2% of patients taking Ticagrelor (BRILINTA) 60 mg twice daily and in 5.5% of patients taking ASA alone. As in PLATO, most reported dyspnoea was mild to moderate in intensity (see section 4.4).

In THEMIS patients who had undergone PCI, dyspnoea was reported in 22.0% of patients taking Ticagrelor (BRILINTA) twice daily in combination with ASA and in 7.5% of patients taking ASA alone. Most reported dyspnoea was mild to moderate in intensity (see section 4.4).

In THALES, dyspnoea led to study drug discontinuation in 1.0% and 0.2% of patients taking Ticagrelor (BRILINTA) 90 mg in combination with ASA vs. ASA alone, respectively.

4.9 Overdose and Treatment

There is currently no known antidote to reverse the effects of Ticagrelor (BRILINTA), and Ticagrelor (BRILINTA) is not dialysable (see section 5.2). Treatment of overdose should follow local standard medical practice. The expected effect of excessive Ticagrelor (BRILINTA) dosing is prolonged duration of bleeding risk associated with platelet inhibition. If bleeding occurs, appropriate supportive measures should be taken.

Ticagrelor is well tolerated in single doses up to 900 mg. GI toxicity was dose-limiting in a single ascending dose study. Other clinically meaningful adverse effects which may occur with overdose include dyspnoea and ventricular pauses.

In the event of overdose, observe for these potential adverse effects and consider ECG monitoring.

5. Pharmacological properties

Pharmacotherapeutic group (ATC code): B01AC24

Pharmacotherapeutic group: Platelet aggregation inhibitors excluding heparin

5.1 Pharmacodynamic properties

Mechanism of action

Ticagrelor (BRILINTA) contains Ticagrelor, a member of the chemical class cyclopentyl-triazolo-pyrimidines (CPTP), which is an oral, direct acting, selective, and reversibly binding P2Y₁₂ receptor antagonist that prevents adenosine diphosphate (ADP)-mediated P2Y₁₂ dependent platelet activation and aggregation. Ticagrelor does not prevent ADP binding, but when bound to the P2Y₁₂ receptor prevents ADP-induced signal transduction. Since platelets participate in the initiation and/or evolution of thrombotic complications of atherosclerotic disease, inhibition of platelet function has been shown to reduce the risk of cardiovascular events such as CV death, MI, or stroke.

Ticagrelor has an additional mechanism of action, increasing local endogenous adenosine levels by inhibiting equilibrative nucleoside transporter-1 (ENT-1). Adenosine is formed locally at sites of hypoxia and tissue damage through degradation of released adenosine tri- and di-phosphate (ATP and ADP). As adenosine degradation is essentially restricted to the intracellular space, inhibition of ENT-1 by ticagrelor prolongs the half-life of adenosine and thereby increases its local extracellular concentration providing enhanced local adenosine responses. Ticagrelor has no clinically significant direct effect on adenosine receptors (A₁, A_{2A}, A_{2B}, A₃) and is not metabolised to adenosine. Adenosine has been documented to have a number of effects that include: vasodilation, cardioprotection, platelet inhibition, modulation of inflammation, and induction of dyspnoea, which may contribute to the clinical profile of ticagrelor.

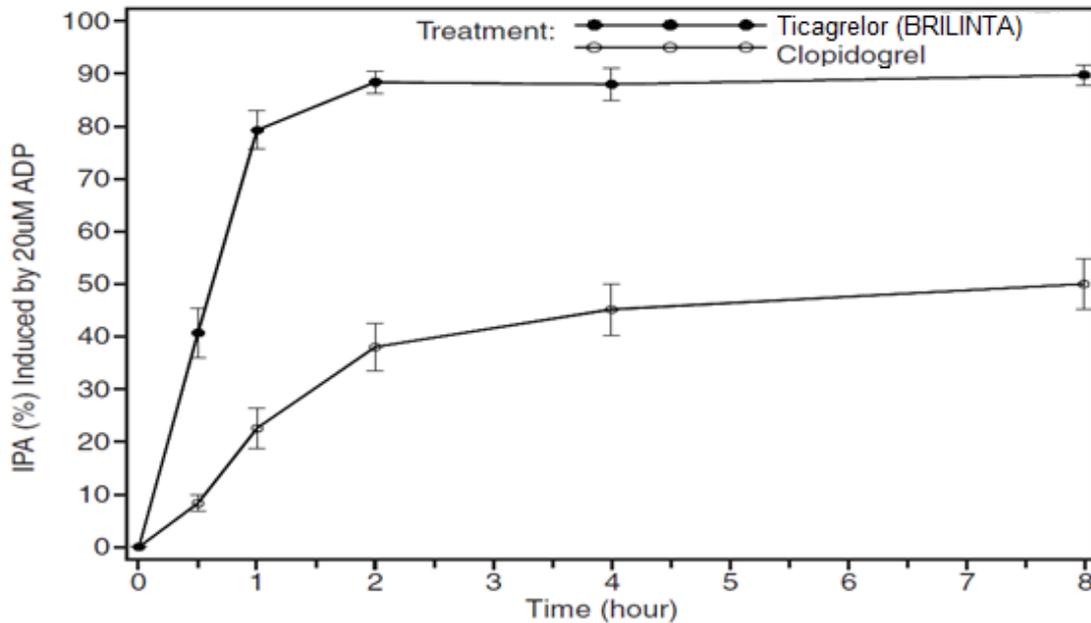
Pharmacodynamic effects

Onset of action:

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 20µM ADP as the platelet aggregation agonist in patients with stable coronary artery disease (CAD) on ASA. The onset was evaluated following a loading dose of 180 mg ticagrelor or 600 mg clopidogrel.

Ticagrelor (BRILINTA) demonstrates a rapid onset of pharmacological effect as demonstrated by a mean IPA for Ticagrelor (BRILINTA) at 0.5 hours after 180 mg loading dose of about 41%, with the maximum IPA effect of 87.9% to 89.6% by 2-4 hours post dose. 90% of patients had final extent IPA >70% by 2 hours post dose. The high IPA effect of Ticagrelor (BRILINTA) between 87%-89% was maintained between 2-8 hours.

Figure 1 Mean final extent Inhibition (\pm SE) of Platelet Aggregation (IPA) following single oral doses of 180 mg Ticagrelor (BRILINTA) or 600 mg clopidogrel in patients with stable CAD

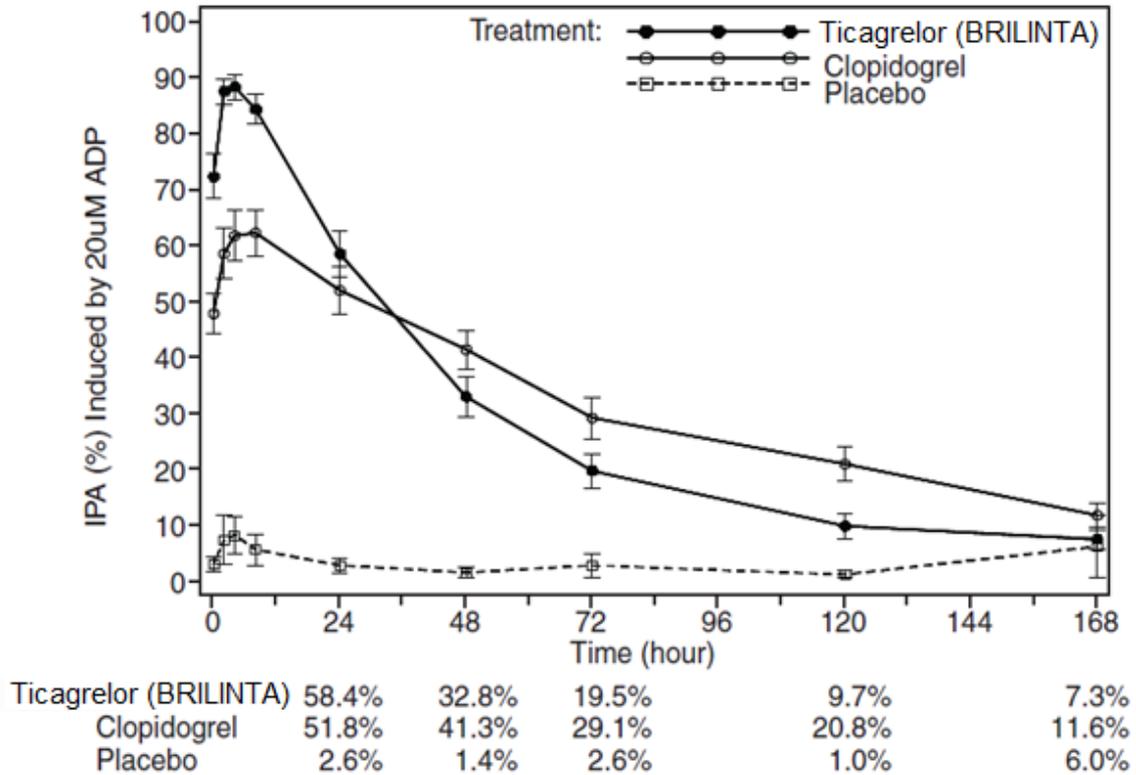


Offset of effect

The offset was examined after 6 weeks on ticagrelor 90 mg twice daily or clopidogrel 75 mg once daily, again in response to 20 μ M ADP. After the Ticagrelor (BRILINTA) and the active metabolite concentrations decline to a level less than that required for receptor saturation, IPA gradually decreases with declining plasma concentrations. Since Ticagrelor (BRILINTA) binds reversibly, the recovery of platelet function does not depend on replacement of platelets. Ticagrelor (BRILINTA) has a faster rate of offset of IPA as compared to clopidogrel as determined by the slope of offset from 4-72 hours after last dose (see section 4.4).

