16 December 2021
EMA/CHMP/125700/2022
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal assessment report

Brilique

International non-proprietary name: ticagrelor

Procedure No. EMEA/H/C/001241/II/0049

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Status of this report and steps taken for the assessment				
Current step[1]	Description	Planned date	Actual Date	Need for discussion[2]
☐	Start of procedure	20 Jun 2020	20 Jun 2020	☐
☐	CHMP Rapporteur Assessment Report	14 Aug 2020	13 Aug 2020	☐
☐	CHMP Co-Rapporteur Assessment Report	14 Aug 2020	31 Jul 2020	☐
☐	PRAC Rapporteur Assessment Report	21 Aug 2020	13 Aug 2020	☐
☐	PRAC members comments	26 Aug 2020	n/a	☐
☐	Updated PRAC Rapporteur Assessment Report	27 Aug 2020	n/a	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	04 Sep 2020	03 Sep 2020	☐
☐	CHMP members comments	07 Sep 2020	07 Sep 2020	☐
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	10 Sep 2020	11 Sep 2020	☐
☐	Request for supplementary information and extension of timetable adopted by the CHMP on	17 Sep 2020	17 Sep 2020	☐
☐	Re-start of procedure	30 Nov 2020	30 Nov 2020	☐
☐	CHMP Rapporteur Assessment Report	22 Dec 2020	22 Dec 2020	☐
☐	PRAC Rapporteur Assessment Report	04 Jan 2021	22 Dec 2020	☐
☐	PRAC members comments	06 Jan 2021	n/a	☐
☐	Updated PRAC Rapporteur Assessment Report	07 Jan 2021	n/a	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	14 Jan 2021	14 Jan 2021	☐
☐	CHMP members comments	18 Jan 2021	18 Jan 2021	☐
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	21 Jan 2021	22 Jan 2021	☐
☐	2nd Request for supplementary information	28 Jan 2021	28 Jan 2021	☐
☐	Re-start of procedure	23 April 2021	23 April 2021	☐
☐	CHMP Rapporteur Assessment Report	25 May 2021	26 May 2021	☐
☐	PRAC Rapporteur Assessment Report	28 May 2021	26 May 2021	☐
☐	PRAC members comments	2 June 2021	n/a	☐
☐	Updated PRAC Rapporteur Assessment Report	3 June 2021	n/a	☐

Status of this report and steps taken for the assessment				
☐	PRAC endorsed relevant sections of the assessment report[3]	10 June 2021	10 June 2021	☐
☐	CHMP members comments	14 June 2021	14 June 2021	☐
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	17 June 2021	17 June 2021	☐
☐	3rd Request for supplementary information	24 June 2021	24 June 2021	☐
☐	Re-start of procedure	13 Sept 2021	13 Sept 2021	☐
☐	CHMP Rapporteur Assessment Report	16 Nov 2021	17 Nov 2021	☒
☐	PRAC Rapporteur Assessment Report	19 Nov 2021	N/A	☐
☐	PRAC members comments	24 Nov 2021	N/A	☐
☐	Updated PRAC Rapporteur Assessment Report	25 Nov 2021	N/A	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	2 Dec 2021	N/A	☐
☐	CHMP members comments	6 Dec 2021	6 Dec 2021	☐
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	9 Dec 2021	10 Dec 2021	☒
☐	Oral explanation	15 Dec 2021	15 Dec 2021	☒
☒	Notification of withdrawal	15 Dec 2021	15 Dec 2021	☒
☐	Opinion	16 Dec 2021		☐

Procedure resources	
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List of abbreviations

ABCD^2	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).
AE	adverse event
ALT	alanine aminotransferase
ASA	acetylsalicylic acid
AST	aspartate aminotransferase
bd	twice daily
CI	confidence interval
CV	cardiovascular
DAE	premature permanent discontinuation of investigational product due to adverse event
DAPT	dual antiplatelet therapy
HR	hazard ratio
ICH	intracranial haemorrhage
IP	investigational product (ticagrelor and placebo)
KM	Kaplan-Meier
Max	maximum
MI	myocardial infarction
Min	minimum
mRS	modified Rankin Scale
N	number of patients in treatment group
n	number of patients included in analysis
NNH	number needed to harm
NNT	number needed to treat
NIHSS	National Institutes of Health Stroke Scale
P	placebo
R	randomisation
SAE	serious adverse event
T	ticagrelor 90 mg bd
TC	telephone contact
TIA	transient ischaemic attack
ULN	Upper Limits of Normal

1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, AstraZeneca AB submitted to the European Medicines Agency on 19 May 2020 an application for a variation.

The following changes were proposed:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of the indication to include, in co-administration with acetylsalicylic acid (ASA), the prevention of stroke in adult patients with acute ischaemic stroke or transient ischaemic attack (TIA), based on the final results of study D5134C00003 (THALES), a phase III, international, multicentre, randomised, double-blind, placebo-controlled 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; as a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The applicant did not propose any changes to the Package Leaflet. Version 13 of the RMP has also been submitted.

The requested variation proposed amendments to the Summary of Product Characteristics and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0205/2018 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP has not yet been completed as some measures were deferred.

On 19 July 2018, the PDCO issued the decision that the indication “prevention of stroke and death in patients with acute ischaemic stroke or transient ischaemic attack” falls under the scope of the above mentioned Decision, as the indication is considered to be covered by the condition “prevention of thromboembolic events” listed in the Agency Decision.

Information relating to orphan market exclusivity

N/A

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

AstraZeneca requested Scientific Advice from the Committee for Medicinal Products for Human Use (CHMP) on the proposed THALES study design with regards to the study population, study treatment and comparator, study duration, safety data collection, endpoint definition, Investigator reporting of events, and statistical methodology. Following a discussion with AstraZeneca, written advice was received by AstraZeneca (15 December 2016) with the following key feedback on the proposed study design:

- The proposed primary endpoint (all strokes) was not supported. A composite primary endpoint that included all strokes and all-cause death would be acceptable.
- The proposed study treatments were endorsed.
- It is important to quantify the effect of dual antiplatelet treatment on MI through secondary endpoints.
- A follow-up period was requested to provide data to assess the benefit-risk.

Subsequent to this feedback, the primary endpoint was revised. The study duration was modified so that patients received randomised treatment for 30 days, after which patients entered a 30-day follow-up period and received standard-of-care therapy.

Pre-submission meeting

A pre-submission meeting with the CHMP Rapporteur was held on 18 February 2020.

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Cerebrovascular disease refers to conditions that affect the circulation of blood to the brain and includes acute ischaemic stroke and transient ischaemic attack (TIA). Acute ischaemic stroke and TIA may occur when an artery supplying part of the brain is completely or partially occluded. The pathophysiology varies depending on the origin of the obstruction to blood circulation (e.g., small- or large-vessel thrombosis or cardiac embolism). Thrombotic acute ischaemic events occur when an atherosclerotic plaque erodes or ruptures, activating circulating platelets and the coagulation cascade. Adherence and aggregation of platelets promote the formation of a thrombus, which can partially or totally occlude a vessel, leading to an ischaemic stroke or TIA. An ischaemic stroke is a cerebral infarction with persistent neurological dysfunction, and a TIA is a transient episode of neurological dysfunction due to cerebral ischaemia without detected acute infarction (AHA/ASA 2009). Depending on the degree of cerebral damage, the sequelae of these events range from mild and nondisabling to severe and disabling, requiring nursing care and constant attention.

Cerebrovascular disease is a leading cause of death and serious long-term disability worldwide. In 2017, there were globally an estimated 6.2 million stroke-related deaths and 132 million DALYs due to stroke, of which 2.7 million deaths and 55.1 million DALYs were due to ischaemic stroke (GBD 2017 Causes of Death Collaborators 2018, GBD 2017 DALYs and HALE Collaborators 2018). The global incidence of TIA has been reported to range between 20 and 110 per 100000 person-years in studies conducted between years 2000 and 2013 (Jiang et al. 2017, Madsen et al. 2019), although true TIA incidence may be higher due to undiagnosed/misdiagnosed events (AHA/ASA 2009).

Individuals who experience an ischaemic stroke or TIA are at high risk for a subsequent stroke. The risk is particularly high within the first month after the initial event, with a large proportion of events occurring within the first week (Amarenco et al. 2016, Johnston et al. 2016, Johnston et al. 2018, Wang et al. 2013). Immediate intervention is important to prevent a subsequent stroke that may be disabling or fatal; reducing subsequent strokes, especially disabling strokes, improves long-term outcomes of disability and death (Ganesh et al. 2017).

Treatment options in the acute setting

The underlying causes of ischaemic stroke and TIA are the same, and the preventive approaches and treatment options available are applicable to both of these manifestations of cerebrovascular disease. The aim of treatment is to minimise disability from the initial event and prevent the occurrence of subsequent strokes. Acute stroke management includes rapid reperfusion of the occluded blood vessel through thrombolysis and thrombectomy. However, these therapies have several limitations, including large demands on healthcare logistics and short time windows for treatment administration. Thrombolysis and thrombectomy are aimed to treat potentially disabling and/or severe strokes and target the incident stroke only, not subsequent events (AHA/ASA 2013, Turc et al. 2019).

Optimal management of stroke and TIA patients should include secondary preventive measures to improve outcomes. Interventions to prevent subsequent events include pharmacological and non-pharmacological treatment of risk factors (e.g., hypertension, diabetes mellitus, hypercholesterolaemia, and smoking) (AHA/ASA 2018, ESO 2008, Wang et al. 2017). Platelets play a major role in thrombotic complications of atherosclerotic disease, and the use of antiplatelet agents is recommended to reduce the risk of recurrent stroke and other CV events in patients with non-cardioembolic acute ischaemic stroke (AHA/ASA 2018, AHA/ASA 2013). For patients with cardioembolic stroke, guidelines recommend treatment with oral anticoagulants (AHA/ASA 2014, AHA/ASA 2019, ESO 2008, Wang et al. 2017); these patients were not included in THALES.

Antiplatelet monotherapy

Acetyl salicylic acid (ASA) is the antiplatelet agent recommended with the highest level of evidence in current treatment guidelines to reduce the risk of death or subsequent stroke in patients who have had a non-cardioembolic acute ischaemic stroke or TIA (Class I, Level of Evidence A) (AHA/ASA 2014, ESO 2008). ASA is the global standard-of-care treatment for these patients. However, even with ASA treatment, the risk of recurrent stroke remains high. In recent clinical studies, the risk of a subsequent event was approximately 5% to 10% during the first month (Wang et al. 2013, Johnston et al. 2018, Johnston et al. 2016).

Clopidogrel (a P2Y12 receptor antagonist) monotherapy has not been studied in patients with ischaemic stroke or TIA in the acute setting. Clopidogrel monotherapy was compared with ASA in patients with atherosclerotic vascular disease in the CAPRIE study (CAPRIE Steering Committee 1996), which included a subgroup of patients with recent ischaemic stroke (onset 1 week up to 6 months before randomisation). Based on the results from CAPRIE, clopidogrel has been approved for the treatment of patients with ischaemic stroke in the EU (from 7 days after a stroke) and the US (for ‘recent stroke’).

Dual antiplatelet therapy

Previous studies of clopidogrel in combination with ASA suggest that more intensive antiplatelet therapy with dual antiplatelet therapy (DAPT) may improve outcomes in stroke/TIA patients when initiated in the acute setting: the pilot study FASTER (Kennedy et al. 2007) and the CHANCE (Wang et al. 2013) and POINT (Johnston et al. 2018) studies. A meta-analysis of these studies also showed a benefit of DAPT on recurrent stroke (Hao et al. 2018).

CHANCE included 5170 patients in China randomised within 24 hours of an index event to clopidogrel in combination with ASA or ASA alone and treated for 21 days (after which the clopidogrel plus ASA group was switched to clopidogrel alone until Day 90) (Wang et al. 2013). In CHANCE, DAPT with clopidogrel in combination with ASA was superior to ASA alone in reducing the risk of stroke at 90 days and did not increase the risk of severe bleeding, although there was a trend toward more bleeding events in patients administered DAPT. POINT included 4881 patients primarily from the US randomised within 12 hours of an index event and showed similar efficacy of DAPT at 90 days as in CHANCE but an increased rate of major bleeding (Johnston et al. 2018). The evaluation of safety and efficacy in POINT resulted in the study being terminated prematurely at the recommendation from the Data and Safety Monitoring Board.

Based on the results from CHANCE and POINT, the combination of clopidogrel and ASA within 24 hours of a minor ischaemic stroke (NIHSS ≤ 3) or TIA ($ABCD^2$ score ≥ 4) and its continuation for 21 days is

listed as a treatment option in the US and Chinese treatment guidelines (AHA/ASA 2014, AHA/ASA 2019, Wang et al. 2017). To AstraZeneca's knowledge, at the start of this procedure there was no indication approved by a regulatory authority for clopidogrel as part of DAPT with ASA in patients with acute ischaemic stroke or TIA.

A limitation of clopidogrel is that it is a prodrug that must be converted to an active metabolite by CYP enzymes, including CYP2C19, to be effective. According to AstraZeneca, clopidogrel may therefore be less effective for reducing the risk of a new stroke after an ischaemic stroke or TIA in patients who are carriers of CYP2C19 loss-of-function alleles (Pan et al. 2017, Wang et al. 2016).

2.1.2. About the product

Ticagrelor and its mechanism of action

Ticagrelor is a member of the chemical class cyclopentyltriazolopyrimidines. It is an oral, direct-acting, selective, and reversibly binding P2Y12 receptor antagonist that prevents ADP mediated platelet activation and aggregation without requiring metabolic activation, unlike the thienopyridines (clopidogrel, prasugrel, ticlopidine). A major circulating metabolite of ticagrelor, AR-C124910XX, has similar potency as ticagrelor and thus contributes to its antiplatelet effect. Ticagrelor does not prevent ADP binding, but when bound to the P2Y12 receptor, prevents ADP-induced signal transduction.

Ticagrelor has a rapid offset due to its reversible binding. Recovery of platelet function depends on the elimination of ticagrelor and AR-C124910XX, which have half-lives of 8 and 12 hours, respectively (Teng et al. 2010). In contrast, recovery of platelet function following irreversible inhibition with a thienopyridine or ASA requires the generation of new platelets, which takes approximately 10 days.

Ticagrelor, co-administered with acetylsalicylic acid (ASA), is currently indicated for the prevention of atherothrombotic events in adult patients with:

- acute coronary syndromes (ACS) or
- a history of myocardial infarction (MI) and a high risk of developing an atherothrombotic event.

Rationale for the development of ticagrelor for the treatment of patients with acute ischaemic stroke or TIA

Even with standard-of-care treatment, the risk of a subsequent event remains high in patients with acute ischaemic stroke or TIA, and more effective therapeutic options are needed. Ticagrelor with its rapid onset/offset and consistent, high-level antiplatelet effect has the potential to provide additional benefit over current treatment options to prevent subsequent strokes during the period when the risk for a new event is at its highest.

Previous studies in the ticagrelor clinical programme have indicated that ticagrelor has a positive effect on stroke prevention in patients with atherothrombotic disease (Bhatt et al. 2019, Bonaca et al. 2016, Kolls et al. 2019). The efficacy and safety of ticagrelor monotherapy compared with ASA monotherapy over 90 days in patients with acute ischaemic stroke or TIA was investigated in the SOCRATES study (D5134C00001) (Johnston et al. 2016). In SOCRATES, there were numerically fewer primary endpoint events (stroke, MI, and death) in the ticagrelor group compared with the ASA group at Day 90,

although the difference was not statistically significant. The majority of the primary endpoint events were strokes, and there were fewer ischaemic strokes and strokes overall in the ticagrelor group compared with the ASA group. There was no increase in major bleeding events in the ticagrelor group compared with the ASA group.

A subgroup analysis indicated that the benefit of ticagrelor in SOCRATES was greater in patients who received ASA within 7 days of randomisation, including those who received a single dose after the start of the index event (Wong et al. 2018); these patients would effectively have received DAPT during the first days of the study due to the irreversible inhibition of platelet cyclooxygenase 1 by ASA. Thus, while SOCRATES did not show ticagrelor monotherapy to be superior to ASA, data from this study suggested that DAPT with ticagrelor and ASA could be a promising treatment in this population, consistent with the additional clinical benefit shown in other DAPT studies.

In the open-label PRINCE study in Chinese patients with acute ischaemic stroke or TIA, DAPT with ticagrelor and ASA was superior to DAPT with clopidogrel and ASA in reducing the proportion of patients with high platelet reactivity (Wang et al. 2019). While the study was not powered to compare clinical effect, there were numerically fewer strokes in patients treated with ticagrelor and ASA than in patients treated with clopidogrel and ASA.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

A Scientific Advice from the Committee for Medicinal Products for Human Use was requested in 2016. A composite primary endpoint that included all strokes and all-cause death was proposed. See details about the scientific advice in section 1.

Global marketing authorisations of ticagrelor 90 mg twice daily for use in adult patients following an ACS event were based on data from the PLATO study (Wallentin et al. 2009), supported by a programme of 41 Phase I and 4 Phase II studies providing data on the pharmacokinetics, absorption, distribution, metabolism, excretion, pharmacodynamics, dose-finding, and safety of ticagrelor. The findings from this programme supported the further evaluation of the potential benefits of ticagrelor in other types of atherothrombotic disease.

In the PEGASUS study, ticagrelor (60 mg or 90 mg) twice daily was superior to placebo in reducing the risk of atherothrombotic events in patients with a history of MI (1 to 3 years prior to randomisation) and at high risk of developing a thrombotic event on background ASA therapy (Bonaca et al. 2015).

In the THEMIS study (D513BC00001), compared with placebo plus aspirin, ticagrelor plus aspirin had a lower incidence of ischemic cardiovascular events but a higher incidence of major bleeding in patients with stable coronary artery disease (CAD) and diabetes without a history of myocardial infarction (MI) or stroke. (Bhatt et al., 2019).In the EUCLID study (D5135C00001), ticagrelor monotherapy was not shown to be superior to clopidogrel monotherapy in preventing atherothrombotic events for patients with symptomatic peripheral artery disease (Hiatt et al. 2017).

The current submission is based on the THALES study, which was designed to test the hypothesis that ticagrelor is superior to placebo in reducing the rate of the composite of stroke and death in patients who have had an acute ischaemic stroke or TIA and are on background ASA therapy (Johnston et al. 2019).

2.1.4. General comments on compliance with GCP

The applicant has ensured the clinical trial supporting this variation meets the ethical requirements of Directive 2001/20/EC. Details of the site audits and Regulatory Authority inspection are provided.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable.

2.2.1. Ecotoxicity/environmental risk assessment

Summary of Environmental Risk Assessment for the Use of Brilique (Ticagrelor)

The risk of an adverse environmental impact from the use of the drug substance ticagrelor (as Brilique™) has already been evaluated (EMEA/H/C1241; EMEA/H/C1241/0029/G; EMEA/H/C/1241/X/0034) and last approved on 18 May 2017. An Environmental Risk Assessment (ERA) has been undertaken for BRILINTA™/ BRILIQUE™ in accordance with the EMA Guidance EMEA/CPMP/SWP/4447/00 corr, (2006) and EMA/CHMP/SWP/44609/2010 (March 2011). The assessment, including the results from the environmental fate and effects testing, is included in the ERA report (Doc ID-004256398, module 1.6.1, summarised in Appendix 1).

BRILIQUE co-administered with acetylsalicylic acid (ASA) is indicated for the prevention of atherothrombotic events (cardiovascular death, myocardial infarction and stroke) in adult patients with acute coronary syndromes (ACS) or a history of myocardial infarction (MI) and a high risk of developing an atherothrombotic event. In the EU, treatment with BRILIQUE™ 90 mg BID/twice daily is approved for treating patients with ACS or 60 mg BID/twice daily for treating patients with a history of MI. This current application is seeking regulatory approval for a new indication: BRILIQUE™, coadministered with acetylsalicylic acid (ASA), is indicated for the prevention of stroke in patients with acute ischaemic stroke or transient ischaemic attack (TIA).

The environmental risk assessment for ticagrelor previously submitted in the EU (EMEA/H/C/1241/0029/G, approved on 18 February 2016), uses a maximum daily dose of 180 mg and a default Fpen value of 0.01 in the calculation of the Predicted Environmental Concentration (PEC). The daily dose recommended for this proposed indication is equivalent, and thus there is no change to the existing approved maximum daily dose. A revised assessment has been provided to update the indication information; however, the default risk assessment and conclusions remain essentially unchanged.

The assessment showed that in domestic sewage, ticagrelor will not significantly partition into the solid phase during wastewater treatment. Furthermore, ticagrelor is not readily biodegradable. Therefore, it is anticipated that ticagrelor will pass into the natural aquatic environment. Ticagrelor was found to be hydrolytically stable at pHs 7 and 9 with half-life at 25°C >1 year, although some hydrolysis was observed at pH 5 it is not expected to be a significant environmental fate process. Once in the aquatic environment, the evidence suggests that ticagrelor will partition into, and degrade within, aquatic sediments. The octanol-water partition coefficient (Log Dow >4.02) value is >3 but <4.5 indicating that the risk of bioaccumulation in aquatic organisms is low; however, a bioaccumulation study in fish was conducted. The BCF study in rainbow trout (*Oncorynchus mykiss*) resulted in a BCF of 6.36, confirming a low risk of bioaccumulation.

Based on these results, ticagrelor does not fulfil the criteria to be classified as a Persistent, Bioaccumulative and Toxic (PBT) or very Persistent, very Bioaccumulative (vPvB) compound. The Predicted Environmental Concentration (PEC)/ Predicted No Effect Concentration (PNEC) ratios for groundwater, surface water and sediment are below 1, and the PEC/PNEC ratio for microorganisms is below 0.1. Therefore, ticagrelor is not predicted to present a significant risk to the environment.

Details on the determination of the separate study results can be found in Module 1.6.1 nongmo-environmental-risk-assessment (Brilinta™/Brilique™ [Ticagrelor, co-administered with acetylsalicyclic acid (ASA)] - for the prevention of stroke in adult patients with acute ischaemic stroke or transient ischaemic attack (TIA), Doc ID-004256398, May 1st, 2020).

2.2.2. Conclusion on the non-clinical aspects

No new non-clinical data were provided.

Based on the updated data submitted in this application, the new/extended indication leads to a significant increase in environmental exposure further to the use of ticagrelor.

Considering the above data and the environmental risk assessment, ticagrelor is neither PBT nor vPvB and ticagrelor is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- the single, pivotal THALES study, a randomised, parallel-group, placebo-controlled, double-blind, event-driven study designed to test the hypothesis that ticagrelor is superior to placebo in reducing the rate of the composite of stroke or death in patients who have had an acute ischaemic stroke or TIA and are on background ASA therapy.

GCP

The clinical trials were performed in accordance with GCP as claimed by the MAH

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Tabular overview of clinical studies

The application is based on the single pivotal THALES study:

Table 1: Description of the THALES study

Study ID	D5134C00003 (THALES)

Number of centres [a] Number of countries Locations	414 28 Argentina, Australia, Belgium, Brazil, Bulgaria, Canada, China, Czechia, France, Germany, Hong Kong, Hungary, India, Italy, Mexico, Peru, Poland, Romania, Russia, Saudi Arabia, Slovakia, South Korea, Spain, Sweden, Taiwan, Thailand, Ukraine, Vietnam
Study start (FSI) completion (LSLV)	22 January 2018 13 December 2019
Total enrolled / randomised	11073 / 11016
Design and duration	Randomised, placebo-controlled, double-blind, parallel-group Study treatment duration 30 days, follow-up duration 30 days
Diagnosis	Patients ≥ 40 years of age with acute ischaemic stroke or TIA, randomised within 24 hours after onset of symptom
% acute ischaemic stroke % TIA	90.6% 9.4%
Study and control drugs	Ticagrelor 180 mg loading dose on Day 1, then 90 mg twice daily (oral doses); Placebo
Patients randomised/ completed treatment	Ticagrelor: 5523 / 4715 Placebo: 5493 / 4825
Sex Median age (range)	38.8% F, 61.2% M 65.0 years (40 to 100 years)
Primary variable	Time from randomisation to first subsequent stroke or death

2.4. Clinical pharmacology

No new pharmacokinetics or pharmacodynamics studies have been submitted in this application, which is considered acceptable. Pharmacology, pharmacokinetics and pharmacodynamics of ticagrelor were extensively discussed in the initial MAA.

2.5. Clinical study

2.5.1. Description

This application was based on the single, pivotal THALES study, a randomised, parallel-group, placebo-controlled, double-blind, event-driven study designed to test the hypothesis that ticagrelor is superior to placebo in reducing the rate of the composite of stroke or death in patients who have had an acute ischaemic stroke or TIA and are on background ASA therapy. Patients were randomised within 24 hours of symptom onset in a 1:1 ratio to 30 days treatment with ticagrelor or placebo. After the 30-day treatment period, patients were followed for an additional 30 days.

2.5.2. Methods

2.5.2.1. Study participants

The THALES study was conducted in 28 countries worldwide. The target population included patients ≥ 40 years of age with noncardioembolic acute ischaemic stroke or high-risk TIA randomised within 24 hours of symptom onset. Patients were included in the THALES study based upon symptomatic disease and neurological deficit.

The inclusion criteria were:

1. Provision of signed informed consent prior to any study-specific procedure
2. ≥ 40 years of age
3. Acute onset of cerebral ischaemia due to
    a. Acute ischaemic stroke with NIHSS ≤ 5. Acute ischaemic stroke is defined as acute onset of neurological deficit attributed to focal brain ischaemia, and either of the following:
        i. Persistent signs or symptoms of the ischaemic event at the time of randomisation, OR
        ii. Acute ischaemic brain lesion documented before randomisation by CT scan or 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:
        i. $ABCD^2$ score ≥ 6 and TIA symptoms not limited to isolated numbness, isolated visual changes, or isolated dizziness/vertigo
        ii. 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
        iii. 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
5. CT or MRI performed after symptom onset ruling out ICH or other pathology, such as vascular malformation, tumour, or abscess that according to the Investigator could explain symptoms or contraindicate study treatment

The exclusion criteria were:

1. Need for or an anticipated need for any of the following:
    a. DAPT with ASA and P2Y12 inhibitors (including patients with carotid artery stenting and percutaneous coronary intervention)

b. Antiplatelets other than ASA (eg, GPIIb/IIIa inhibitors, clopidogrel, ticlopidine, prasugrel, dipyridamole, ozagrel, cilostazol, ticagrelor) and other antithrombotic agents with antiplatelet effects, including traditional/herbal medicine agents

c. Anticoagulants (eg, warfarin, oral thrombin and factor Xa inhibitors, bivalirudin, hirudin, argatroban, fondaparinux, or unfractionated heparin and long-term treatment with low-molecular weight heparins). Short-term treatment (≤ 7 days) with low-dose low-molecular weight heparin may be used in immobilised patients at the discretion of the Investigator

2. Any history of atrial fibrillation/flutter, ventricular aneurysm, or suspicion of other cardioembolic pathology for TIA or stroke
3. Patients who should receive or have received any intravenous or intra-arterial thrombolysis or mechanical thrombectomy within 24 hours prior to randomisation
4. Planned carotid endarterectomy that requires halting IP within 3 days of randomisation or is expected to require unblinding of IP (planned carotid endarterectomy is in itself not an exclusion criterion)
5. History of previous ICH at any time (asymptomatic microbleeds do not qualify), gastrointestinal haemorrhage within the past 6 months, or major surgery within 30 days
6. Patients considered to be at risk of bradycardic events (eg, known sick sinus syndrome or second- or third-degree atrioventricular block) unless already treated with a permanent pacemaker
7. Inability of the patient to understand and/or comply with study procedures and/or follow-up, in the opinion of the Investigator
8. Known hypersensitivity to ticagrelor or ASA
9. Need for or an anticipated need for oral or intravenous therapy with any of the following:

    a. Strong cytochrome P450 3A4 (CYP3A4) inhibitors (eg, ketoconazole, clarithromycin [but not erythromycin or azithromycin], nefazadone, ritonavir, atazanavir) that cannot be stopped for the course of the study

    b. Long-term (> 7 days) non-steroidal anti-inflammatory drugs

10. Known bleeding diathesis or coagulation disorder (eg, thrombotic thrombocytopenic purpura)
11. Known severe liver disease (eg, ascites or signs of coagulopathy)
12. Renal failure requiring dialysis
13. Pregnancy or breastfeeding. Women of child-bearing potential who are not willing to use a medically accepted method of contraception that is considered reliable in the judgment of the Investigator
14. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site)
15. Previous enrolment or randomisation in the present study
16. Participation in another clinical study with an IP at any time during the 30 days prior to randomisation (regardless of when treatment with the IP was discontinued)

2.5.2.2. Objectives

The primary objective was:

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

The secondary objectives were:

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

The safety objective was:

- To assess the safety of ticagrelor and ASA compared with that of placebo and ASA in acute ischaemic stroke/TIA patients, in particular with respect to major bleeding events

The exploratory objectives were:

- To assess the efficacy of ticagrelor and ASA compared with placebo and ASA in acute ischaemic stroke/TIA patients with ipsilateral atherosclerotic stenosis in the prevention of stroke and death at 30 days
- To assess the efficacy of ticagrelor and ASA compared with placebo and ASA in acute ischaemic stroke/TIA patients in reducing disabling stroke at 30 days
- To describe health-related quality of life in acute ischaemic stroke/TIA patients after treating with ticagrelor and ASA or placebo and ASA for 30 days

2.5.2.3. Study design

Patients ≥ 40 years of age with non-cardioembolic acute ischaemic stroke with National Institutes of Health Stroke Scale (NIHSS) score ≤ 5 OR TIA with ABCD^2 score ≥ 6 or with large-vessel disease (ie, ipsilateral ≥ 50% stenosis of extra- or intracranial artery) were randomised within 24 hours of symptom onset in a 1:1 ratio to 30 days treatment with ticagrelor or placebo. After 30 days of treatment with IP, patients were given standard-of-care treatment of the Investigator's choice and followed for an additional 30 days.