Median final extent IPA measured after the last dose of Ticagrelor (BRILINTA) is approximately 20-30% higher for Ticagrelor (BRILINTA) compared to clopidogrel. However, by 24 hours post-dose, %IPA is similar between Ticagrelor (BRILINTA) and clopidogrel, and is lower for Ticagrelor (BRILINTA) from 72 hours through 7 days compared with the clopidogrel. Mean %IPA for Ticagrelor (BRILINTA) at 72 hours (Day 3) post last dose was comparable to clopidogrel at Day 5, and % IPA for Ticagrelor (BRILINTA) at Day 5 was similar to clopidogrel at Day 7, which is not statistically different from placebo.

Figure 2 Mean final extent Inhibition (\pm SE) of Platelet Aggregation (IPA) following the last maintenance dose of 90 mg Ticagrelor (BRILINTA) or 75 mg clopidogrel or placebo



Responders to Ticagrelor (BRILINTA):

IPA induced by Ticagrelor (BRILINTA) has less variability at peak plasma concentrations of Ticagrelor (BRILINTA) observed with the 90 mg twice daily dose compared to clopidogrel 75 mg once daily. Patients with stable CAD predetermined to have low IPA response to clopidogrel (non-responders), and given a concomitant dose of ASA, exhibited higher mean IPA response after administration of Ticagrelor (BRILINTA) as compared to clopidogrel. In non-responders to clopidogrel, the IPA response to Ticagrelor (BRILINTA) was observed to be higher and more consistent. Ticagrelor (BRILINTA) treatment resulted in consistently higher IPA compared with clopidogrel, and this was apparent post dose for both responders and non-responders.

Switching data:

Switching from clopidogrel 75 mg once daily to Ticagrelor (BRILINTA) 90 mg results in an absolute IPA increase of 26.4% and switching from Ticagrelor (BRILINTA) to clopidogrel results in an absolute IPA decrease of 24.5%. Patients can be switched from clopidogrel to Ticagrelor (BRILINTA) without interruption of antiplatelet effect (see section 4.2).

Adenosine mechanism (ENT-1):

Ticagrelor increased plasma adenosine concentrations in ACS patients and has been shown to augment several physiological responses to adenosine. Adenosine is a vasodilator; ticagrelor has been shown to augment adenosine-induced coronary blood flow increases in healthy volunteers and ACS patients. Adenosine is an endogenous platelet inhibitor; ticagrelor has been shown to augment adenosine-mediated inhibition of platelet aggregation in addition to platelet inhibition due to its P2Y₁₂ antagonism. Adenosine has been linked to the cardio-protective effect of preconditioning; ticagrelor has been shown to reduce infarct size via an adenosine-mediated mechanism in a rat model of reperfusion injury. Adenosine also induces dyspnoea; ticagrelor has been shown to augment adenosine-induced dyspnoea in healthy volunteers. Thus, the dyspnoea observed in some patients taking ticagrelor (see section 4.8) may partly be mediated by adenosine.

Clinical efficacy

The clinical evidence for the efficacy of Ticagrelor (BRILINTA) is derived from four phase 3 trials:

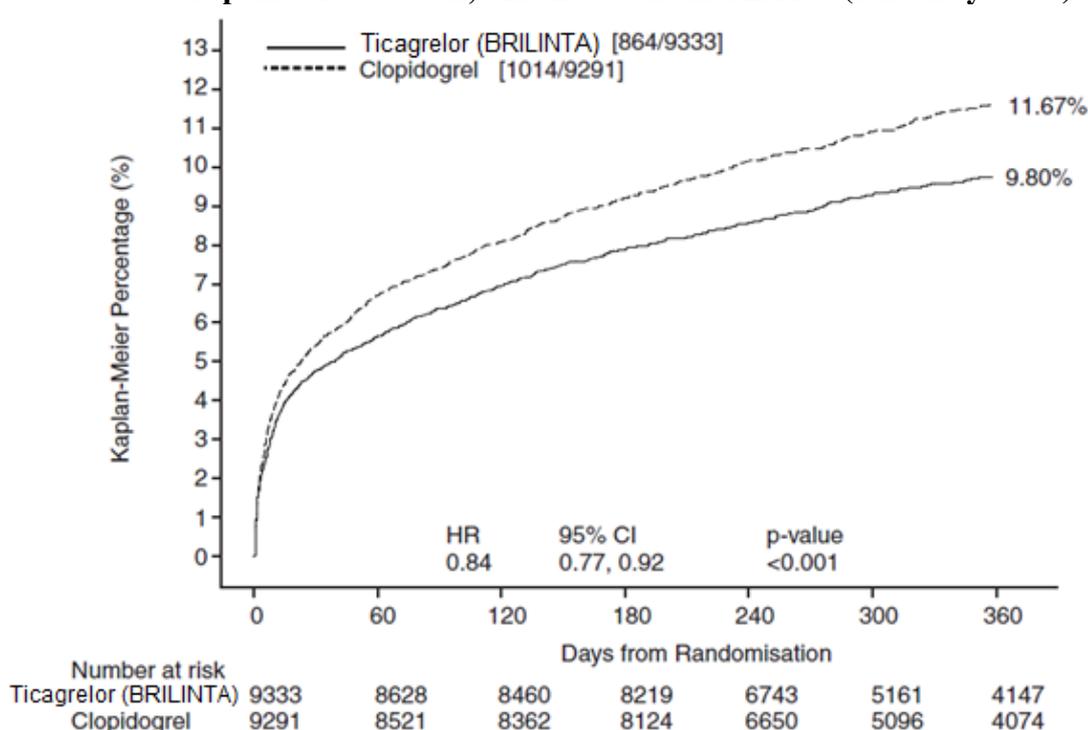
- The PLATO [PLATElet Inhibition and Patient Outcomes] Study, a comparison of Ticagrelor (BRILINTA) to clopidogrel, both given in combination with ASA and other standard therapy.
- The PEGASUS TIMI-54 [PrEvention with TicaGrelor of SecondAry Thrombotic Events in High-RiSk AcUte Coronary Syndrome Patients] study, a comparison of Ticagrelor (BRILINTA) treatment combined with ASA to ASA therapy alone.
- The THEMIS [Effect of Ticagrelor on Health Outcomes in diabEtes Mellitus patients Intervention Study] Study, a comparison of Ticagrelor (BRILINTA) treatment combined with ASA to ASA therapy alone.
- The THALES [Acute STroke or Transient IscHaemic Attack Treated with TicAgreLor and ASA for PrEvention of Stroke and Death] Study, a comparison of Ticagrelor (BRILINTA) treatment combined with ASA to ASA therapy alone.

PLATO study (Acute Coronary Syndromes)

The PLATO Study was a 18,624 patient randomised, double-blind, parallel group, phase 3, efficacy and safety study of Ticagrelor (BRILINTA) compared with clopidogrel for prevention of thrombotic events (CV death, MI and stroke) in patients with ACS (unstable angina, non-ST elevation MI [NSTEMI] or ST elevation MI [STEMI]). The median treatment duration for Ticagrelor (BRILINTA) was 276 days.

The Study was comprised of patients who presented within 24 hours of onset of the most recent episode of chest pain or symptoms. Patients were randomised to receive clopidogrel (75 mg once daily, with an initial loading dose of 300 mg), or a loading dose of 180 mg of Ticagrelor (BRILINTA) followed by a maintenance dose of 90 mg of Ticagrelor (BRILINTA) twice daily. Patients could have been medically managed, treated with PCI or CABG.

Figure 3 Kaplan-Meier plot and analysis of the primary clinical composite endpoint of CV death, MI and stroke in PLATO (full analysis set)



Ticagrelor (BRILINTA) reduced the occurrence of the primary composite endpoint compared to clopidogrel in both the UA/NSTEMI and STEMI population.