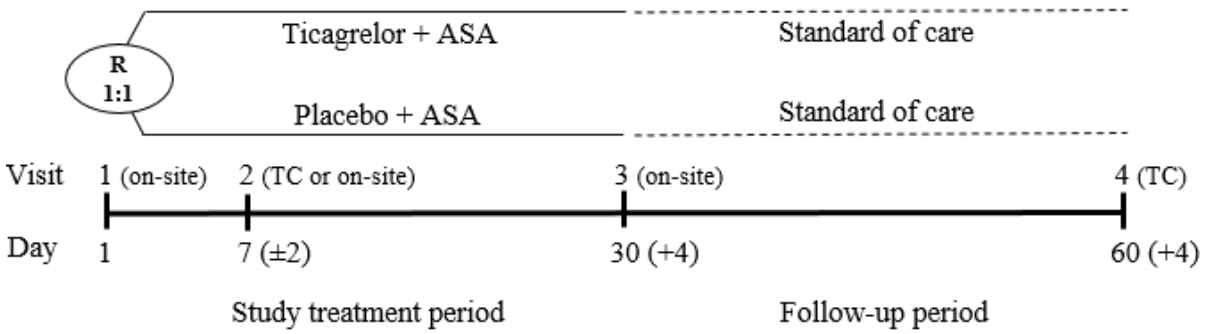


Figure 1. Flow chart of the study design

2.5.2.4. Sample size

At least 647 primary endpoint events were needed to provide 90% power assuming a HR of 0.775 in favour of ticagrelor at the significance level of 4.996%, adjusted for the planned efficacy interim analysis (647 events corresponding to a critical value of 0.857).

Based on data from the SOCRATES study, a primary endpoint rate of 6.7% in the placebo group was assumed at 30 days following randomisation. Hence, randomising approximately 11000 patients to ticagrelor or placebo in a 1:1 ratio was expected to yield the 647 events needed. The study was event-driven, and the final number of randomised patients was determined based on blind data review.

The assumed treatment effect and the power for the primary endpoint were revised from the initial CSP following a recommendation from the Executive Committee. The recommendation was based on the evolving evidence on DAPT use in stroke patients, partially triggered by a meta-analysis of stroke studies comparing clopidogrel and ASA with ASA alone (Hao et al. 2018). As a result of the revised HR and power, the estimated number of events needed and hence the sample size for the study were revised.

2.5.2.5. Treatments

Investigational product and comparator(s)

At randomisation (Visit 1/Day 1), eligible patients were randomly assigned to 1 of 2 treatments: ticagrelor or placebo (investigational product [IP]). Treatments were given orally with loading doses on Day 1 followed by maintenance treatment until Visit 3 (Day 30 to 34).

Patients were treated with:

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

In addition to the IP, all patients were to be treated with ASA as part of standard of care.

Patients were to receive an ASA loading dose on Day 1. The recommended loading dose was 300 to 325mg ASA. Any dose of ASA given after symptom onset but before randomisation was to be taken into account (for instance, if a patient had received 300mg ASA just prior to randomisation, the patient did not need to receive a second loading dose after randomisation).

Thereafter, patients were to be treated with ASA 75 to 100mg once daily.

There were 4 batches of ticagrelor and matching placebo used in this study.

Timing of loading doses and first maintenance doses

<u>Ticagrelor/placebo</u>

The loading dose of ticagrelor/placebo was to be given immediately after randomisation (i.e., on Day 1).

The first maintenance dose was to be given > 6 to ≤ 12 hours after the loading dose. The second maintenance dose was to be given > 6 to ≤ 12 hours after the first maintenance dose, adjusting the timing such that subsequent doses can be taken in the morning and evening.

Thereafter, ticagrelor/placebo was to be taken morning and evening at approximately 12-hour intervals for the remainder of the treatment period.

ASA

The ASA loading dose was to be given on Day 1, and the first maintenance dose of ASA was to be taken in the morning of Day 2.

Duration of treatment

Patients were treated for 30 days and thereafter followed for an additional 30 days during which they received standard-of-care treatment.

The study included 4 visits: on Day 1 (enrolment/randomisation; Visit 1), on Day 5 to 9 (Visit 2), on Day 30 to 34 (end of the treatment period; Visit 3), and on Day 60 to 64 (end of follow-up period; Visit 4).

2.5.2.6. Outcomes/endpoints

Table 2. Objections and endpoints

Objective			Endpoint
Priority	Type	Description	Description
Primary	Efficacy	To demonstrate superior efficacy of ticagrelor and ASA compared with placebo and ASA in acute ischaemic stroke/TIA patients in the prevention of the composite of stroke and death at 30 days	Time from randomisation to first subsequent stroke or death
Secondary	Efficacy	To demonstrate superior efficacy of ticagrelor and ASA compared with placebo and ASA in acute ischaemic stroke/TIA patients in the prevention of ischaemic stroke at 30 days	Time from randomisation to first subsequent ischaemic stroke
Secondary	Efficacy	To demonstrate superior efficacy of ticagrelor and ASA compared with placebo and ASA in acute ischaemic stroke/TIA patients in reducing overall disability at 30 days	mRS score > 1 at Visit 3

	Safety	To assess the safety of ticagrelor and ASA compared with that of placebo and ASA in acute ischaemic stroke/TIA patients, in particular with respect to major bleeding events	Time from randomisation to first bleeding event that fulfils SAE criteria and is categorised as GUSTO Severe Time from randomisation to first ICH or fatal bleeding event Time from randomisation to first bleeding event that fulfils SAE criteria and is categorised as GUSTO Moderate/Severe Time from randomisation to premature permanent discontinuation of IP due to bleeding Occurrence of SAE Occurrence of DAE
Exploratory	Efficacy	To assess the efficacy of ticagrelor and ASA compared with placebo and ASA in acute ischaemic stroke/TIA patients with ipsilateral atherosclerotic stenosis in the prevention of stroke or death at 30 days	Time from randomisation to first subsequent stroke or death in patients with ipsilateral atherosclerotic stenosis
Exploratory	Efficacy	To assess the efficacy of ticagrelor and ASA compared with placebo and ASA in acute ischaemic stroke/TIA patients in reducing disabling stroke at 30 days	mRS score > 2 at Visit 3 in patients with subsequent stroke
Exploratory	Patient reported outcomes	To describe health-related quality of life in acute ischaemic stroke/TIA patients after treating with ticagrelor and ASA or placebo and ASA for 30 days	EQ-5D-5L profile

The mRS is a scale used to measure the degree of disability or dependency in patients who have experienced a stroke, where dependency (requirement for outside assistance to, e.g., perform daily tasks) corresponds to mRS > 2. The definition of each mRS score is shown in Table 3.

Table 3. mRS scores

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities

Score	Description
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

Randomisation

Randomisation codes were assigned strictly sequentially within each centre as patients became eligible for randomisation. The randomisation codes were computer-generated by AstraZeneca R&D using the AstraZeneca Global Randomisation system AZRand and loaded into the Interactive Voice/Web Response System database. The randomisation codes were generated in blocks to ensure approximate balance (1:1) between the 2 treatment groups. Once a block is exhausted, the next available block was allocated by Interactive Voice/Web Response System to a centre upon their next randomisation.

The first doses of IP and ASA (loading doses) were to be taken on Day 1. Patients were randomised as soon as possible and within 24 hours after symptom onset.

Blinding (masking)

The ticagrelor tablets and the placebo tablets for ticagrelor were identical in size, colour, smell, and taste. Each bottle was labelled with a unique kit ID number that was used to assign the treatment to the patient but did not indicate treatment allocation to the Investigator or patient.

Statistical methods

All efficacy and safety analyses were based on the intention-to-treat principle using the full analysis set, including all randomised patients. The primary and secondary variables were included in the confirmatory analyses and were tested in sequential order; the secondary variables were only to be tested in a confirmatory sense if the primary comparison was significant.

The time-to-event variables were analysed using the Cox proportional hazards model with a factor for treatment group. The HR, 95% confidence interval (CI), and p-value were reported. The time-to-event safety variables were analysed in the same way as the primary variable, but were not included in the confirmatory testing procedure. The adverse events (AEs) were presented by treatment group using descriptive statistics.

Analysis of the primary variable

For the primary variable, time from randomisation to first subsequent stroke or death, the null hypothesis of no treatment effect,

H0: HR (ticagrelor divided by placebo) = 1,

versus the alternative hypothesis,

H1: HR ≠1,

was tested at the 4.996% 2-sided significance level. Patients who had not experienced a primary event were censored at Visit 3, Day 34, or the date of last event assessment, whichever occurred earlier. If Visit 3 had occurred within the visit window, Day 30 to 34, events were included up to the date of Visit 3 (inclusive). If Visit 3 had occurred outside of the visit window (or was missing), it was replaced by Day 34 for event inclusion and censoring. Time was calculated as the number of days + 1 between the date of randomisation and the date of the first occurrence of the event, or, if no event had occurred, the date of censoring.

Explorative and sensitivity analyses of the primary variable

If there were patients lost to follow-up in the ticagrelor group, a sensitivity ('tipping point') analysis was to be performed by adding events to the ticagrelor group (at the time of censoring) until a non-significant result was obtained. A sensitivity analysis 'on treatment' was performed, including events from the date of the first dose of IP up to the date of the last dose of IP + 7 days (inclusive). Event-free patients were censored at the date of the last dose of IP + 7 days or the date of last event assessment, whichever occurred earlier. Patients who never received any dose of IP were censored at Day 1.

As an explorative analysis, primary events up to the end of the follow-up period were analysed by repeating the primary analysis with event-free patients censored at Visit 4 (or Day 64) instead of Visit 3 (or Day 34). If Visit 4 had been performed within the visit window, Day 60 to 64, events were included up to the date of Visit 4 (inclusive). If Visit 4 had been performed outside of the visit window (or was missing), it was replaced by Day 64 for event inclusion and censoring.

Subgroup analyses of the primary variable

Subgroup analyses of the primary variable were performed to evaluate variation of treatment effect. Tests for interaction between treatment and each subgroup variable were performed in Cox proportional hazards models with factors for treatment, subgroup variable, and the interaction between treatment and subgroup variable if at least 15 events had occurred in each subgroup category. The subgroup categories were examined in Cox proportional hazards models with a factor for treatment group. KM estimates, HRs, and 95% CIs were reported if at least 15 events had occurred within the subgroup category.

Analysis of the secondary variables

The secondary variables were included in the confirmatory testing procedure. Only if the treatment effect on the primary variable was significant at the 4.996% level would the secondary variables be tested in a confirmatory sense in the following order:

Time from randomisation to first subsequent ischaemic stroke (including strokes classified as undetermined)

mRS score > 1 at Visit 3

The hypothesis testing would continue at the 4.996% significance level until the first statistically non-significant treatment difference ($p \geqslant 0.04996$) was observed.

Time from Randomisation to First Subsequent Ischaemic Stroke

The time from randomisation to first subsequent ischaemic stroke was analysed in the same manner as the primary variable.

mRS Score > 1 at Visit 3

The proportion of patients with mRS score > 1 at Visit 3 was analysed using a logistic regression model with treatment group, history of stroke, and baseline NIHSS score as explanatory variables. A sensitivity analysis was performed where missing mRS scores were imputed as > 1.

The mRS score for patients who had died prior to Visit 3 was by definition 6. No other imputation for missing data was made. If Visit 3 had occurred prior to Day 30 and the patient had died prior to or at Day 34, the mRS score was 6.

Analysis of the safety variables

The time-to-event safety variables were analysed in the same manner as the primary variable, but were not included in the confirmatory testing procedure. Sensitivity analyses 'on treatment' were performed. Subgroup analyses, were performed for GUSTO Severe bleeding events. Furthermore, the analysis of GUSTO Severe bleeding events was repeated with event-free patients censored at Visit 4 (or Day 64) instead of Visit 3 (or Day 34).

For the time-to-event safety variables, patients who had not experienced the event were censored at Visit 3, Day 34, or the date of last event assessment, whichever occurred earlier; or, for the time from randomisation to discontinuation due to bleeding variable only, the day of the last dose of IP, if earlier. Patients who never received any dose of IP were censored at Day 1 for the discontinuation due to bleeding variable. If Visit 3 had occurred outside of the visit window (or was missing), it was replaced by Day 34 for event inclusion and censoring. SAEs, DAEs, and AEs with the outcome of death, summarised by system organ class and PT using the Medical Dictionary for Regulatory Activities, were presented by treatment group using descriptive statistics. AEs were reported according to start date. The reported outcome of an AE starting during the treatment period could occur at any time during the study.

Analysis of the exploratory variables

Time from Randomisation to First Subsequent Stroke or Death in Patients with Ipsilateral Atherosclerotic Stenosis

The time from randomisation to first subsequent stroke or death in patients with ipsilateral atherosclerotic stenosis was analysed in the same manner as the primary variable. Four analyses were performed: 1) in patients with ipsilateral atherosclerotic stenosis $\geqslant$ 50% (extracranial and intracranial combined and separately), 2) in patients with ipsilateral atherosclerotic stenosis $\geqslant$ 30% (extracranial and intracranial combined and separately) (main category for reporting), 3) in patients with atherosclerosis in any vascular bed (including cerebrovascular atherosclerosis or medical history of coronary artery bypass grafting, MI, percutaneous coronary intervention, coronary artery disease, or peripheral arterial occlusive disease), and 4) in patients with ipsilateral stenosis who undergo carotid endarterectomy/intervention.

mRS Score > 2 at Visit 3 in Patients with Subsequent Stroke and Other Analyses of Disabling Stroke

The proportion of patients with subsequent stroke and mRS score > 2 at Visit 3 was analysed using a logistic regression model with treatment group, history of stroke, and baseline NIHSS score as explanatory variables. Additional analyses of disabling stroke were performed by varying the threshold for the mRS score (> 1 and > 3) and by utilising the 3 categories no stroke, non-disabling stroke (mRS score $\leqslant$ 2), and disabling stroke (mRS score > 2). Strokes needed to occur prior to or at the date of the mRS measurement to be classified as non-disabling/disabling.

EQ-5D-5L Profile

EQ-5D-5L data were presented by treatment group using descriptive statistics.

Description of analysis sets

All variables, including safety variables, were analysed using the FAS. All patients who were randomised to IP were included in the FAS irrespective of their protocol adherence and continued participation in the study. Patients were analysed according to their randomised IP irrespective of whether an event occurred before or following discontinuation of IP. The rationale for using a single analysis set was the short time between randomisation and expected first dose of IP and the short duration of IP treatment; almost all patients were expected to receive at least one dose of IP and the time 'off treatment' for patients who prematurely and permanently discontinued IP would have been very limited. Supportive 'on treatment' analyses were performed, however.

Interim analyses

One interim analysis was performed by the Data Monitoring Committee after the accrual of 70% of the planned primary events (453). The efficacy stopping boundary at the interim was a 2- sided p-value < 0.001 for the primary endpoint (corresponding to a critical value of for the HR equal to 0.734).

The interim p-value was small enough for the final analysis, based on the accrual of all events, to be conducted at a significance level of 4.996%, with the family-wise error rate controlled at 5.00%. This boundary was estimated in East V6.4 (copyright 1994-2016, Cytel Inc) using the Haybittle-Peto procedure.