Table 6 – Analysis of primary and secondary efficacy endpoints in PLATO (full analysis set)

Primary Endpoint	Patients with Events		Relative Risk Reduction ^a (%)	Hazard Ratio (95% CI)	p-value
	Ticagrelor (BRILINTA) 90 mg twice daily (%) N=9333	Clopidogrel 75 mg once daily (%) N=9291			
Composite of CV Death/MI (excl. silent MI)/Stroke	9.3	10.9	16	0.84(0.77,0.92)	p=0.0003
CV death	3.8	4.8	21	0.79(0.69,0.91)	p=0.0013
MI (excl. silent MI) ^a	5.4	6.4	16	0.84(0.75,0.95)	p=0.0045
Stroke	1.3	1.1	-17	1.17(0.91,1.52)	p=0.2249
Secondary Endpoints					
Composite of CV Death/MI (excl. silent MI)/Stroke – intent to invasively manage	8.5	10.0	16	0.84(0.75,0.94)	p=0.0025

Composite of all-cause mortality/MI (excl. silent MI)/Stroke	9.7	11.5	16	0.84(0.77,0.92)	p=0.0001
Composite of CV Death/Total MI/Stroke/SRI ^b /RI ^c /TIA ^d /Other ATE ^e	13.8	15.7	12	0.88(0.81,0.95)	p=0.0006
All-cause mortality	4.3	5.4	22	0.78(0.69,0.89)	p=0.0003**

^aRRR= (1-Hazard Ratio) x 100%. Values with a negative relative risk reduction indicate a relative risk increase

^bSRI = Severe Recurrent Cardiac Ischaemia.

^cRI = Recurrent Cardiac Ischaemia

^dTIA = Transient Ischaemic Attack

^eATE = Arterial Thrombotic events.

**nominal p-value

Ticagrelor (BRILINTA) is superior to clopidogrel in the prevention of thrombotic events (relative risk reduction [RRR] 16%, absolute risk reduction [ARR] 1.9%, NNT =54) of the composite efficacy endpoint CV death, MI, and stroke) over 12 months. The difference in treatments was driven by cardiovascular death and myocardial infarction with no difference on strokes. Ticagrelor (BRILINTA) demonstrated a statistically significant RRR of 16% (ARR 1.1%) for MI and a 21% relative risk reduction (ARR 1.1%) for CV death. Treating 91 patients with Ticagrelor (BRILINTA) instead of clopidogrel will prevent 1 CV death.

Ticagrelor (BRILINTA) showed superiority to clopidogrel in preventing the composite endpoint CV death, MI, or stroke). This result appeared early (ARR 0.6% and RRR of 12% at 30 days), with a constant treatment effect over the entire 12-month period, yielding ARR 1.9% per year with RRR of 16%. This suggests it is appropriate to treat for at least 12 months (see section 4.2).

In PLATO, a large number of subgroup comparisons were conducted for the primary efficacy endpoint to assess the robustness and consistency of the overall benefit. The treatment effect of Ticagrelor (BRILINTA) vs. clopidogrel appears consistent across multiple patient subgroups by demographic characteristics including weight, gender, medical history, concomitant therapy, and by final index event diagnosis (STEMI, NSTEMI, and UA).

A weakly significant treatment interaction was observed with region whereby the hazard ratio (HR) for the primary endpoint favours Ticagrelor (BRILINTA) in the rest of world but favours clopidogrel in North America, which represented approximately 10% of the overall population studied (interaction p-value=0.045).

This apparent treatment-by-region interaction observed in PLATO could plausibly be attributed to chance, at least in part. Additional analyses suggest that the efficacy of Ticagrelor (BRILINTA) relative to clopidogrel is associated with ASA dose during maintenance therapy. The data show greater efficacy of Ticagrelor compared to clopidogrel when used in conjunction with low maintenance dose ASA (75-150 mg). The relative efficacy of Ticagrelor versus clopidogrel when used with high doses of ASA (>300 mg) is less certain. Based on this observed relationship between

maintenance ASA dose and relative efficacy of Ticagrelor compared to clopidogrel, it is recommended that Ticagrelor (BRILINTA) is used with a low maintenance dose of ASA 75-150 mg (see sections 4.2 and 4.4).

The benefits associated with Ticagrelor (BRILINTA) were also independent of the use of other acute and long-term cardiovascular therapies, including heparin, low molecular weight heparin (LMWH), intravenous GpIIb/IIIa inhibitors, lipid-lowering drugs, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists, and proton pump inhibitors (see section 4.5).

Ticagrelor (BRILINTA) demonstrated a statistically significant RRR in the composite endpoint of CV death, MI, and stroke in ACS patients planned for invasive management (RRR 16%, ARR 1.7%, $p=0.0025$). In an exploratory analysis, Ticagrelor (BRILINTA) demonstrated an RRR of the primary composite endpoint in ACS patients intended for medical management (RRR 15%, ARR 2.3%, nominal $p=0.0444$). Consistent with the primary endpoint of the study, the effect in these two groups was driven by CV death and MI with no effect on stroke. In patients receiving stents, there were numerically fewer definite stent thromboses among patients treated with Ticagrelor compared to clopidogrel (73 vs. 107, RRR 32%, ARR 0.6%, nominal $p=0.0123$).

Ticagrelor (BRILINTA) demonstrated a statistically significant RRR of 16% (ARR 2.1%) for the composite of all-cause mortality, MI, and stroke compared to clopidogrel.

The final secondary endpoint (all-cause mortality) was evaluated. Ticagrelor (BRILINTA) demonstrated a RRR of 22% for all-cause mortality compared to clopidogrel at a nominal significance level of $p=0.0003$ and an ARR of 1.4%.

Holter Substudy

To study the occurrence of ventricular pauses and other arrhythmic episodes during PLATO, investigators performed Holter monitoring in a subset of nearly 3,000 patients, of whom approximately 2,000 had recordings both in the acute phase of their ACS and after one month. The primary variable of interest was the occurrence of ventricular pauses ≥ 3 seconds. More patients had ventricular pauses with Ticagrelor (BRILINTA) (6.0%) than with clopidogrel (3.5%) in the acute phase; and 2.2% and 1.6%, respectively, after 1 month. More patients had ventricular pauses with Ticagrelor (BRILINTA) than with clopidogrel, however, there were no adverse clinical consequences associated with this imbalance (including pacemaker insertions) in this population of patients.

Genetic Substudy

In PLATO, 10,285 patients provided genetic samples for genotype determination of CYP2C19 and ABCB1 loci. An analysis provided these associations of genotype groupings on efficacy and safety outcomes in PLATO. The superiority of ticagrelor over clopidogrel in reducing major CV events was not significantly affected by patient CYP2C19 or ABCB1 genotype.

Similar to the overall PLATO Study, Total Major Bleeding did not differ between ticagrelor and clopidogrel regardless of CYP2C19 or ABCB1 genotype. Non-CABG PLATO Major bleeding was increased with ticagrelor compared to clopidogrel in

patients with one or more CYP2C19 LOF allele, but was similar to clopidogrel in patients with no loss of function allele.

Combined Efficacy and Safety Composite

A combined efficacy and safety composite (CV death, MI, stroke, or PLATO-defined ‘Total Major’ bleeding) supports the clinical benefit of Ticagrelor compared to clopidogrel (RRR 8%, ARR 1.4%, HR 0.92; p=0.0257) over 12 months after ACS events.

PEGASUS Study (History of Myocardial Infarction)

The PEGASUS TIMI-54 Study was a 21,162 patient, event-driven, randomised, double blind, placebo controlled, parallel group, international multicentre study to assess the prevention of thrombotic events with ticagrelor given at 2 doses (either 90 mg twice daily or 60 mg twice daily) combined with low dose ASA (75-150 mg) compared to ASA therapy alone in patients with history of MI and additional risk factors for atherothrombosis. The median treatment duration for Ticagrelor (BRILINTA) 60 mg was 29.4 months.

Patients were eligible to participate if they were aged 50 years or over, with a history of MI (1 to 3 years prior to randomisation), and had at least one of the following risk factors for atherothrombosis: age ≥65 years, diabetes mellitus requiring medication, a second prior MI, evidence of multivessel CAD, or chronic non-end-stage renal dysfunction.

Figure 4 Kaplan-Meier plot and analysis of primary clinical composite endpoint of CV death, MI, and stroke in PEGASUS (full analysis set)

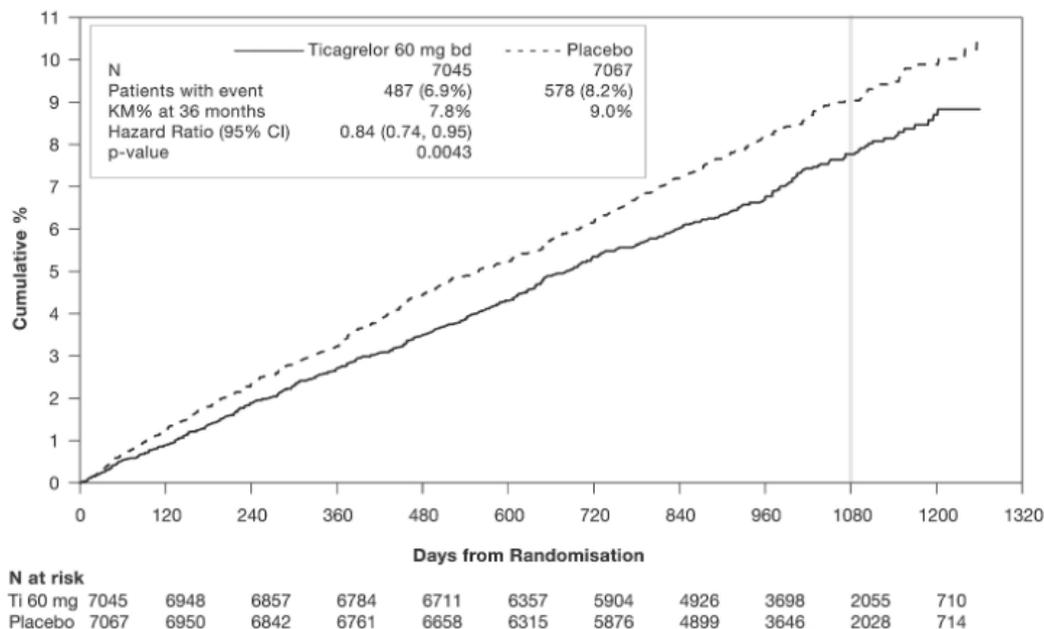


Table 7 Analysis of primary and secondary efficacy endpoints in PEGASUS (full analysis set)

	Ticagrelor (BRILINTA) 60 mg twice daily + ASA N = 7045			ASA alone N = 7067		<i>p</i> -value
Characteristic	Patients with events	KM%	HR (95% CI)	Patients with events	KM%	
Primary endpoint						
Composite of CV Death/MI /Stroke	487 (6.9%)	7.8%	0.84 (0.74, 0.95)	578 (8.2%)	9.0%	0.0043 (s)
CV death	174 (2.5%)	2.9%	0.83 (0.68, 1.01)	210 (3.0%)	3.4%	0.0676
MI	285 (4.0%)	4.5%	0.84 (0.72, 0.98)	338 (4.8%)	5.2%	0.0314
Stroke	91 (1.3%)	1.5%	0.75 (0.57, 0.98)	122 (1.7%)	1.9%	0.0337
Secondary endpoint						
CV death	174 (2.5%)	2.9%	0.83 (0.68, 1.01)	210 (3.0%)	3.4%	-
All-cause mortality	289 (4.1%)	4.7%	0.89 (0.76, 1.04)	326 (4.6%)	5.2%	-

Hazard ratio and *p*-values are calculated separately for ticagrelor vs. ASA alone from Cox proportional hazards model with treatment group as the only explanatory variable.

Kaplan-Meier percentage calculated at 36 months.

Note: the number of events for the components CV Death, MI and stroke are the actual number of first events for each component and do not add up to the number of events in the composite endpoint

(s) Indicates statistical significance.

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

Both 60 mg twice daily and 90 mg twice daily regimens of Ticagrelor (BRILINTA), in combination with ASA, were superior to ASA alone in the prevention of thrombotic events (composite endpoint: CV death, MI, and stroke), with a consistent treatment effect over the entire study period, yielding a 16% RRR and 1.27% ARR for ticagrelor 60 mg and a 15% RRR and 1.19% ARR for ticagrelor 90 mg.

Although the efficacy profile of ticagrelor 90 mg and 60 mg were similar, there is evidence that the lower dose has a better tolerability and safety profile in relation to risk of the bleeding and dyspnoea. Therefore, Ticagrelor (BRILINTA) 60 mg twice daily co-administered with ASA is recommended for the prevention of thrombotic events (CV death, MI and stroke) in patients with a history of myocardial infarction (MI occurred at least one year ago) and a high risk of developing a thrombotic event.

Relative to ASA alone, Ticagrelor (BRILINTA) 60 mg twice daily significantly reduced the primary composite endpoint of CV death, MI, and stroke. Each of the components contributed to the reduction in the primary composite endpoint (CV death 17% RRR, MI 16% RRR, and stroke 25% RRR).

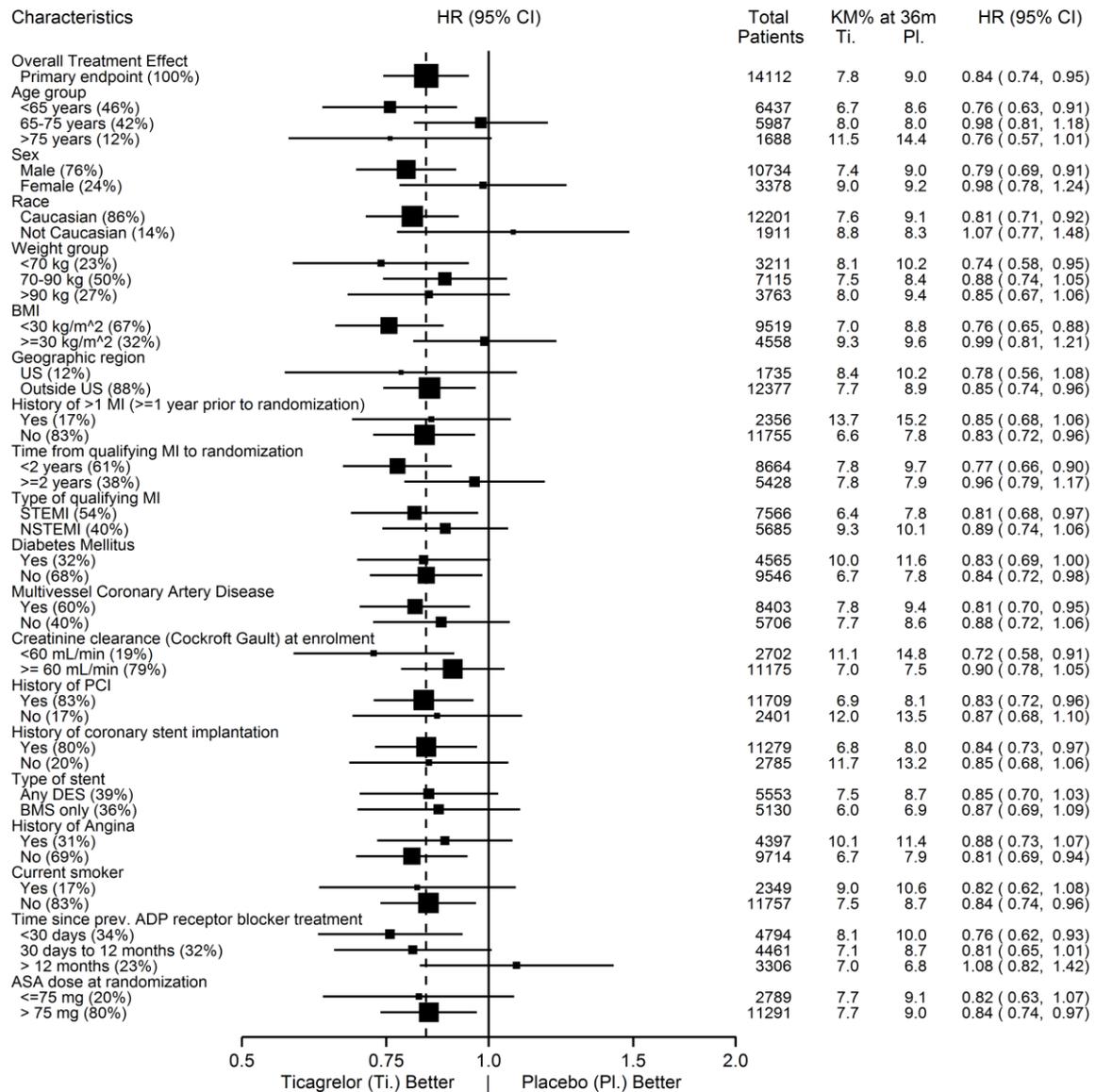
Treating 79 patients for up to 36 months with Ticagrelor (BRILINTA) 60 mg twice daily in combination with ASA instead of ASA therapy alone will prevent one primary composite endpoint event.

The benefit of ticagrelor seen on the primary composite endpoint was also reflected across the two secondary endpoints, with a numerical decrease in both CV death and all-cause mortality for ticagrelor 60 mg combined with ASA compared to ASA therapy alone, but this did not reach statistical significance (see Table 7).