If a recommendation to stop the study for efficacy was made at the interim, all subsequent testing of secondary efficacy variables was to be done at a significance level of 0.1%. The study could be stopped for futility if the observed HR for the primary endpoint was > 0.933 (taking all available study information into account), corresponding to a predictive power of 5% or less.

2.5.3. Results

2.5.3.1. Recruitment/ Numbers analysed

In total, 11073 patients were enrolled at 414 sites in 28 countries. The largest proportions of patients were randomised in Europe (51.0%) and Asia and Australia (42.9%). Patient disposition was similar between treatment groups. A total of 11.016 patients were randomised into the study: 5523 patients to the ticagrelor group and 5493 patients to the placebo group.

Patients were considered to have completed the study if they did not withdraw consent. Few patients withdrew consent: 8 patients in the ticagrelor group and 7 patients in the placebo group. Almost all randomised patients (11001 patients, 99.9%) completed the study up to the end of the follow-up period (ie, Visit 4). There was 1 patient with unknown vital status at the end of the treatment period (ie, at planned Visit 3). This patient had not withdrawn consent and was therefore considered lost to follow-up.

Overall, 99.6% of the randomised patients received at least one dose of randomised IP: 5506 (99.7%) patients in the group randomised to ticagrelor and 5470 (99.6%) patients in the group randomised to placebo. During the treatment period, almost all patients, 99.5%, were on a background of ASA therapy.

A numerically larger proportion of patients prematurely and permanently discontinued IP in the ticagrelor group (14.3%) than in the placebo group (11.7%). The most common reason for premature permanent discontinuation of IP in both treatment groups was AEs: 9.6% in the ticagrelor group and 7.5% in the placebo group. Adverse events include efficacy endpoint events, and it was the Investigator's decision whether to continue or prematurely and permanently discontinue IP after a subsequent stroke.

The overall proportion of patients who completed treatment was 86.6%: 85.4% in the ticagrelor group and 87.8% in the placebo group (see Table 4).

Table 4. Patient disposition

	Number (%) of patients		
	Ticagrelor 90 mg bd	**Placebo**	**Total**
Patients enrolled [a]			11073
Patients randomised	5523 (100.0)	5493 (100.0)	11016 (100.0)
Patients who were not randomised			57
Patient did not meet inclusion/exclusion criteria			52
Patient decision			5
Patients who died			0
Patients who received treatment	5506 (99.7)	5470 (99.6)	10976 (99.6)
Patients who did not receive treatment	17 (0.3)	23 (0.4)	40 (0.4)
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)
Adverse event [b]	530 (9.6)	411 (7.5)	941 (8.5)
Patient decision	177 (3.2)	145 (2.6)	322 (2.9)
Other	84 (1.5)	89 (1.6)	173 (1.6)
Vital status at visit 3			
Patients who withdrew 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)
Vital status at visit 4			
Patients who withdrew consent before visit 4	8 (0.1)	7 (0.1)	15 (0.1)
Alive	8 (0.1)	7 (0.1)	15 (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 4	5515 (99.9)	5486 (99.9)	11001 (99.9)
Alive	5467 (99.0)	5444 (99.1)	10911 (99.0)
Dead	47 (0.9)	42 (0.8)	89 (0.8)
Vital status unknown	1 (0.0)	0 (0.0)	1 (0.0)

[a] Informed consent received
[b] Includes patients with subsequent stroke

2.5.3.2. Conduct of the study

Quality of study conduct was demonstrated by the high rate of complete follow up of primary endpoint events (99.8% of patients), the low number of patients lost to follow-up (one patient), and high rate of compliance with IP in both treatment groups. A review of important protocol deviations including the use of prohibited concomitant medications, did not raise any concerns regarding study conduct, the safety of patients, or interpretation of results. Changes to the multiple testing procedure were made, see statistical methods.

2.5.3.3. Baseline data

The demographic characteristics of patients were balanced between treatment groups (Table 5). The population was predominantly White (53.7%) or Asian (42.6%); the mean age was 65.1 years; and 61.2% of patients were male. The mean BMI was 26.4 kg/m2, and the proportion of patients with a BMI <30 kg/m2 was 81.1% (Table 6).

Table 5. Demographic characteristics (full analysis set)

Demographic characteristic		Ticagrelor 90 mg bd (N=5523)	Placebo (N=5493)	Total (N=11016)
Age (years)	n	5523	5493	11016
	Mean	65.2	65.1	65.1
	SD	11.0	11.1	11.0
	Median	65.0	65.0	65.0
	Min	40	40	40
	Max	100	98	100
Age group (years) n (%)	<65	2676 (48.5)	2632 (47.9)	5308 (48.2)
	65-75	1749 (31.7)	1809 (32.9)	3558 (32.3)
	>75	1098 (19.9)	1052 (19.2)	2150 (19.5)
	Total	5523 (100.0)	5493 (100.0)	11016 (100.0)
Sex n (%)	Male	3415 (61.8)	3322 (60.5)	6737 (61.2)
	Female	2108 (38.2)	2171 (39.5)	4279 (38.8)
	Total	5523 (100.0)	5493 (100.0)	11016 (100.0)
Race n (%)	White	2973 (53.8)	2948 (53.7)	5921 (53.7)
	Black or African American	21 (0.4)	32 (0.6)	53 (0.5)
	Asian	2353 (42.6)	2339 (42.6)	4692 (42.6)
	Native Hawaiian or other Pacific Islander	1 (0.0)	3 (0.1)	4 (0.0)
	American Indian or Alaska Native	173 (3.1)	168 (3.1)	341 (3.1)
	Other	2 (0.0)	3 (0.1)	5 (0.0)
	Total	5523 (100.0)	5493 (100.0)	11016 (100.0)
Ethnic group n (%)	Hispanic or Latino	517 (9.4)	504 (9.2)	1021 (9.3)
	Not Hispanic or Latino	5006 (90.6)	4989 (90.8)	9995 (90.7)
	Total	5523 (100.0)	5493 (100.0)	11016 (100.0)

Table 6. Patient characteristics (full analysis set)

Patient characteristic		Ticagrelor 90 mg bd (N=5523)	Placebo (N=5493)	Total (N=11016)
Height (cm)	n	5495	5460	10955
	Mean	166.0	165.8	165.9
	SD	8.9	8.9	8.9
	Median	165.0	165.0	165.0
	Min	125	101	101
	Max	200	198	200
Weight (kg)	n	5498	5461	10959
	Mean	73.1	72.7	72.9
	SD	15.3	15.3	15.3
	Median	72.0	70.0	71.0
	Min	27	31	27
	Max	140	150	150
Weight group (kg) n (%)	n	5498	5461	10959
	<70	2324 (42.3)	2388 (43.7)	4712 (43.0)
	≥70	3174 (57.7)	3073 (56.3)	6247 (57.0)
Body Mass Index (kg/m^2)	n	5493	5455	10948
	Mean	26.4	26.3	26.4
	SD	4.6	4.6	4.6
	Median	25.9	25.7	25.8
	Min	12	13	12
	Max	52	56	56
Body Mass Index group (kg/m^2) n (%)	n	5493	5455	10948
	<30	4446 (80.9)	4429 (81.2)	8875 (81.1)
	≥30	1047 (19.1)	1026 (18.8)	2073 (18.9)

The diagnosis and severity of the index events were balanced between treatment groups (Table 7). The diagnosis of index events at randomisation was acute ischaemic stroke for 90.6% of patients and TIA for 9.4% of patients. Of the randomised patients, 60.6% had an acute ischaemic stroke with NIHSS scores ≤ 3, 30.1% had an acute ischaemic stroke with NIHSS scores 4 to 5, and 8.2% had a TIA event with $ABCD^2$ scores ≥ 6. A small proportion of TIA patients were included in the study based on symptomatic intra- or extracranial stenosis known at randomisation.

Times from symptom onset to randomisation and loading dose were similar between treatment groups. Overall, 32.6% of patients were randomised within 12 hours of symptom onset. The proportion of patients who received the IP loading dose within 24 hours of symptom onset was 97.7%.

Table 7. Description of index event (full analysis set)

Characteristic	Number (%) of patients Ticagrelor 90 mg bd (N=5523)	Placebo (N=5493)	Total (N=11016)
Index event, diagnosis at randomisation			
Acute ischaemic stroke	5032 (91.1)	4953 (90.2)	9985 (90.6)
High risk TIA	491 (8.9)	540 (9.8)	1031 (9.4)
Patients with acute ischaemic stroke			
NIHSS score at randomisation			
≤3	3359 (60.8)	3312 (60.3)	6671 (60.6)
4-5	1671 (30.3)	1641 (29.9)	3312 (30.1)
>5	2 (0.0)	0 (0.0)	2 (0.0)
Persistent signs or symptoms at the time of randomisation	4905 (88.8)	4798 (87.3)	9703 (88.1)
Acute ischaemic brain lesion at the time of randomisation	2510 (45.4)	2490 (45.3)	5000 (45.4)
Patients with high risk TIA			
ABCD^2 score at randomisation			
0-5	60 (1.1)	71 (1.3)	131 (1.2)
6	377 (6.8)	395 (7.2)	772 (7.0)
7	54 (1.0)	74 (1.3)	128 (1.2)
Symptomatic intracranial arterial occlusive disease[a]	42 (0.8)	40 (0.7)	82 (0.7)
Internal carotid arterial occlusive disease[b]	71 (1.3)	73 (1.3)	144 (1.3)
Time from symptom onset to randomisation			
≤6 hours	524 (9.5)	535 (9.7)	1059 (9.6)
>6 to ≤12 hours	1289 (23.3)	1242 (22.6)	2531 (23.0)
>12 to ≤18 hours	1298 (23.5)	1386 (25.2)	2684 (24.4)
>18 to ≤24 hours	2407 (43.6)	2327 (42.4)	4734 (43.0)
>24 hours	5 (0.1)	3 (0.1)	8 (0.1)
Time from symptom onset to loading dose			
≤6 hours	439 (7.9)	435 (7.9)	874 (7.9)
>6 to ≤12 hours	1266 (22.9)	1261 (23.0)	2527 (22.9)
>12 to ≤18 hours	1272 (23.0)	1310 (23.8)	2582 (23.4)
>18 to ≤24 hours	2420 (43.8)	2360 (43.0)	4780 (43.4)
>24 hours	81 (1.5)	80 (1.5)	161 (1.5)
Missing	45 (0.8)	47 (0.9)	92 (0.8)

a Stenosis >=50% in intracranial artery supplying the ischemic field known at randomisation.
b Stenosis >=50% in carotid artery supplying the ischemic field known at randomisation.

The medical and surgical history of patients was similar between treatment groups (Table 8). In total, 77.3% of patients had a history of hypertension, 37.6% had a history of dyslipidaemia, 28.6% had a history of diabetes, 16.5% had a history of ischaemic stroke, 4.7% of the patients had a history of TIA, 3.1% had a history of MI, 26.6% were current smokers, and 17.3% were former smokers. Imaging of extracranial and/or intracranial arteries was performed as part of clinical practice in 79.9% of patients. Overall, 21.3% of the randomised patients had ≥ 30% stenosis of the ipsilateral artery.

Table 8. Medical and surgical history and smoking status (full analysis set)

	Number (%) of patients		
Condition	**Ticagrelor 90 mg bd (N=5523)**	**Placebo (N=5493)**	**Total (N=11016)**
Current smoker	1504 (27.2)	1428 (26.0)	2932 (26.6)
Former smoker	980 (17.7)	925 (16.8)	1905 (17.3)
Hypertension	4298 (77.8)	4222 (76.9)	8520 (77.3)
Dyslipidaemia	2098 (38.0)	2049 (37.3)	4147 (37.6)
Type 2 diabetes mellitus	1557 (28.2)	1521 (27.7)	3078 (27.9)
Type 1 diabetes mellitus	32 (0.6)	36 (0.7)	68 (0.6)
Angina pectoris	192 (3.5)	205 (3.7)	397 (3.6)
Myocardial infarction	169 (3.1)	177 (3.2)	346 (3.1)
Coronary artery disease	452 (8.2)	459 (8.4)	911 (8.3)
Percutaneous coronary intervention	112 (2.0)	117 (2.1)	229 (2.1)
Coronary artery bypass grafting	38 (0.7)	42 (0.8)	80 (0.7)
Congestive heart failure	207 (3.7)	204 (3.7)	411 (3.7)
Atrial fibrillation	5 (0.1)	7 (0.1)	12 (0.1)
Atrial flutter	0 (0.0)	0 (0.0)	0 (0.0)
Transient ischaemic attack	275 (5.0)	240 (4.4)	515 (4.7)
Ischaemic stroke	901 (16.3)	914 (16.6)	1815 (16.5)
Haemorrhagic stroke	8 (0.1)	3 (0.1)	11 (0.1)
Cerebrovascular accident NOS	2 (0.0)	0 (0.0)	2 (0.0)
Peripheral arterial occlusive disease	102 (1.8)	102 (1.9)	204 (1.9)
Chronic kidney disease	196 (3.5)	228 (4.2)	424 (3.8)

2.6. Clinical efficacy

2.6.1. Primary variable: Time from randomisation to first subsequent stroke or death

The primary objective of the THALES study was met. In patients with acute ischaemic stroke or TIA on background ASA therapy, ticagrelor was superior to placebo in reducing the rate of the composite of stroke and death up to Day 30 (HR 0.83 [95% CI 0.71, 0.96], p = 0.015) (Table 9). The KM percentages for the composite of stroke and death at Day 30 were 5.4% in the ticagrelor group and 6.5% in the placebo group (Figure 2). Most primary endpoint events occurred early and the KM curves separated shortly after randomisation. The KM curves remained separated during the treatment period. When analysing the primary variable by study day, the HR for ticagrelor versus placebo was consistent throughout the treatment period, indicating an increasing benefit of ticagrelor during the treatment period.

Most primary endpoint events were strokes (93.7% and 95.9% in the ticagrelor and the placebo group respectively; Table 9). The risk reduction observed in the ticagrelor group was driven by a reduction in the stroke component of the primary endpoint. During the treatment period, there were 36 and 27 deaths in the ticagrelor group and the placebo group, respectively. Of these, 19 deaths contributed to the primary endpoint in the ticagrelor group, and 15 deaths contributed to the primary endpoint in the placebo group (Table 10).

Table 9. Analysis of the composite of stroke and death (primary endpoint) and its components up to visit 3 (full analysis set) [First events]

	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

Table 10. Summary statistics for stroke and death (primary endpoint events) up to visit 3 (full analysis set) [First and subsequent events]

	Total number of events		Number (%) of first events in given group		Number (%) of first events in the primary endpoint composite[a]	
	Ticagrelor 90 mg bd (N=5523)	Placebo (N=5493)	Ticagrelor 90 mg bd (N=5523)	Placebo (N=5493)	Ticagrelor 90 mg bd (N=5523)	Placebo (N=5493)
Composite of stroke/death	326	383	303 (5.5)	362 (6.6)	303	362
Stroke	290	356	284 (5.1)	347 (6.3)	284 (93.7)	347 (95.9)
Ischaemic stroke	280	354	276 (5.0)	345 (6.3)	276 (91.1)	345 (95.3)
Haemorrhagic stroke	10	2	10 (0.2)	2 (0.0)	8 (2.6)	2 (0.6)
Death	36	27	36 (0.7)	27 (0.5)	19 (6.3)	15 (4.1)

a Percentages are based on the number of first events of the given type, divided by the number of events in the primary endpoint composite.
Undetermined strokes are analysed as ischaemic strokes.

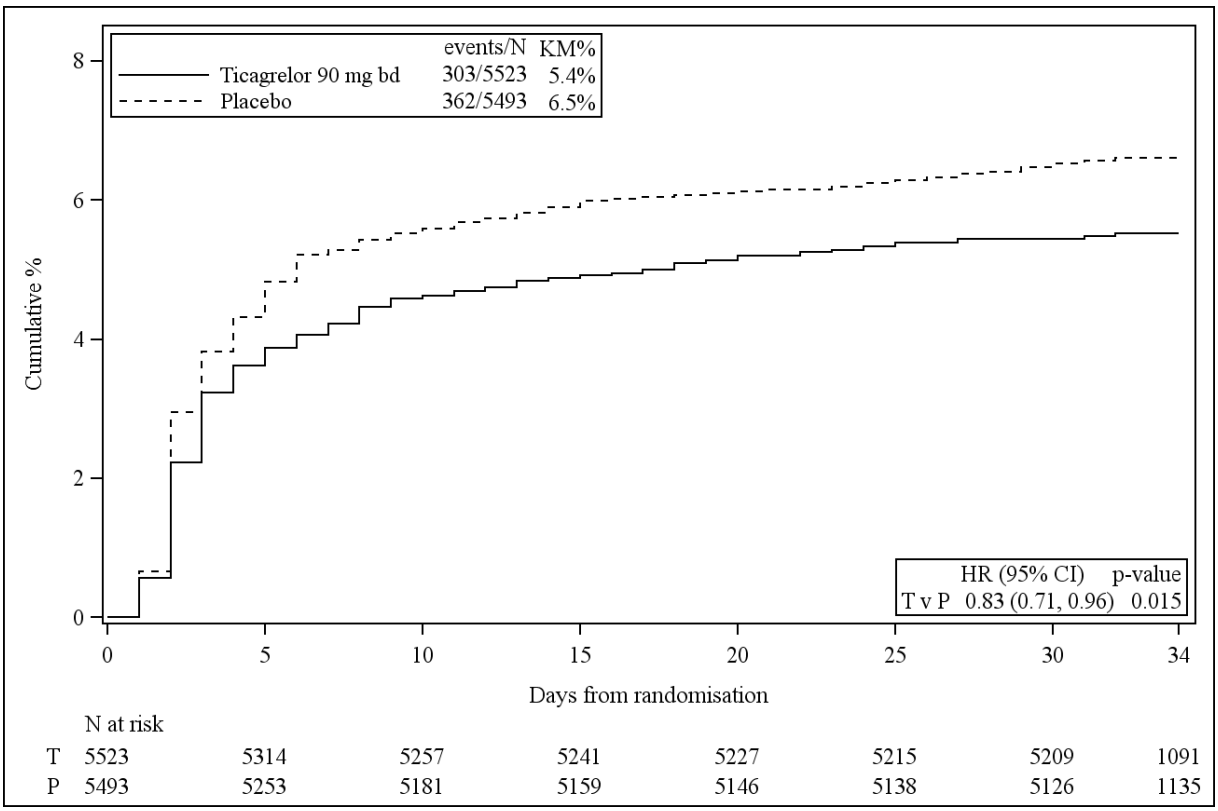


Figure 2. Kaplan-Meier plot of the composite of stroke and death (primary endpoint) (full analysis set)

Subgroup analyses

The treatment effect in the ticagrelor group compared with the placebo group was seen consistently across all predefined patient subgroups.

Table 11. Analysis of the composite of stroke and death (primary endpoint) by subgroup (full analysis set)

		Ticagrelor 90 mg bd (N=5523)			Placebo (N=5493)						
Characteristic	Group	n	Patients with events (%)	KM%	n	Patients with events (%)	KM%	Hazard ratio	95% CI	p-value	p-value interaction
Age (years)	<65	2676	132 (4.9)	4.9	2632	164 (6.2)	6.1	0.79	(0.63, 0.99)	0.041	0.832
	65-75	1749	101 (5.8)	5.7	1809	122 (6.7)	6.8	0.85	(0.65, 1.11)	0.226	
	>75	1098	70 (6.4)	6.4	1052	76 (7.2)	7.1	0.88	(0.64, 1.22)	0.446	
Sex	Male	3415	198 (5.8)	5.7	3322	235 (7.1)	7.0	0.82	(0.68, 0.99)	0.035	0.819
	Female	2108	105 (5.0)	5.0	2171	127 (5.8)	5.9	0.85	(0.65, 1.10)	0.206	
Race	White	2973	108 (3.6)	3.6	2948	137 (4.6)	4.6	0.78	(0.60, 1.00)	0.050	
	Black or African American	21	2 (9.5)		32	2 (6.3)					
	Asian	2353	186 (7.9)	7.9	2339	213 (9.1)	9.0	0.86	(0.71, 1.05)	0.140	
	Other	176	7 (4.0)	3.4	174	10 (5.7)	5.8	0.69	(0.26, 1.82)	0.459	
Weight (kg)	<70	2324	127 (5.5)	5.5	2388	162 (6.8)	6.7	0.80	(0.63, 1.01)	0.060	0.708
	≥70	3174	172 (5.4)	5.3	3073	195 (6.3)	6.3	0.85	(0.69, 1.04)	0.119	
BMI (kg/m^2)	<30	4446	258 (5.8)	5.8	4429	301 (6.8)	6.7	0.85	(0.72, 1.00)	0.055	0.424
	≥30	1047	41 (3.9)	3.8	1026	56 (5.5)	5.4	0.71	(0.48, 1.06)	0.097	
Geographic region	Asia and Australia	2373	184 (7.8)	7.7	2356	213 (9.0)	8.9	0.85	(0.70, 1.04)	0.111	
	Europe	2814	105 (3.7)	3.7	2803	131 (4.7)	4.6	0.79	(0.61, 1.03)	0.079	
	North America	12	1 (8.3)		11	0 (0.0)					
	Central and South America	324	13 (4.0)	3.7	323	18 (5.6)	5.6	0.71	(0.35, 1.46)	0.353	
Diagnosis of index event	Stroke NIHSS score ≤3	3359	158 (4.7)	4.7	3312	190 (5.7)	5.7	0.82	(0.66, 1.01)	0.060	0.985
	Stroke NIHSS score >3	1673	129 (7.7)	7.6	1641	150 (9.1)	9.1	0.84	(0.66, 1.06)	0.136	
	TIA	491	16 (3.3)	3.3	540	22 (4.1)	3.7	0.80	(0.42, 1.52)	0.494	
Time from index event to randomisation (hours)	<12	1812	98 (5.4)	5.4	1776	114 (6.4)	6.3	0.84	(0.64, 1.10)	0.196	0.930
	≥12	3711	205 (5.5)	5.5	3717	248 (6.7)	6.6	0.82	(0.69, 0.99)	0.041	
Time from index event to loading dose (hours)	<12	1655	89 (5.4)	5.3	1659	106 (6.4)	6.3	0.84	(0.63, 1.11)	0.214	0.900
	≥12	3823	211 (5.5)	5.5	3787	254 (6.7)	6.7	0.82	(0.68, 0.98)	0.031	
Diabetes mellitus	Yes	1589	115 (7.2)	7.2	1557	121 (7.8)	7.6	0.93	(0.72, 1.20)	0.572	0.265
	No	3934	188 (4.8)	4.7	3936	241 (6.1)	6.1	0.78	(0.64, 0.94)	0.009	
Hypertension	Yes	4298	228 (5.3)	5.3	4222	286 (6.8)	6.7	0.78	(0.65, 0.93)	0.005	0.138
	No	1225	75 (6.1)	6.0	1271	76 (6.0)	6.0	1.02	(0.74, 1.41)	0.888	
Prior ischaemic stroke or TIA	Yes	1122	59 (5.3)	5.3	1101	88 (8.0)	7.7	0.65	(0.46, 0.90)	0.010	0.099
	No	4401	244 (5.5)	5.5	4392	274 (6.2)	6.2	0.89	(0.75, 1.05)	0.169	
Prior ischaemic heart disease[a]	Yes	532	31 (5.8)	5.6	533	30 (5.6)	5.5	1.04	(0.63, 1.71)	0.891	0.357
	No	4991	272 (5.4)	5.4	4960	332 (6.7)	6.6	0.81	(0.69, 0.95)	0.010	
Prior ASA[b]	Yes	754	41 (5.4)	5.3	679	36 (5.3)	5.3	1.02	(0.65, 1.60)	0.921	0.329
	No	4769	262 (5.5)	5.5	4814	326 (6.8)	6.7	0.81	(0.69, 0.95)	0.010	
Prior statin treatment[b]	Yes	865	41 (4.7)	4.6	879	46 (5.2)	5.2	0.90	(0.59, 1.37)	0.624	0.672
	No	4658	262 (5.6)	5.6	4614	316 (6.8)	6.8	0.82	(0.69, 0.96)	0.016	
Smoking status	Current	1504	83 (5.5)	5.5	1428	102 (7.1)	7.1	0.77	(0.57, 1.03)	0.074	0.729
	Former	980	52 (5.3)	5.3	925	53 (5.7)	5.4	0.93	(0.63, 1.36)	0.714	
	Never	3038	168 (5.5)	5.5	3140	207 (6.6)	6.6	0.83	(0.68, 1.02)	0.075	

a Coronary artery bypass grafting, myocardial infarction, percutaneous coronary intervention, or coronary artery disease.
b At least one dose taken within 2-7 days prior to randomisation.
Placebo is the reference treatment.
Kaplan-Meier (KM) percentage is calculated at 30 days.
Hazard ratios and p-values are calculated for ticagrelor vs. placebo from Cox proportional hazards model with treatment as the only explanatory variable.
The p-value for the interaction is calculated from Cox proportional hazards model with treatment, the relevant subgroup, and their interaction as explanatory variables.
Kaplan-Meier estimates, hazard ratios, and CIs are calculated if at least 15 events have occurred within the subgroup category, and the interaction between treatment and subgroup if at least 15 events have occurred in each subgroup category.

2.6.2. Secondary endpoints

Ischaemic stroke

Ticagrelor was superior to placebo in reducing the rate of ischaemic stroke up to Day 30 (the first secondary objective) in patients who have had an acute ischaemic stroke or TIA and were on background ASA therapy (Figure 3).

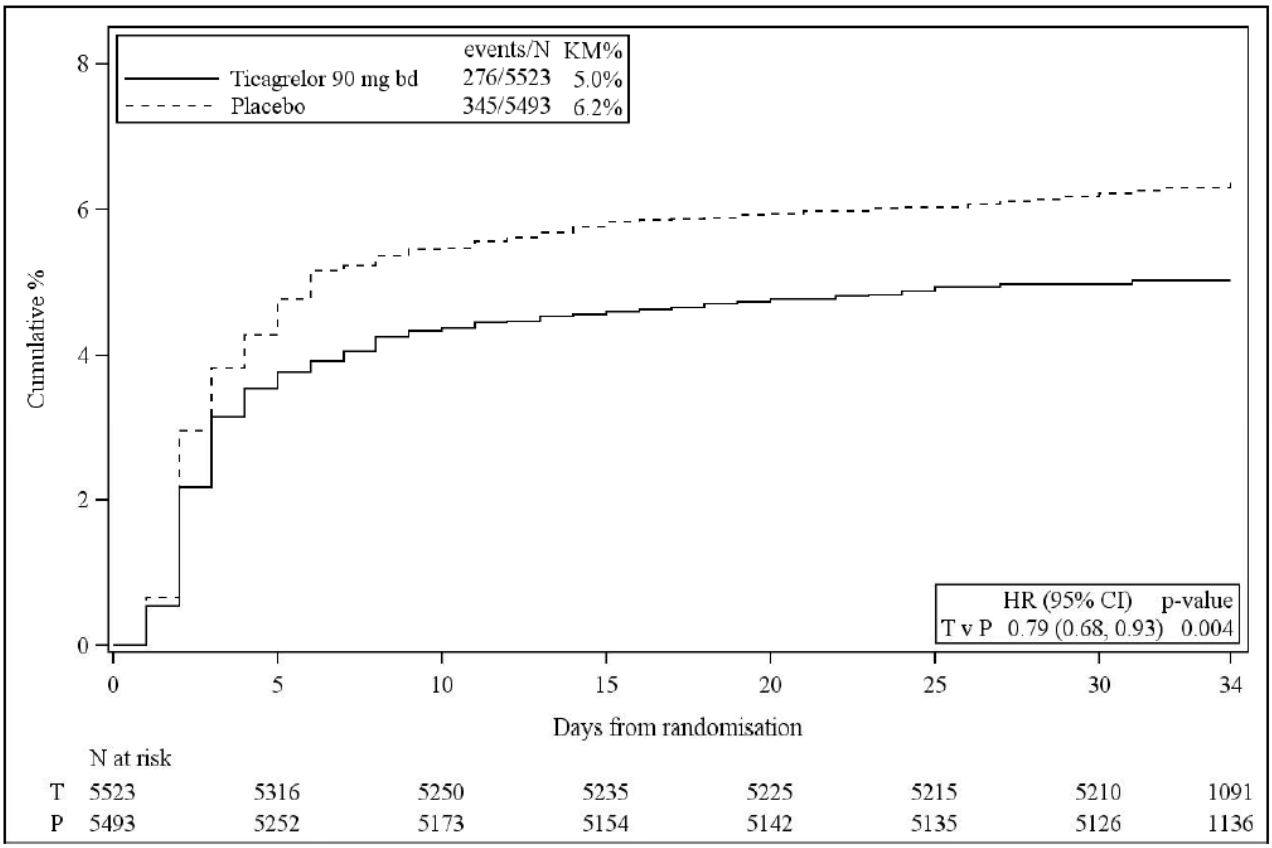


Figure 3. Kaplan-Meier plot of ischaemic stroke (secondary endpoint) (full analysis set)

Overall disability

There was no 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).

Table 12. 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)		

2.6.3. Exploratory endpoints

Composite of stroke and death (Primary Endpoint) up to visit 4

As an exploratory analysis, primary events were analysed up to the end of the follow-up period (Visit 4), during which patients received standard-of-care treatment. Most patients (97.4%) received antithrombotic treatment during the follow-up period, and the percentages were similar between treatment groups. The most common antithrombotic medications during the follow-up period were ASA, taken by 93.1% of patients, followed by clopidogrel, taken by 6.4% of patients. The treatment effect was maintained during the follow-up period, with numerically fewer primary events in the ticagrelor group compared with the placebo group up to Day 60 (HR 0.83 [95% CI 0.72, 0.96]).