The RRR for the composite endpoint from 1 to 360 days (17% RRR) and from 361 days and onwards (16% RRR) was similar. This effect was consistent throughout the study, with duration up to 47 months (median 33 months). The consistency of RRR over time suggests that it is appropriate to continue treatment with ticagrelor as long as the patient remains at high risk of developing thrombotic events (see section 4.2).

The treatment effect of Ticagrelor (BRILINTA) 60 mg twice daily vs. ASA was consistent across major subgroups, see Figure 5.

Figure 5 Hazard ratios and rates of the primary clinical composite endpoint of CV death, MI, and stroke by patient subgroup in PEGASUS (full analysis set)



The treatment effect of Ticagrelor (BRILINTA) 60 mg twice daily vs. ASA therapy alone was consistent across multiple patient subgroups, based on demographic characteristics including weight, gender, medical history, and region.

The benefits associated with Ticagrelor (BRILINTA) were also independent of the use of other cardiovascular therapies including lipid-lowering drugs, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists, calcium channel blockers, nitrates, and proton pump inhibitors (see section 4.5).

THEMIS Study (Coronary Artery Disease and Type 2 Diabetes Mellitus)

The THEMIS study was a 19,220 patient, event-driven, randomised, double-blind, placebo-controlled, parallel group, international multi-centre study to assess the prevention of thrombotic events with Ticagrelor (BRILINTA) combined with low

dose ASA (75-150 mg) compared to ASA therapy alone in patients with Coronary Artery Disease and Type 2 Diabetes Mellitus. The median ticagrelor treatment duration was 33.2 months.

Patients were eligible to participate if they were aged 50 years or over, had Coronary Artery Disease defined as history of percutaneous coronary intervention (58% of study population) or coronary artery bypass graft (29%) or no history of coronary revascularisation but angiographic evidence of $\geq 50\%$ lumen stenosis of at least 1 coronary artery (20%) and Type 2 Diabetes Mellitus treated with glucose-lowering medication for at least 6 months prior to study start. Patients with a history of MI or stroke were not eligible.

In the total THEMIS study population, Ticagrelor (BRILINTA) twice daily in combination with ASA, was superior to ASA alone in the prevention of thrombotic events (composite endpoint: CV death, MI and stroke), HR 0.90 (95% CI: 0.81, 0.99, $p=0.0378$), corresponding to a relative risk reduction (RRR) of 10% and an absolute risk reduction (ARR) of 0.73%. The effect was driven by the individual components MI (HR 0.84, 95% CI: 0.71, 0.98) and stroke (HR 0.82, 95% CI: 0.67, 0.99), with no difference in CV death (HR 1.02, 95% CI: 0.88, 1.18). Of the secondary endpoints not assessed as part of the primary composite endpoint, Ticagrelor (BRILINTA) reduced the number of ischemic stroke events (HR 0.80, 95% CI: 0.64, 0.99) with no difference in all-cause death (HR 0.98, 95% CI 0.87, 1.10).

In THEMIS patients who had undergone PCI, treatment with Ticagrelor (BRILINTA) in combination with ASA, compared to ASA alone, resulted in the prevention of thrombotic events (composite endpoint: CV death, MI and stroke), HR 0.85 [95% CI: 0.74, 0.97] (see Table 8) corresponding to a 15% RRR, a 1.19% ARR with a more favourable benefit-risk balance than the total THEMIS study population. Fewer events were reported on Ticagrelor (BRILINTA) in combination with ASA, compared to ASA alone, for each of the components of the composite endpoint.

Table 8 Analysis of primary and secondary efficacy endpoints in THEMIS PCI patients (full analysis set)

Characteristic	Ticagrelor (BRILINTA) twice daily + ASA N=5558			ASA alone N=5596		p-value ^a
	Patients with events	KM%	HR (95% CI)	Patients with events	KM%	
Primary endpoint						

	Ticagrelor (BRILINTA) twice daily + ASA N=5558			ASA alone N=5596		<i>p</i> -value ^a
Characteristic	Patients with events	KM%	HR (95% CI)	Patients with events	KM%	
Composite of CV Death/MI/Stroke	404 (7.3%)	6.5%	0.85 (0.74, 0.97)	480 (8.6%)	7.7%	0.0133
CV death	174 (3.1%)	2.7%	0.96 (0.78, 1.18)	183 (3.3%)	2.6%	0.6803
MI	171 (3.1%)	2.8%	0.80 (0.65, 0.97)	216 (3.9%)	3.8%	0.0266
Stroke	96 (1.7%)	1.6%	0.74 (0.57, 0.96)	131 (2.3%)	2.1%	0.0243
Secondary endpoint						
CV death	174 (3.1%)	2.7%	0.96 (0.78, 1.18)	183 (3.3%)	2.6%	0.6803
MI	171 (3.1%)	2.8%	0.80 (0.65, 0.97)	216 (3.9%)	3.8%	0.0266
Ischaemic Stroke	88 (1.6%)	1.4%	0.79 (0.59, 1.04)	113 (2.0%)	1.8%	0.0888
All-cause death ^b	282 (5.1%)	4.2%	0.88 (0.75, 1.03)	323 (5.8%)	4.5%	0.1067

KM percentage calculated at 36 months.

Hazard ratio and *p*-values are calculated for Ticagrelor (BRILINTA) twice daily + ASA vs ASA alone from Cox proportional hazards model with treatment as the only explanatory variable.

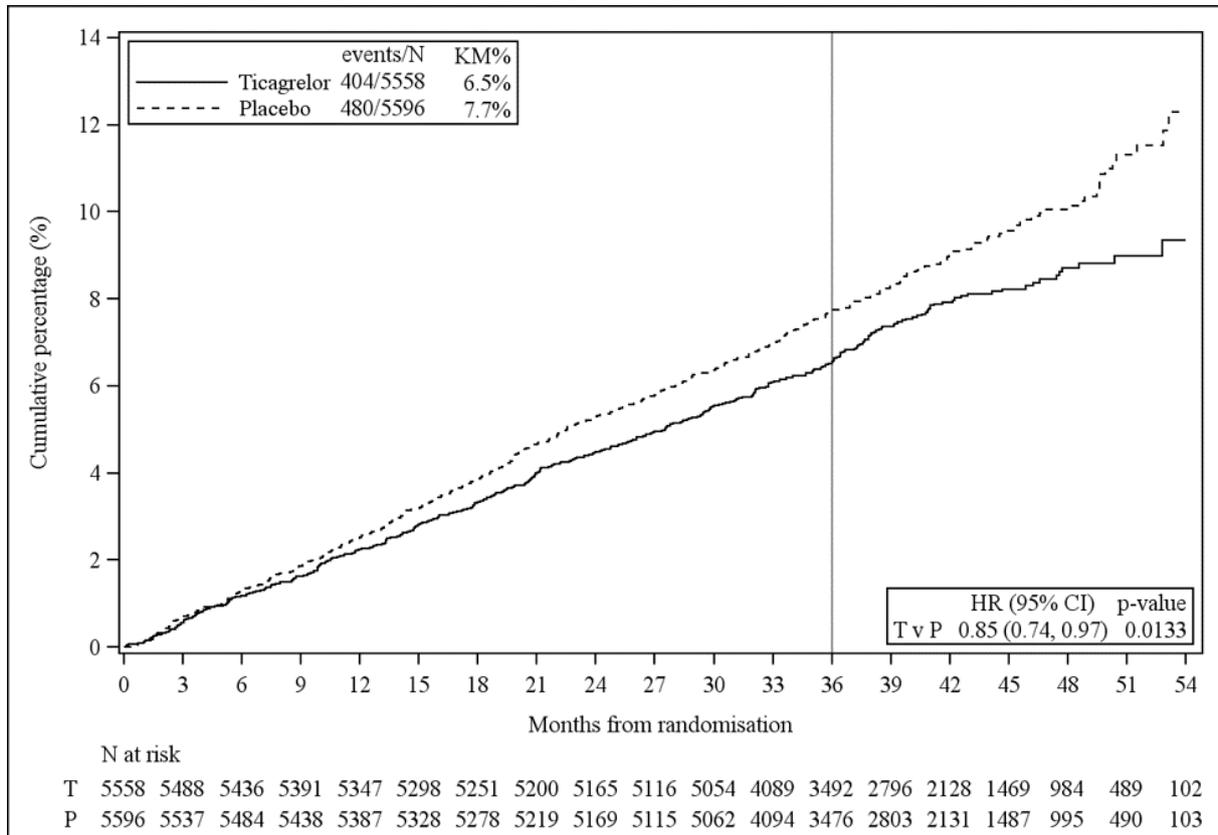
The number of first events for the components CV death, MI and stroke are the actual number of first events for each component and do not add up to the number of events in the composite endpoint

CI = Confidence interval; CV = Cardiovascular; HR = Hazard ratio; KM = Kaplan-Meier; MI = Myocardial infarction; N = Number of patients in treatment group.

^a *p*-values are nominal.

^b Includes deaths based on publicly available vital status data in patients who have withdrawn consent.

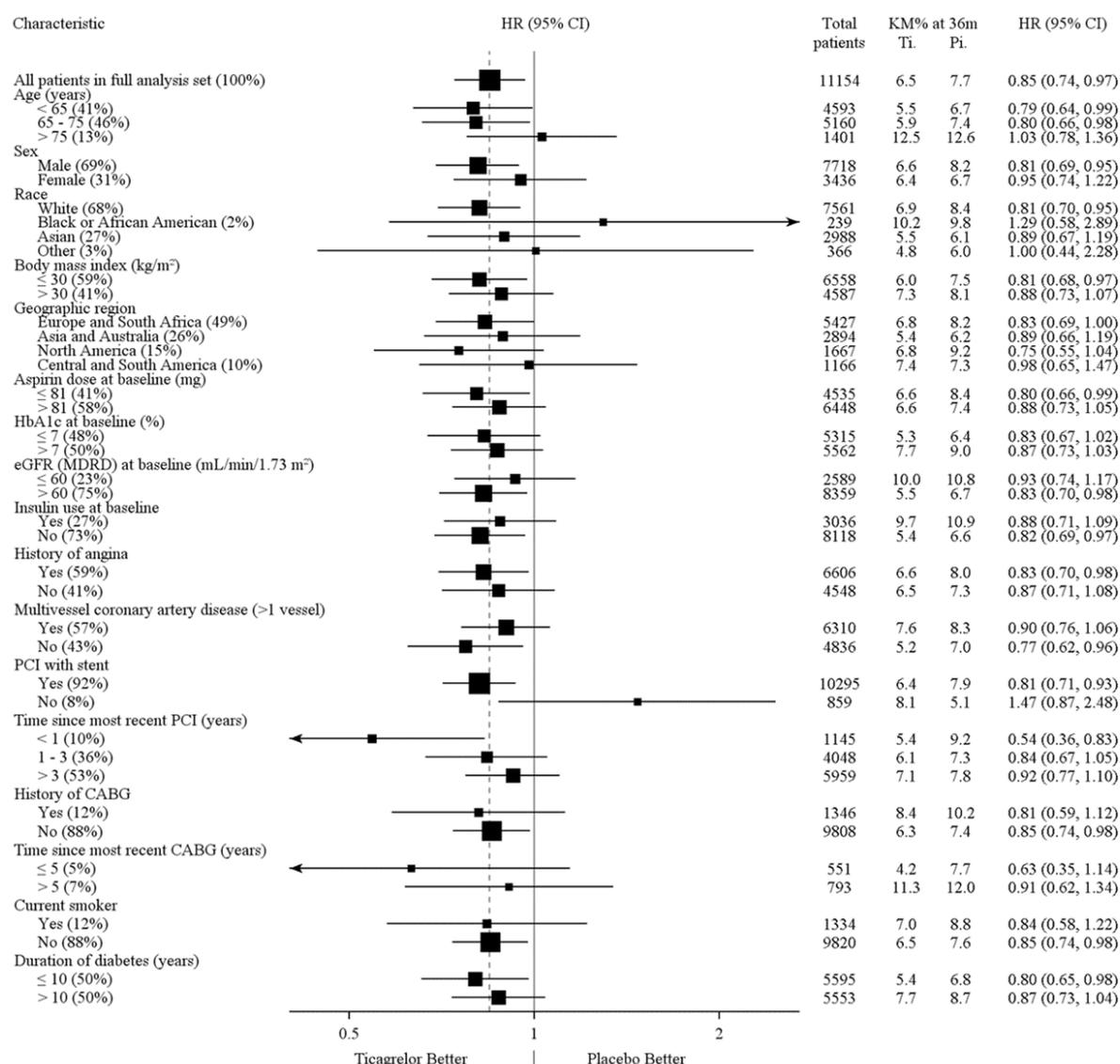
Figure 6 Kaplan-Meier plot and analysis of primary clinical composite endpoint of CV death, MI and stroke in THEMIS PCI patients (full analysis set)



The risk reduction in the primary composite endpoint seen over time up to 54 months with Ticagrelor (BRILINTA) (Figure 6) suggests that it is appropriate to continue treatment with Ticagrelor (BRILINTA) as long as the patient remains at risk of developing a thrombotic event (see section 4.2).

The treatment effect of Ticagrelor (BRILINTA) was consistent across patient subgroups, based on patient characteristics including weight, gender, medical history, and geographic region (see Figure 7).

Figure 7 Hazard ratios and rates of the primary clinical composite endpoint of CV death, MI and stroke by patient subgroup in THEMIS PCI patients (full analysis set)



THALES Study (Acute Ischaemic Stroke or Transient Ischaemic Attack)

The THALES study was a 11,016 patient, event-driven, randomised, double-blind, placebo-controlled, parallel group, international multi-centre phase 3 study to test the hypothesis that Ticagrelor (BRILINTA) 90 mg in combination with ASA is superior to ASA alone in preventing stroke and death in patients with acute ischaemic stroke or transient ischaemic attack (TIA).

Patients were eligible to participate if they were aged 40 years or over, with non-cardioembolic acute ischaemic stroke (NIHSS score ≤5) or high-risk TIA (defined as ABCD 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 randomisation were not eligible.

The study was comprised of patients who were randomised within 24 hours of onset of an acute ischaemic stroke or TIA. Patients received ticagrelor (90 mg twice daily, with an initial loading dose of 180 mg) and ASA or ASA alone for 30 days. The recommended ASA dose was 75-100 mg once daily and an initial loading dose of 300-325 mg. The median treatment duration was 31 days.

Figure 8 Kaplan-Meier plot of primary clinical composite endpoint of stroke and death in THALES (full analysis set)

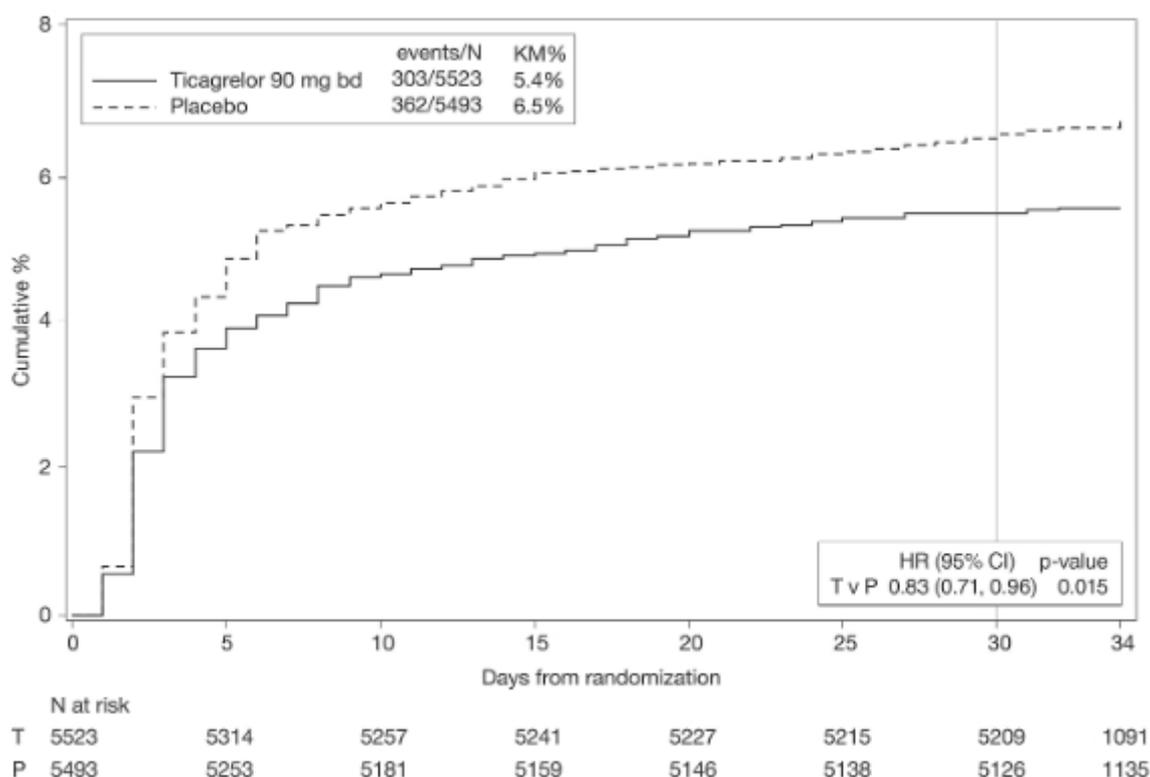


Table 9 Analysis of primary and secondary efficacy endpoints in THALES (full analysis set)