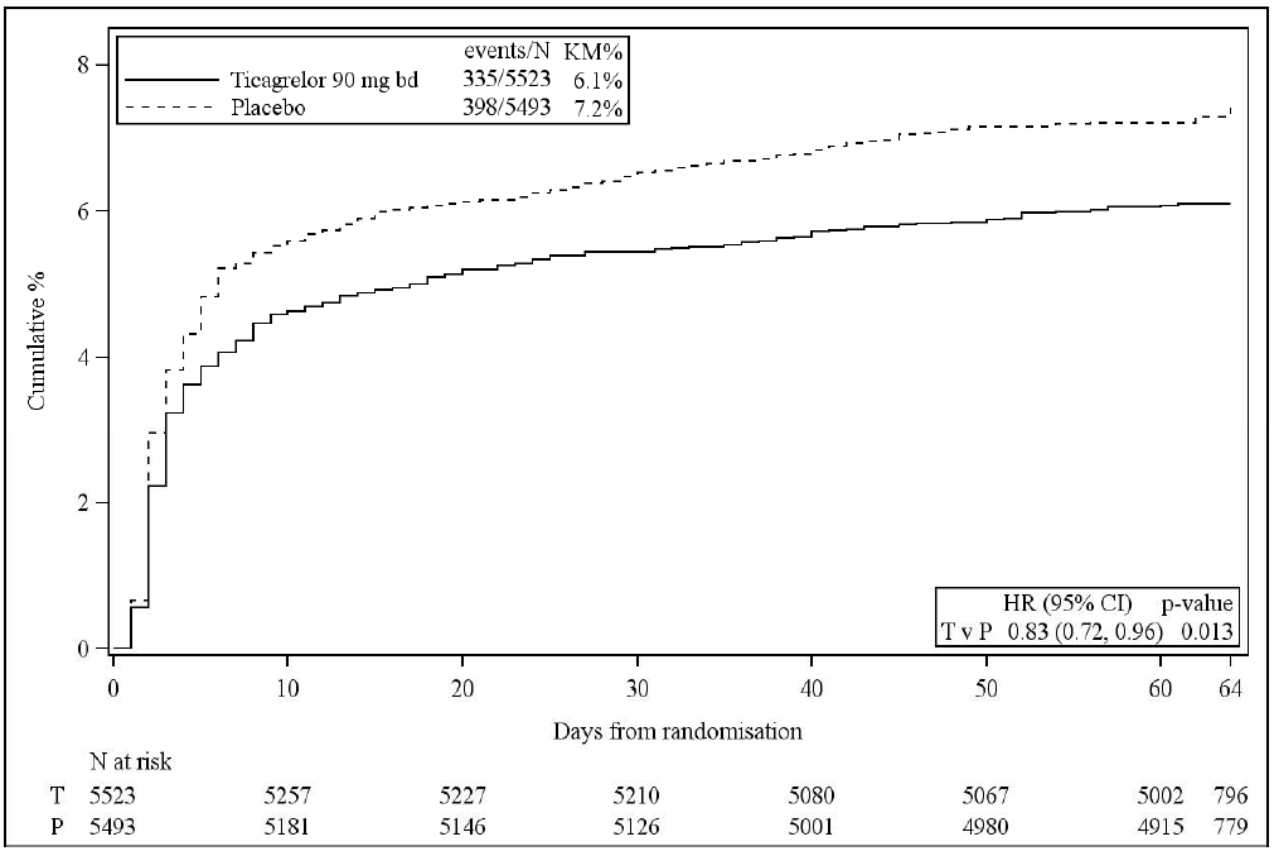


Figure 4. Kaplan-Meier plot of the composite of stroke and death (primary endpoint) up to visit 4 (full analysis set)

Stroke and death in patients with ipsilateral atherosclerotic stenosis

The number of patients with ipsilateral atherosclerotic stenosis ≥ 30% was balanced between treatment groups. Patients with acute ischaemic stroke or TIA with ipsilateral atherosclerotic stenosis ≥ 30% had a numerically higher risk of a primary endpoint event (composite of stroke and death) than the overall study population up to Day 30 (Table 13). For patients with ipsilateral atherosclerotic stenosis ≥ 30% there were numerically fewer patients in the ticagrelor group with a primary endpoint event compared with the placebo group at Day 30 (HR 0.73 [CI 95% 0.56, 0.96], Table 13).

Table 13. Exploratory analysis of stroke and death (primary endpoint) by ipsilateral atherosclerotic stenosis subgroup (full analysis set)

	Ticagrelor 90 mg bd (N=5523)			Placebo (N=5493)					
Characteristic	n	Patients with events (%)	KM%	n	Patients with events (%)	KM%	Hazard ratio	95% CI	p-value
Patients with ipsilateral atherosclerotic stenosis ≥50%	719	73 (10.2)	9.9	767	100 (13.0)	13.0	0.77	(0.57, 1.04)	0.087
Patients with ipsilateral atherosclerotic stenosis in extracranial artery ≥ 50%	459	46 (10.0)	10.0	475	56 (11.8)	11.8	0.85	(0.57, 1.25)	0.401
Patients with ipsilateral atherosclerotic stenosis in intracranial artery ≥ 50%	382	44 (11.5)	11.0	416	66 (15.9)	15.9	0.71	(0.49, 1.05)	0.085
Patients with ipsilateral atherosclerotic stenosis ≥ 30%	1136	92 (8.1)	7.9	1215	132 (10.9)	10.9	0.73	(0.56, 0.96)	0.023
Patients with ipsilateral atherosclerotic stenosis in extracranial artery ≥ 30%	834	63 (7.6)	7.6	873	78 (8.9)	8.9	0.84	(0.60, 1.17)	0.306
Patients with ipsilateral atherosclerotic stenosis in intracranial artery ≥ 30%	516	53 (10.3)	9.9	558	85 (15.2)	15.2	0.66	(0.47, 0.93)	0.016
Patients with atherosclerosis in any vascular bed	3481	227 (6.5)	6.5	3432	262 (7.6)	7.6	0.85	(0.71, 1.01)	0.070
Patients with ipsilateral stenosis who undergo carotid endarterectomy	34	2 (5.9)	NC	28	4 (14.3)	NC	NC	NC	NC
Patients with carotid percutaneous stenting	12	2 (16.7)	NC	11	6 (54.5)	NC	NC	NC	NC

Subsequent disabling stroke

There were numerically fewer patients with a subsequent disabling stroke at Day 30 in the ticagrelor group compared with the placebo group, as defined by patients with a subsequent stroke and having an mRS score > 2 at Visit 3: 150 (2.7%) and 188 (3.5%), respectively (OR 0.78 [95% CI 0.62, 0.97]). A similar reduction in disabling strokes was observed when the mRS cut-off was set to either > 1 or > 3.

Table 14. Analysis of disabling stroke using mRS scores in patients with subsequent [ischaemic + haemorrhagic] 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

Consistent results were also observed when analysing subsequent ischaemic strokes. There were numerically fewer patients with a subsequent disabling ischaemic stroke at Day 30 (as defined by patients with a subsequent ischaemic stroke and having an mRS score > 2 at Visit 3) in the ticagrelor group compared with the placebo group (OR 0.75 [CI 95% 0.60, 0.93] (see Table 15).

Table 15. Analysis of disabling ischaemic stroke using mRS scores in patients with subsequent ischaemic 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 ischaemic stroke and mRS score >2 at visit 3	5472	143 (2.6)	5430	186 (3.4)	0.75	(0.60, 0.93)	0.011
Subsequent ischaemic stroke and mRS score >1 at visit 3	5472	194 (3.5)	5430	243 (4.5)	0.78	(0.64, 0.94)	0.010
Subsequent ischaemic stroke and mRS score >3 at visit 3	5472	92 (1.7)	5430	116 (2.1)	0.78	(0.59, 1.02)	0.072

Patient Reported Outcomes/Quality of Life

For patient-reported outcomes for each dimension of the EQ-5D descriptive system (version EQ-5D-5L used), see Table 16. Health status outcomes for mobility, self-care, usual activities, pain/discomfort, and anxiety/depression were numerically improved between baseline and Visit 3, and similar between treatment groups.

The VAS is a scale from 0 to 100 that measures how bad or good a patient feels, with 0 as the worst health imaginable and 100 as the best health imaginable. There was a numerical improvement in how patients rated their health between baseline and Visit 3, as measured by change in the VAS score. The mean improvement was similar between treatment groups: from 63.2 (baseline) to 77.0 (Visit 3) in the ticagrelor group and from 63.1 (baseline) to 77.1 (Visit 3) in the placebo group.

Table 16. Summary statistics for EQ-5D-5L Visual analog scale at visit 1 and visit 3 (full analysis set)

		Ticagrelor 90 mg bd (N=5523)		Placebo (N=5493)	
Time point	Summary statistic	Visual analog scale	Change from baseline	Visual analog scale	Change from baseline
Visit 1	n	5501		5467	
	Mean	63.2		63.1	
	SD	19.2		19.1	
	Median	65.0		65.0	
	Min	0		0	
	Max	100		100	
Visit 3	n	5317	5304	5278	5263
	Mean	77.0	13.8	77.1	14.0
	SD	16.5	19.7	16.5	19.8
	Median	80.0	10.0	80.0	10.0
	Min	0	-90	0	-85
	Max	100	95	100	100

Table 17. Summary statistics for mRS score at visit 3 in patients with subsequent ischaemic stroke (full analysis set)

		Number (%) of patients	
		Ticagrelor 90 mg bd (N=5523)	Placebo (N=5493)
mRS score	0	15 (0.3)	15 (0.3)
	1	54 (1.0)	72 (1.3)
	2	51 (0.9)	57 (1.0)
	3	51 (0.9)	70 (1.3)
	4	69 (1.2)	90 (1.6)
	5	13 (0.2)	16 (0.3)
	6	11 (0.2)	10 (0.2)
	Missing	12 (0.2)	15 (0.3)

N = Number of patients in treatment group. bd = Twice daily. mRS = Modified Rankin Scale.

2.6.4. Additional analysis

Additional analyses were performed based on the request of the Rapporteur during the pre-submission meeting. Details concerning the risk of bleeding during ticagrelor use are discussed in the safety section. Further, additional analyses are described based on information provided during the assessment procedure.

Absolute risk difference between ticagrelor and placebo

The applicant included a forest plot of the absolute risk difference between ticagrelor and placebo at 30 days in the clinical overview (Figure 5). Expressed as NNT and NNH, 84 patients would need to be treated for 30 days to prevent one ischaemic stroke or death, while 345 patients would need to be

treated for 30 days to cause one event of ICH or fatal bleeding. The primary efficacy endpoint included both potential benefits and risks of antiplatelet therapy, therefore, some events are double-counted in this analysis. Ticagrelor compared to placebo reduced the risk of the composite of stroke/ death (NNT 92) but resulted in an increase of GUSTO severe bleeding (NNH 263). Including GUSTO Moderate bleedings in the benefit-risk analysis resulted in a NNH of 221, which is acceptable.

Benefit-risk analysis on treatment

An 'on treatment' analysis of the benefit-risk profile (where 'on treatment' comprises the time from the date of first dose of IP until 7 days after the last dose of IP) was consistent with the main analysis (Figure 5 and Figure 6).

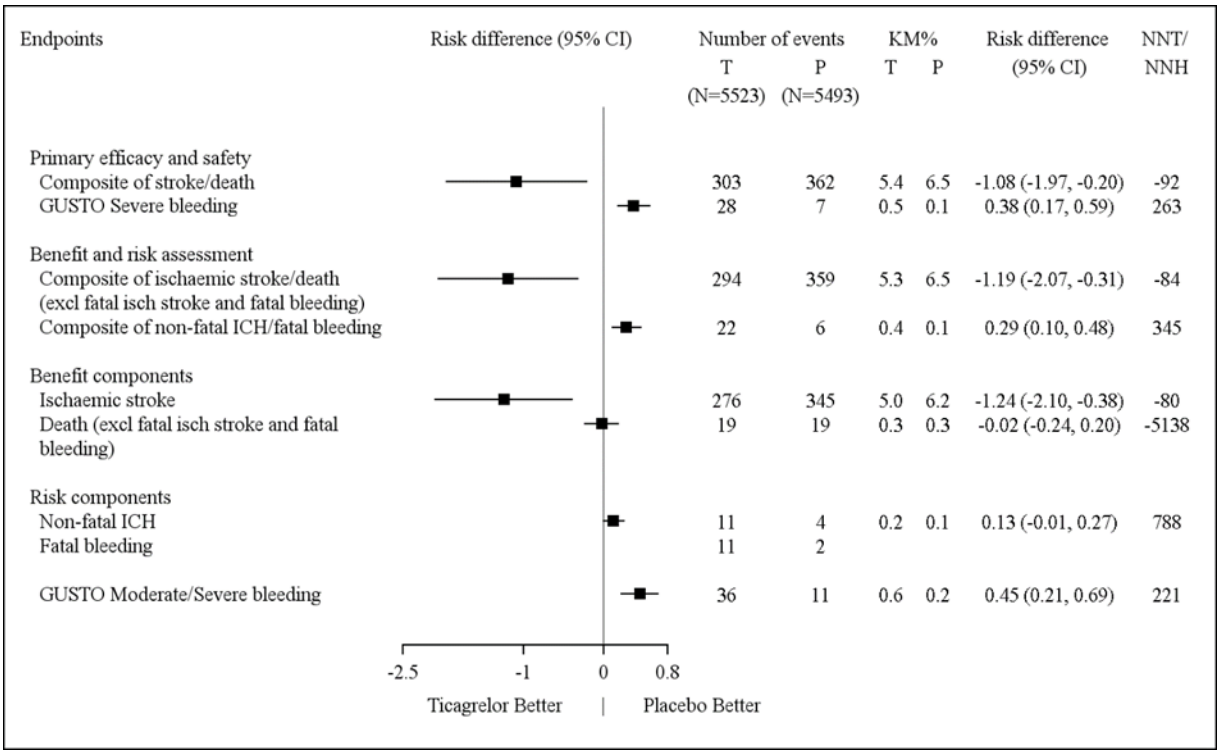


Figure 5. Forest plot of absolute risk difference between ticagrelor and placebo at 30 days (full analysis set)

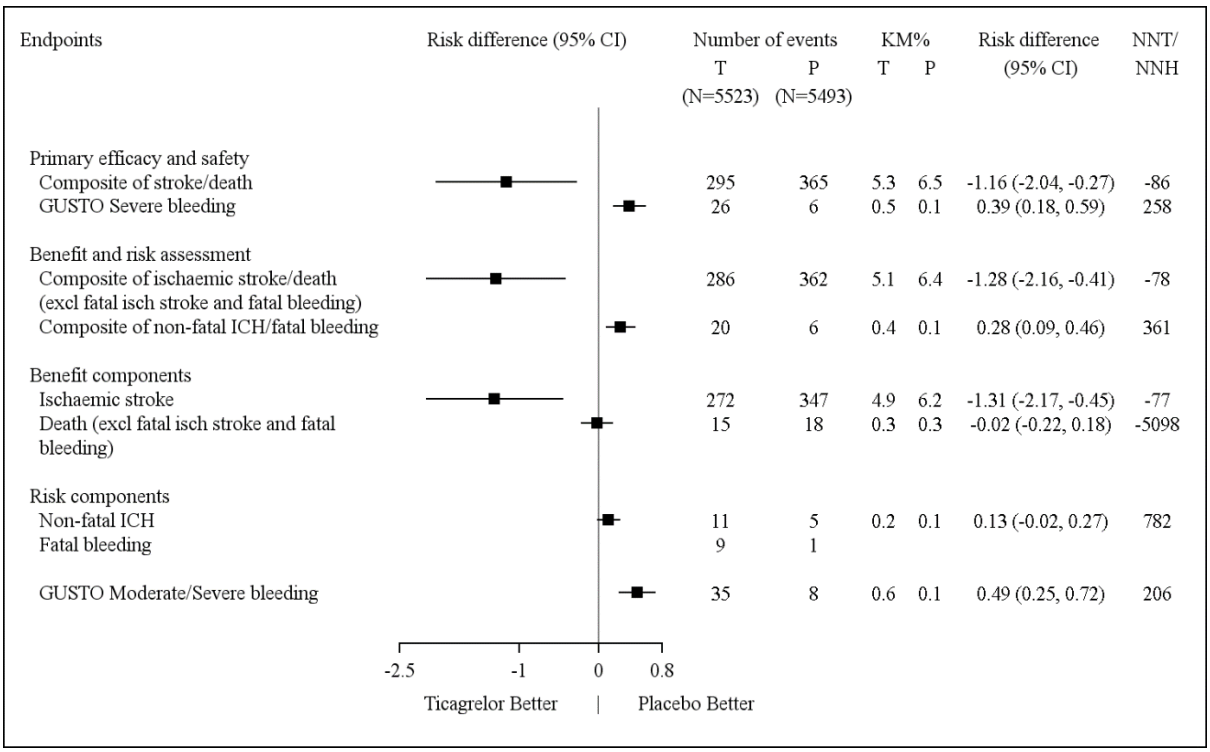


Figure 6. Forest plot of absolute risk difference between ticagrelor and placebo at 30 days, on treatment (full analysis set)

Benefit-risk profile over time

The benefit on ischaemic stroke and death was observed early and was maintained during the treatment period. The risk for ICH/fatal bleeding followed a similar pattern (Figure 7). The results were consistent when analysing the benefit-risk profile on treatment (Figure 8). When analysing the benefit-risk composite by study day, the HR for ticagrelor versus placebo was consistent throughout the treatment period, indicating an increasing benefit of ticagrelor over time (Table 18).