Characteristic	Ticagrelor (BRILINTA) 90 mg twice daily + ASA N=5523			ASA alone N=5493		p-value
	Patients with events	KM%	HR (95% CI)	Patients with events	KM%	
Primary endpoint						

	Ticagrelor (BRILINTA) 90 mg twice daily + ASA N=5523			ASA alone N=5493		p-value
Characteristic	Patients with events	KM%	HR (95% CI)	Patients with events	KM%	
Composite of stroke/death	303 (5.5%)	5.4%	0.83 (0.71, 0.96)	362 (6.6%)	6.5%	0.015 (s)
Stroke	284 (5.1%)	5.1%	0.81 (0.69, 0.95)	347 (6.3%)	6.3%	0.008
Death	36 (0.7%)	0.6%	1.33 (0.81, 2.19)	27 (0.5%)	0.5%	0.264
Secondary endpoint						
Ischaemic stroke	276 (5.0%)	5.0%	0.79 (0.68, 0.93)	345 (6.3%)	6.2%	0.004 (s)

Hazard ratios and p-values are calculated for Ticagrelor (BRILINTA) 90 mg twice daily + ASA vs. ASA alone from Cox proportional hazards model with treatment group as the only explanatory variable.

Kaplan-Meier percentage calculated at 30 days.

Note: the number of first events for the components stroke and death are the actual number of first events for each component and do not add up to the number of events in the composite endpoint.

(s) Indicates statistical significance.

CI = Confidence interval; HR = Hazard ratio; KM = Kaplan-Meier; N = Number of patients

Ticagrelor (BRILINTA) 90 mg twice daily, in combination with ASA, was superior to ASA alone in prevention of the composite endpoint of stroke and death, which corresponded to a relative risk reduction (RRR) of 17% and an absolute risk reduction (ARR) of 1.1% (Table 9). The effect was driven by a reduction in the stroke component of the primary endpoint (19% RRR, 1.1% ARR).

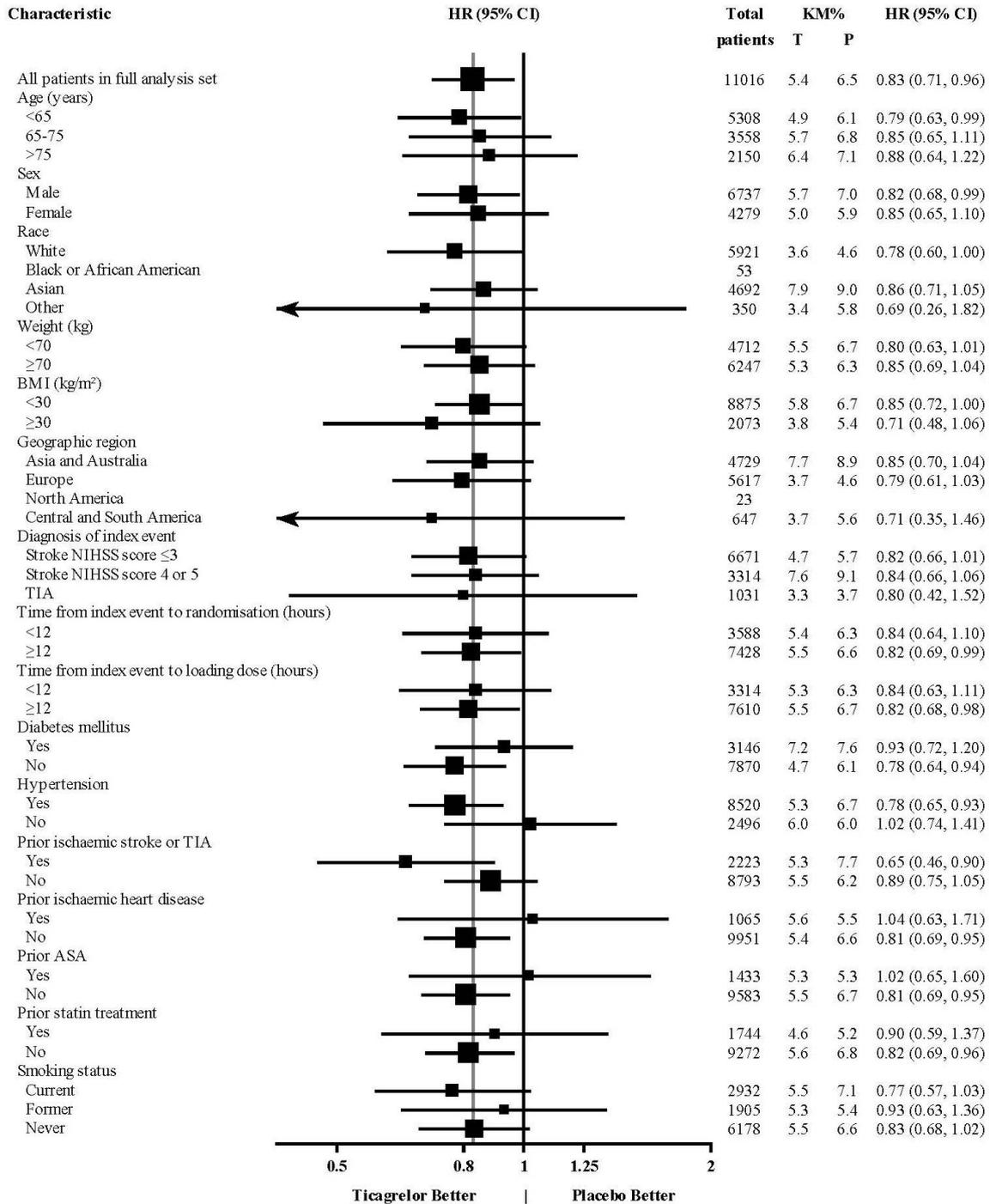
There was a statistically significant reduction in the rate of ischaemic stroke for Ticagrelor (BRILINTA) in combination with ASA compared to ASA alone (21% RRR, 1.2% ARR).

In a pre-defined exploratory analysis, there were fewer subsequent disabling stroke events (defined by patients with a subsequent stroke and having an mRS score >2) in patients treated with Ticagrelor (BRILINTA) 90 mg with ASA compared to ASA alone (150 (2.7%) vs. 188 (3.5%), respectively).

A pre-defined exploratory analysis was performed in patients with ipsilateral atherosclerotic stenosis >30%, in whom there were numerically fewer primary endpoint events (composite of stroke and death) for patients treated with Ticagrelor (BRILINTA) 90 mg with ASA compared to ASA alone (92 (8.1%) vs 132 (10.9%), respectively).

The treatment effect of Ticagrelor (BRILINTA) in combination with ASA vs. ASA alone was consistent across pre-defined subgroups, see Figure 10.

Figure 10 Hazard ratios and rates of the primary clinical composite endpoint of stroke and death by patient subgroup in THALES (full analysis set)



Paediatric population

In a randomised, double-blind, placebo-controlled, phase 3 trial, the primary objective of reducing the rate of vaso-occlusive crises in paediatric patients aged 2 to less than 18 years with sickle cell disease, was not met.

5.2 Pharmacokinetic properties

General

Ticagrelor demonstrates linear pharmacokinetics and exposure to Ticagrelor (BRILINTA) and the active metabolite (AR-C124910XX) are approximately dose proportional.

Absorption

Absorption of Ticagrelor (BRILINTA) is rapid with a median t_{max} of approximately 1.5 hours. The formation of the major circulating metabolite AR-C124910XX (also active) from Ticagrelor (BRILINTA) is rapid with a median t_{max} of approximately 2.5 hours. The C_{max} and AUC of Ticagrelor (BRILINTA) and the active metabolite increased in an approximately proportional manner with dose over the dose range studied (30-1260 mg).

The mean absolute bioavailability of Ticagrelor (BRILINTA) was estimated to be 36% (range 25.4% to 64.0%). Ingestion of a high-fat meal had no effect on Ticagrelor (BRILINTA) C_{max} or the AUC of the active metabolite, but resulted in a 21% increase in Ticagrelor (BRILINTA) AUC and 22% decrease in the active metabolite C_{max} . These small changes are considered of minimal clinical significance; therefore, Ticagrelor (BRILINTA) can be given with or without food.

Ticagrelor 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 the active metabolite). Initial exposure (0.5 and 1 hour post-dose) from crushed ticagrelor tablets mixed in water was higher compared to whole tablets, with a generally identical concentration profile thereafter (2 to 48 hours).