Forest plots of the composite of the THALES primary efficacy endpoint (stroke and death) and primary safety endpoint (GUSTO Severe bleeding) provided in the request for supplementary information by subgroup for Day 7, Day 14, Day 21, and Day 30 to 34 showed consistency by subgroup and over time.

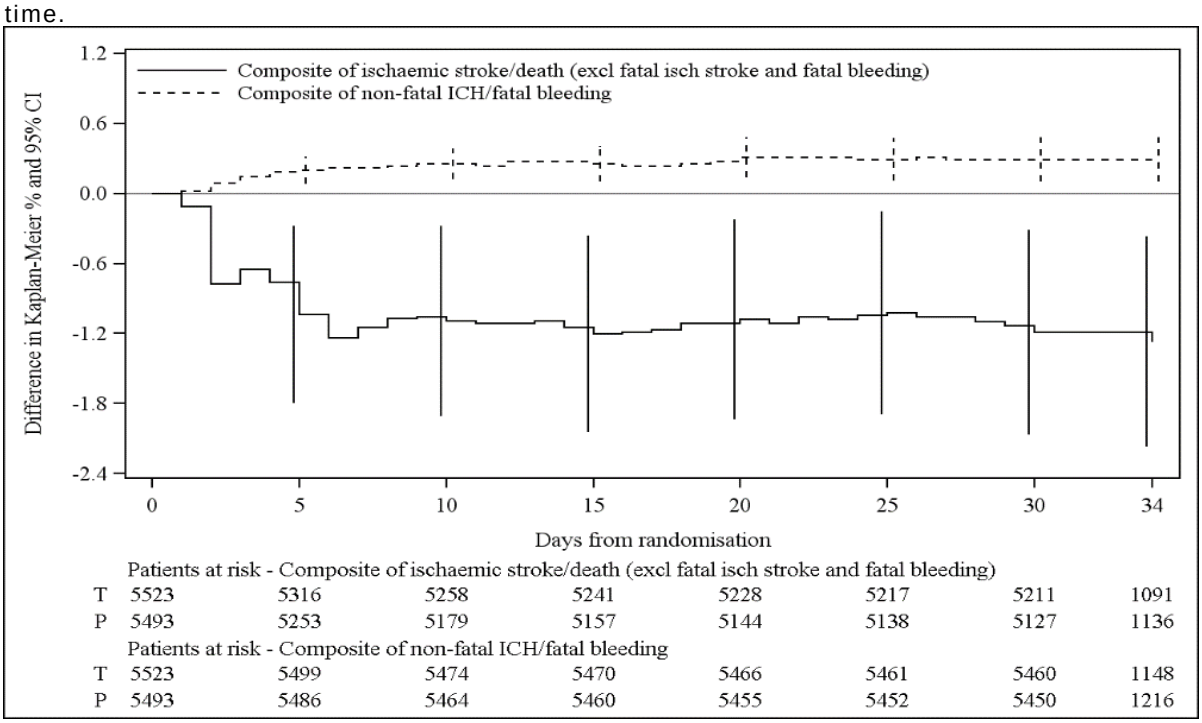


Figure 7. Temporal course of risk difference for ticagrelor 90 mg bd versus placebo (full analysis set)

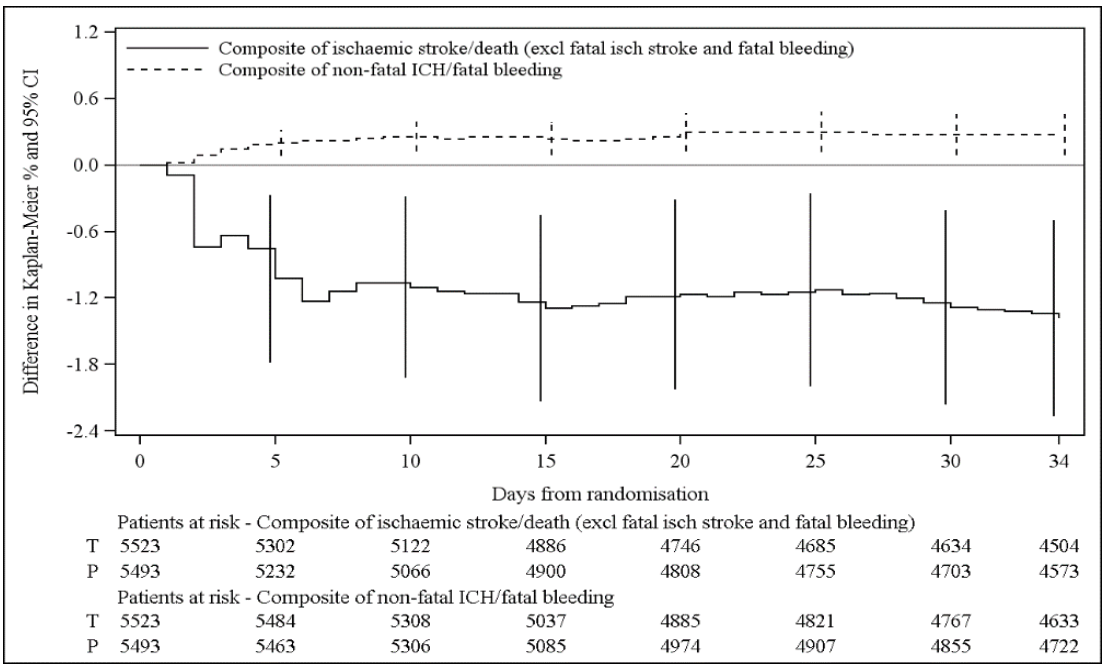


Figure 8. Temporal course of risk difference for ticagrelor 90 mg bd versus placebo, on treatment (full analysis set)

Table 18. Analysis of the composite of ischaemic stroke, death, intracranial haemorrhage and fatal bleeding by study day (full analysis set)

	Ticagrelor 90 mg bd (N=5523)		Placebo (N=5493)				
Study day	Patients with events (%)	KM%	Patients with events (%)	KM%	Hazard ratio	95% CI	p-value
1	31 (0.6)	0.6	36 (0.7)	0.7	0.86	(0.53, 1.38)	0.527
2	125 (2.3)	2.3	162 (2.9)	2.9	0.77	(0.61, 0.97)	0.025
3	182 (3.3)	3.3	210 (3.8)	3.8	0.86	(0.70, 1.05)	0.134
4	205 (3.7)	3.7	237 (4.3)	4.3	0.86	(0.71, 1.03)	0.107
5	219 (4.0)	4.0	265 (4.8)	4.8	0.82	(0.69, 0.98)	0.029
6	229 (4.1)	4.2	286 (5.2)	5.2	0.79	(0.67, 0.94)	0.009
7	238 (4.3)	4.3	290 (5.3)	5.3	0.81	(0.68, 0.96)	0.018
8	251 (4.5)	4.5	298 (5.4)	5.4	0.83	(0.71, 0.99)	0.035
9	258 (4.7)	4.7	303 (5.5)	5.5	0.84	(0.71, 1.00)	0.044
10	260 (4.7)	4.7	307 (5.6)	5.6	0.84	(0.71, 0.99)	0.037
11	264 (4.8)	4.8	312 (5.7)	5.7	0.84	(0.71, 0.99)	0.035
12	268 (4.9)	4.9	315 (5.7)	5.7	0.84	(0.72, 0.99)	0.039
13	273 (4.9)	4.9	319 (5.8)	5.8	0.85	(0.72, 1.00)	0.045
14	275 (5.0)	5.0	324 (5.9)	5.9	0.84	(0.72, 0.99)	0.034
15	277 (5.0)	5.0	330 (6.0)	6.0	0.83	(0.71, 0.98)	0.023
16	279 (5.1)	5.1	332 (6.0)	6.0	0.83	(0.71, 0.98)	0.024
17	282 (5.1)	5.1	334 (6.1)	6.1	0.84	(0.71, 0.98)	0.027
18	287 (5.2)	5.2	335 (6.1)	6.1	0.85	(0.72, 0.99)	0.041
19	290 (5.3)	5.3	337 (6.1)	6.1	0.85	(0.73, 1.00)	0.045
20	295 (5.3)	5.3	338 (6.2)	6.2	0.86	(0.74, 1.01)	0.066
21	295 (5.3)	5.3	340 (6.2)	6.2	0.86	(0.73, 1.00)	0.056
22	298 (5.4)	5.4	340 (6.2)	6.2	0.87	(0.74, 1.01)	0.073
23	299 (5.4)	5.4	342 (6.2)	6.2	0.87	(0.74, 1.01)	0.068
24	302 (5.5)	5.5	345 (6.3)	6.3	0.87	(0.74, 1.01)	0.069
25	305 (5.5)	5.5	347 (6.3)	6.3	0.87	(0.75, 1.01)	0.076
26	305 (5.5)	5.5	349 (6.4)	6.4	0.86	(0.74, 1.01)	0.064
27	308 (5.6)	5.6	353 (6.4)	6.4	0.86	(0.74, 1.01)	0.060
28	308 (5.6)	5.6	355 (6.5)	6.5	0.86	(0.74, 1.00)	0.050
29	308 (5.6)	5.6	357 (6.5)	6.5	0.85	(0.73, 0.99)	0.042
30	308 (5.6)	5.6	360 (6.6)	6.6	0.85	(0.73, 0.99)	0.032
31	310 (5.6)	5.6	362 (6.6)	6.6	0.85	(0.73, 0.99)	0.033
32	311 (5.6)	5.7	363 (6.6)	6.6	0.85	(0.73, 0.99)	0.033
33	311 (5.6)	5.7	363 (6.6)	6.6	0.85	(0.73, 0.99)	0.033
34	311 (5.6)	5.7	364 (6.6)	6.7	0.85	(0.73, 0.98)	0.030

Benefit-risk components in relation to disability

During the 30-day treatment period, treatment with ticagrelor and ASA resulted in a reduction of 69 ischaemic strokes and in an increase of 16 ICHs or fatal bleedings compared with ASA alone (see Figure 9). If only considering disabling strokes, there was a reduction of 48 ischaemic strokes associated with disability (mRS > 1) and 42 ischaemic strokes associated with dependency and disability (mRS > 2) (Figure 9).

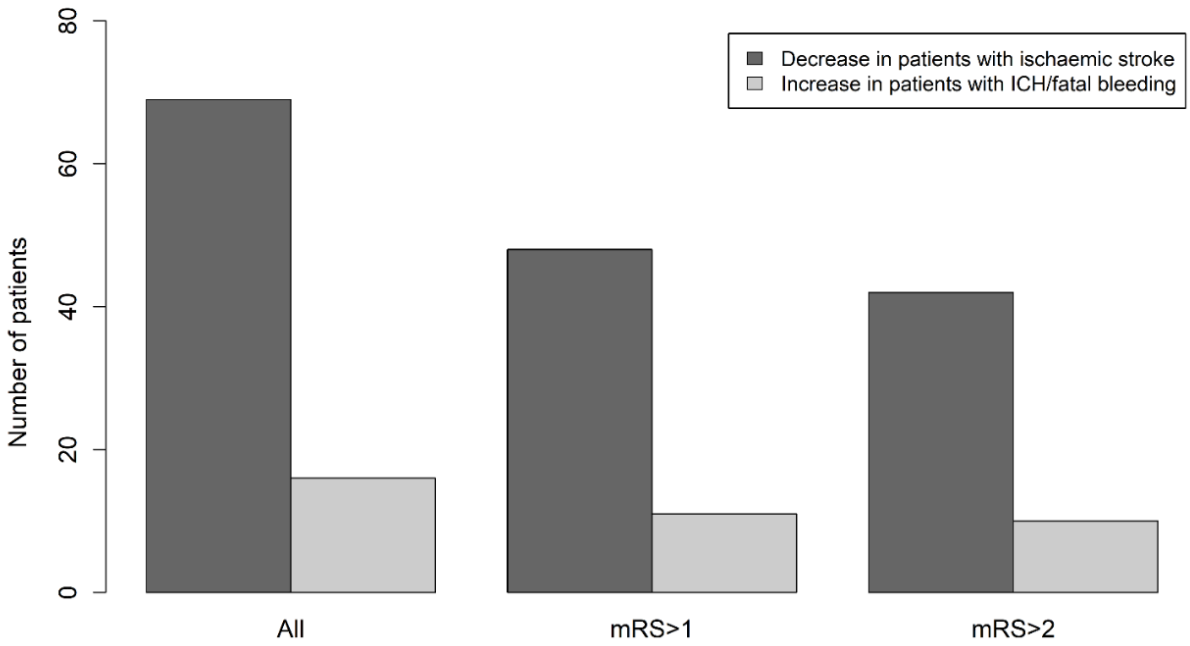


Figure 9. Reduction of patients with ischaemic stroke events and increase of patients with ICH/fatal bleeding events by mRS disability category at Day 30 (full analysis set)

MCDA (Multi Criteria Decision Analysis) benefit risk assessment

An MCDA involves developing weights based on the relative importance (ie, the trade-off) of different endpoints (eg, the importance of a stroke compared with a death) (Lackey et al 2021). The weights are then combined with the scaled performance (Table 19).