Distribution

The steady state volume of distribution of Ticagrelor (BRILINTA) is 87.5 L. Ticagrelor (BRILINTA) and the active metabolite is extensively bound to human plasma protein (>99.0%).

Metabolism

CYP3A is the major enzyme responsible for Ticagrelor (BRILINTA) metabolism and the formation of the active metabolite and their interactions with other CYP3A substrates ranges from activation through to inhibition. Ticagrelor (BRILINTA) and the active metabolite are weak P-glycoprotein inhibitors.

The major metabolite of Ticagrelor (BRILINTA) is AR-C124910XX, which is also active as assessed by *in vitro* binding to the platelet P2Y₁₂ ADP-receptor. The systemic exposure to the active metabolite is approximately 30-40% of that obtained for Ticagrelor (BRILINTA).

Excretion

The primary route of Ticagrelor (BRILINTA) elimination is via hepatic metabolism. When radiolabelled Ticagrelor (BRILINTA) is administered, the mean recovery of radioactivity is approximately 84% (57.8% in faeces, 26.5% in urine). Recoveries of

Ticagrelor (BRILINTA) and the active metabolite in urine were both less than 1% of the dose. The primary route of elimination for the active metabolite is mostly via biliary secretion. The mean $t_{1/2}$ was approximately 6.9 hours (range 4.5-12.8 hours) for Ticagrelor (BRILINTA) and 8.6 hours (range 6.5-12.8 hours) for the active metabolite.

Special populations

Elderly:

Higher exposures to Ticagrelor (BRILINTA) (approximately 60% for both C_{max} and AUC) and the active metabolite (approximately 50% for both C_{max} and AUC) were observed in elderly (≥ 65 years) subjects compared to younger subjects. These differences are not considered clinically significant (see section 4.2).

Paediatric:

Ticagrelor (BRILINTA) is not indicated in a paediatric population (see section 4.2 and 5.1).

Gender:

Higher exposures to Ticagrelor (BRILINTA) (approximately 52% and 37% for C_{max} and AUC, respectively) and the active metabolite (approximately 50% for both C_{max} and AUC) were observed in women compared to men. These differences are not considered clinically significant.

Renal impairment:

Exposure to Ticagrelor (BRILINTA) was approximately 20% lower and exposure to the active metabolite was approximately 17% higher in patients with severe renal impairment compared to subjects with normal renal function. The IPA effect of Ticagrelor (BRILINTA) was similar between the two groups, however there was more variability observed in individual response in patients with severe renal impairment.

In patients with end stage renal disease on haemodialysis AUC and C_{max} of Ticagrelor (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 Ticagrelor (BRILINTA) was administered immediately prior to dialysis showing that Ticagrelor (BRILINTA) is not dialysable. Exposure of the active metabolite increased to a lesser extent. The IPA effect of Ticagrelor (BRILINTA) was independent of dialysis in patients with end stage renal disease and similar to subjects with normal renal function.

No dosing adjustment is needed in patients with renal impairment.

Hepatic impairment:

C_{max} and AUC for Ticagrelor (BRILINTA) were 12% and 23% higher in patients with mild hepatic impairment compared to matched healthy subjects, respectively, however the IPA effect of Ticagrelor (BRILINTA) was similar between the two groups. No dose adjustment is needed for patients with mild hepatic impairment. Ticagrelor (BRILINTA) has not been studied in patients with severe hepatic impairment and there is no pharmacokinetic information in patients with moderate hepatic impairment. (see sections 4.2, 4.3, and 4.4).

Ethnicity:

Patients of Asian descent have a 39% higher mean bioavailability compared to Caucasian patients. Patients self-identified as Black had an 18% lower bioavailability of Ticagrelor (BRILINTA) compared to Caucasian patients. In clinical pharmacology studies, the exposure (C_{max} and AUC) to Ticagrelor (BRILINTA) in Japanese subjects was approximately 40% (20% after adjusting for body weight) higher compared to that in Caucasians. The exposure in patients self-identified as Hispanic or Latino was similar to that in Caucasians.

5.3 Preclinical safety data

Preclinical data for Ticagrelor and major metabolite have not demonstrated unacceptable risk for adverse effects for humans based on conventional studies of safety pharmacology, single and repeated dose toxicity, and genotoxic potential.

Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar or above to clinical exposure levels and with possible relevance to clinical use were as follows: GI toxicity and gastrointestinal irritation.

No compound-related tumours were observed in a 2-year mouse study at oral doses up to 250 mg/kg/day (>18-fold the maximum human therapeutic exposure). There was no increase in tumours in male rats at oral doses up to 120 mg/kg/day (>15-fold the maximum human therapeutic exposure). There was an increase in uterine adenocarcinomas and hepatocellular adenomas plus adenocarcinomas and a decrease in pituitary adenomas and mammary fibroadenomas in female rats only exposed to high doses (>25-fold the maximum human therapeutic exposures). No change in tumour incidence was observed at 60 mg/kg/day (8-fold difference to the maximum human therapeutic exposure). The uterine tumours seen only in rats were found to be the result of a non-genotoxic endocrine effect of hormonal imbalance present in rats given high doses of Ticagrelor. The benign liver tumours are considered secondary to the response by the liver to the metabolic load placed on the liver from the high doses of Ticagrelor.

Ticagrelor has been tested in a range of *in vitro* and *in vivo* tests, and was not shown to be genotoxic.

Ticagrelor was found to have no effect on fertility of female rats at oral doses up to 200 mg/kg/day (approximately 20 times the maximum human therapeutic exposure) and had no effect on fertility of male rats at doses up to 180 mg/kg/day (15.7 times the maximum human therapeutic exposure).

Ticagrelor had no effect on foetal development at oral doses up to 100 mg/kg/day in rats (5.1 times the maximum human therapeutic exposure) and up to 42 mg/kg/day in rabbits (equivalent to the maximum human therapeutic exposure). Ticagrelor had no effects on parturition or postnatal development in rats at doses up to 60 mg/kg/day (4.6 times the maximum human therapeutic exposure).

6. Pharmaceutical particulars

6.1 List of excipients

60 mg Tablet: Mannitol (E421), Dibasic calcium phosphate, Magnesium stearate, Sodium starch glycolate, Hydroxypropyl cellulose, Titanium dioxide (E171), Ferric oxide black (E172), Ferric oxide red (E172), Polyethylene glycol 400, Hypromellose

90 mg Tablet: Mannitol (E421), Dibasic calcium phosphate, Magnesium stearate, Sodium starch glycolate, Hydroxypropyl cellulose, Talc, Titanium dioxide (E171), Ferric oxide yellow (E172), Polyethylene glycol 400, Hypromellose

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

Please refer to the outer carton.

6.4 Special precautions for storage

Store at a temperature not exceeding 30°C.

6.5 Instructions for use, handling and disposal

No special requirements.

6.6 Availability

Ticagrelor (BRILINTA) 60 mg Film-Coated Tablet – Clear PVC/PVDC/Aluminum Blister pack x 10's in box of 60's

Ticagrelor (BRILINTA) 90 mg Film-Coated Tablet – Clear PVC/PVDC/Aluminum Blister pack x 10's in box of 60's

7. Registration Numbers

DR-XY45981 – Ticagrelor (BRILINTA) 60 mg Film-Coated Tablet

DR-XY40759 – Ticagrelor (BRILINTA) 90 mg Film-Coated Tablet

8. Date of First Authorization

Ticagrelor (BRILINTA) 60 mg Film-Coated Tablet – 15 August 2017

Ticagrelor (BRILINTA) 90 mg Film-Coated Tablet – 21 March 2012

CAUTION

Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, please report to the Food and Drug Administration (FDA) at www.fda.gov.ph and to AstraZeneca at patientsafety.ph@astrazeneca.com. The patient should seek medical attention immediately at the first sign of any adverse drug reaction.

Date of Revision of Text: July 2022

Philippine-specific Text ANGEL Reference: Doc ID-003152736 v.11.0

Based on CDS dated 27 October 2021 with ANGEL Reference: Doc ID-003021510 v.13.0

Imported by the Marketing Authorization Holder
AstraZeneca Pharmaceuticals (Phils.), Inc.
16th Floor, Inoza Tower, 40th Street
Bonifacio Global City, Taguig, Philippines

Ticagrelor (BRILINTA) 60 mg Tablet

Manufactured by AstraZeneca AB
Gärtunavägen, SE-151 85, Södertälje, 15185, Sweden

Ticagrelor (BRILINTA) 90 mg Tablet

Manufactured by AstraZeneca AB
Gärtunavägen, SE-151 85, Södertälje, 15185, Sweden
Packed by AstraZeneca Pharmaceutical Co., Ltd.
No. 2, Huangshan Road, Wuxi, Jiangsu, 214028, People's Republic of China

© AstraZeneca 2022

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