The MCDA of THALES showed a benefit of ticagrelor over placebo for the prevention of ischaemic stroke in patients with acute ischaemic stroke or TIA (step 7 and 8 in Table 19). Sensitivity analyses showed that the weight of death relative to non-fatal ischaemic stroke can be increased to 7:1 with a preserved total benefit. Uncertainty analyses showed a beneficial effect in 81% to 83% of cases.

Table 19 MCDA of ticagrelor for preventing stroke and death in patients with acute ischaemic stroke or transient ischaemic attack (THALES)

Step	Description	Application to ticagrelor				
1. Defining the decision problem	Identify objectives, type of decision, alternatives, stakeholders, and output required	To support a regulatory approval decision on an application for a variation of the marketing authorisation for ticagrelor for the prevention of ischaemic stroke in patients with acute ischaemic stroke or TIA. Alternatives: ticagrelor and ASA versus placebo and ASA				
2. Selecting and structuring criteria	Identify criteria relevant for evaluating alternatives	Benefits: Prevention of non-fatal ischaemic stroke Risks: Death, non-fatal GUSTO Severe bleeding, and GUSTO Moderate bleeding				
3. Measuring performance	Gather data about the alternatives' performance on the criteria	Incidence rates (95% CI) per 10000 patients treated for 30 days				
			Non-fatal ischaemic stroke	Death	Non-fatal GUSTO Severe bleeding	GUSTO Moderate bleeding
		Ticagrelor	483 (430-543)	62 (44-86)	31 (19-50)	13 (6-27)
		Placebo	611 (551-678)	47 (32-70)	9 (4-22)	5 (2-17)
4. Scoring alternatives	Elicit stakeholders' preferences for changes within criteria	Within an outcome, individual events were assumed to be of equal importance (eg, all non-fatal ischaemic strokes are equally important).				
5. Weighting criteria	Elicit stakeholders' preferences between criteria	Preferences/weighting criteria were based on literature review. Trade-offs versus non-fatal ischaemic strokes were based on WHO disability criteria and utility decrements. Further details on the approaches to the relative weightings used for the risk components are provided in Sections Error! Reference source not found. and Error! Reference source not found..				
		Trade-offs against non-fatal ischaemic stroke				
		Non-fatal ischaemic stroke		Death	Non-fatal GUSTO Severe bleeding	GUSTO Moderate bleeding
		1:1		2.9:1	1:1	0.4:1
6. Calculating aggregate scores	Use the alternatives' scores in the criteria and the weights for the criteria to get "total value" by which the alternatives are ranked	The MCDA combined the difference in performance with the relative weight of each outcome (see Error! Reference source not found.). Based on the weights used, the total value was positive, demonstrating that ticagrelor provided more benefit than placebo.				
		Difference in value (ticagrelor - placebo). Positive values indicate that ticagrelor is preferred. Difference in value has a possible range from –1 to +1.				
		Total	Non-fatal ischaemic stroke	Death	Non-fatal GUSTO Severe bleeding	GUSTO Moderate bleeding
		0.13	0.26	-0.08	-0.04	-0.01

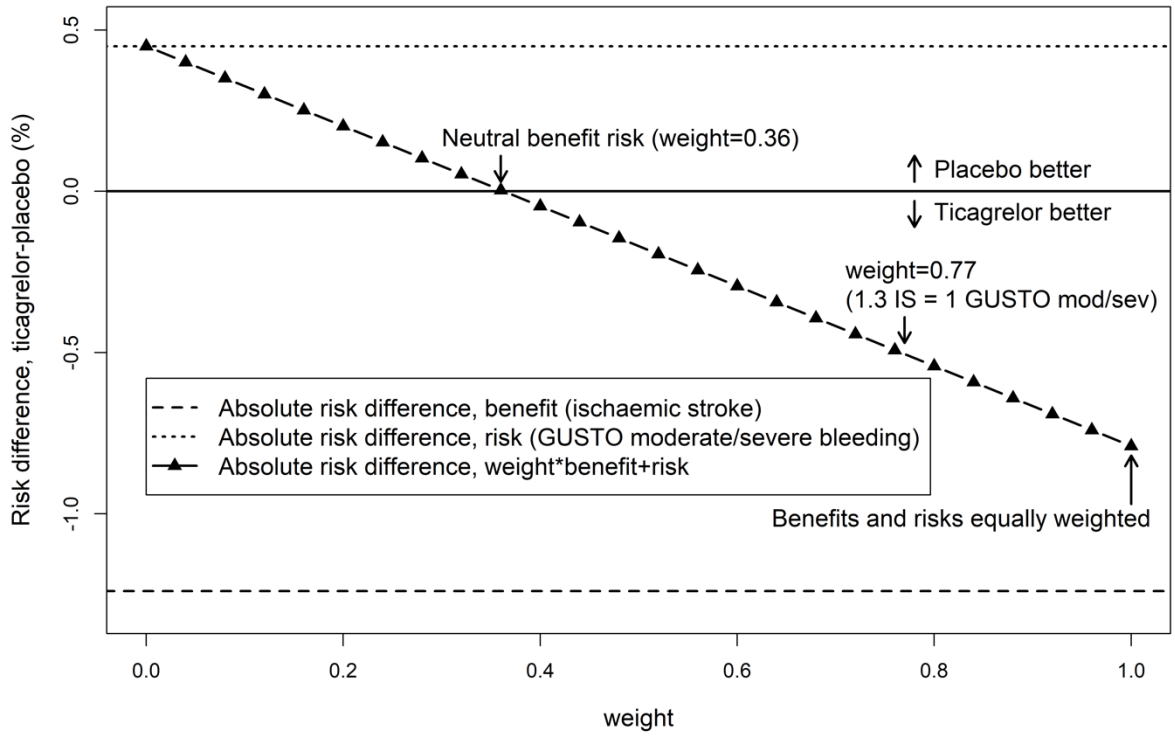
Step	Description	Application to ticagrelor
7. Dealing with uncertainty	Perform uncertainty analysis to understand the level of robustness of the MCDA results	The results show a positive benefit-risk for ticagrelor. Death is the most important risk while the contribution of GUSTO Moderate bleeding to the overall risk is negligible. The total value would remain in favour of ticagrelor even with a 7:1 trade-off for a death versus a non-fatal ischaemic stroke (compared with the 2.9:1 trade-off employed in this analysis), suggesting a robust benefit-risk profile in this patient population. The analysis is based on a weighted sum of 4 treatment effects, all adding variability to the total estimate. To examine the impact of this uncertainty on the result, simulations were performed by randomly assigning events to each endpoint and treatment group based on the 95% CIs of the events rate using the uniform distribution and based on the observed event rates and standard errors using the normal distribution. Ticagrelor was favoured in 81% (uniform distribution) or 83% (normal distribution) of the simulations, whereas placebo was favoured in 19% (uniform distribution) or 17% (normal distribution) of the simulations. The results were consistent with those of the analysis described above in a sensitivity analysis including ischaemic stroke (fatal or non-fatal) as the benefit and fatal bleeding, non-fatal ICH, other non-fatal GUSTO Severe bleeding, and GUSTO Moderate bleeding as the risks.
8. Reporting and examination of findings	Interpret the MCDA outputs, including uncertainty analysis, to support decision-making	Results from the MDCA show a robust benefit of ticagrelor over placebo for the prevention of ischaemic stroke in patients with acute ischaemic stroke or TIA. Sensitivity analyses showed that the trade-off of death relative to non-fatal ischaemic stroke can be increased to 7:1 with a preserved total benefit. Uncertainty analyses showed a beneficial effect in 81% to 83% of cases.

To complement the MCDA, Figure 10 shows a graphical presentation of weighted benefit-risk analyses comparing ischaemic stroke (the main benefit) versus risk components that range from the most severe and restrictive (fatal bleeding) to the most inclusive (GUSTO Moderate/Severe) categories.

The weights for ischaemic stroke versus fatal bleeding, ICH/fatal bleeding, GUSTO Severe bleeding, and GUSTO Moderate/Severe bleeding are 1:2.7, 1:1.8, 1:1.6, and 1:1.3, respectively. If the weight of the ischaemic stroke is adjusted rather than the weight of the bleeding, the corresponding numbers are: 1/2.7 = 0.37, 1/1.8 = 0.56, 1/1.6 = 0.63, and 1/1.3 = 0.77.

The benefit-risk profile would be neutral if an ischaemic stroke is weighted 0.36:1 to GUSTO Moderate/Severe bleeding, ie, when a GUSTO Moderate/Severe bleeding is considered to be approximately 3 times as clinically important as an ischaemic stroke.

Figure 10 Net clinical benefit of ticagrelor by weighting of benefit events against risk events: Ischaemic stroke versus GUSTO moderate/severe bleeding



IS, ischaemic stroke; mod/sev, Moderate/Severe
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Benefit-Risk in subgroups

Multicriteria Decision Analysis of Age and Index Event Subgroups

For index event subgroups, the total difference in value between ticagrelor and placebo was larger in patients with acute ischaemic stroke (0.20; positive values indicate a benefit of ticagrelor over placebo) than in the TIA population (-0.52) and largest in patients with acute ischaemic stroke with NIHSS score > 3 (0.39) *(*Table 20*)*. In patients with TIA as the index event, the total difference in value between ticagrelor and placebo was negative; this difference was driven by a numerical difference in deaths in the small sub-subgroup of TIA patients aged > 75 years (4 of 135 in the ticagrelor group versus 0 of 172 in the placebo group).

For age subgroups, the total difference in value was larger in patients aged ≤ 75 years (0.18) compared with patients aged > 75 years (-0.10); however, when analysing sub-subgroups of patients by both index event and age, patients aged > 75 years with ischaemic stroke had a total difference in value of 0.25, while patients aged > 75 years with TIA had a total difference in value of -2.11.

Table 20 Multicriteria decision analysis by age and index event subgroups: difference between ticagrelor and placebo

Subgroup	Total	Non-fatal ischaemic stroke	Death	Non-fatal GUSTO Severe bleeding	GUSTO Moderate bleeding
Total (N = 11016)	0.13	0.26	-0.08	-0.04	-0.01
Subgroups					
TIA (n = 1031)	-0.52	0.26	-0.74	-0.04	0.00
Stroke NIHSS ≤ 3 (n = 6671)	0.11	0.26	-0.08	-0.07	0.00
Stroke NIHSS > 3 (n = 3314)	0.39	0.29	0.12	0.00	-0.02
Stroke 0-5 (n = 9985)	0.20	0.27	-0.02	-0.04	-0.01
Age ≤ 75 (n = 8866)	0.18	0.28	-0.07	-0.03	0.00
Age > 75 (n = 2150)	-0.10	0.18	-0.14	-0.11	-0.03
Sub-subgroups					
Age ≤ 75 in stroke NIHSS 0-5 (n = 8142)	0.20	0.27	-0.04	-0.03	0.00
Age > 75 in stroke NIHSS 0-5 (n = 1843)	0.25	0.27	0.11	-0.10	-0.03
Age ≤ 75 in TIA (n = 724)	0.09	0.43	-0.34	0.00	0.00
Age > 75 in TIA (n = 307)	-2.11	-0.17	-1.79	-0.15	0.00

Positive values indicate that ticagrelor is preferred.
N, number of patients; n, number of patients included in analysis; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischaemic attack

2.6.5. Discussion on clinical efficacy

The proposed study design and treatment duration of 30 days to assess the efficacy of ticagrelor in reducing the rate of the composite of stroke and death in patients who have had an acute ischaemic stroke or TIA and are on background ASA therapy is acceptable. During the study, notable changes in the sample size and testing procedure were made, but these were advised by committees independent of the applicant; hence the risk that these changes were based on results in the trial seen by the applicant, is small, also in view of the likely effective double-blind design.

The risk of a subsequent stroke occurs mainly in the first 30 days after the initial event of an acute ischaemic stroke or TIA. Inclusion of clopidogrel as a comparator in a third arm would have been of value to compare the results of the THALES study with current guideline recommendations of some European countries and the USA for the treatment of acute ischaemic stroke and TIA. Only patients with a non-cardioembolic acute ischaemic stroke with NIHSS score ≤ 5 OR TIA with ABCD^2 score ≥ 6 or with large-vessel disease (i.e., ipsilateral ≥ 50% stenosis of an extra or intracranial artery) were

included and randomised within 24 hours of symptom onset. Patients with a minor TIA (i.e. limited to isolated numbness, isolated visual changes, or isolated dizziness/vertigo) or acute ischaemic stroke with NIHSS score ≥ 6 were not included in the study. For this group of patients, the benefit versus the risk of ticagrelor might possibly be different. The applicant restricted the indication to the major inclusion and exclusion criteria of the Thales study and proposed to include ipsilateral atherosclerotic stenosis in the indication. Inclusion of ipsilateral atherosclerotic stenosis in the indication next to the ABCD may reflect the studied population more accurately. However, this criterion is unfamiliar in the regulatory field. The applicant provided the analyses of beneficial and unfavourable effects in the group with NIHSS<= 5 and ABCD^2<6 and ipsilateral stenosis >= 50% based on a MCDA exercise. However, any further fine-tuning on the indication has not been further discussed considering the overall negative benefit-risk assessment.

The THALES study assessing the efficacy of ticagrelor in reducing the rate of the composite of stroke or death in patients who have had an acute ischaemic stroke or TIA and are on background ASA therapy showed superior efficacy of ticagrelor and ASA compared with placebo and ASA in acute ischaemic stroke/TIA patients in the prevention of the composite of stroke and death at 30 days (HR 0.83 [95% CI 0.71, 0.96], p = 0.015) (primary objective). However, the primary efficacy result was driven by the ischemic stroke component, while a negative imbalance was found for the death component. The results of performed subgroup analyses were generally in alignment with the results of the primary endpoint.

The reduction of the composite endpoint ischaemic stroke and death was observed early and was maintained during the treatment period. Additional analyses of the composite of the THALES primary efficacy endpoint (stroke and death) and primary safety endpoint (GUSTO Severe bleeding) provided in the request for supplementary information showed consistency over time.

As could be expected based on the results of the primary endpoint and due to significant overlap, the first secondary objective confirmed the primary objective. Ticagrelor was superior to placebo in reducing the rate of ischaemic stroke up to Day 30 in patients who have had an acute ischaemic stroke or TIA and were on background ASA therapy (HR 0.79 [95% CI 0.68, 0.93], p = 0.004).

However, no benefit of ticagrelor with respect to the number of patients with overall disability was observed (23.8% vs. 24.1%), which was defined by a modified Rankin scale score of greater than 1 (signifying more than minimal disability) (second secondary objective). Although, numerically fewer patients with a subsequent disabling stroke with mRS score > 2 at Visit 3 were observed: 150 (2.7%) and 188 (3.5%), respectively (OR 0.78 [95% CI 0.62, 0.97], p = 0.024) (exploratory endpoint). Further, patient-reported outcomes were comparable between patients treated with ticagrelor or placebo (exploratory endpoint). Absence of any benefit on these endpoints may question the clinical relevance of the observed (primary) treatment effect.

For the subgroup of patients with ipsilateral atherosclerotic stenosis ≥ 30% or ≥ 50%, results were in line with the overall results for the primary endpoint, although caution should be exercised in drawing conclusions as this was only 21% and 13%, respectively, of the total study population.

2.6.6. Conclusions on the clinical efficacy

The THALES study demonstrated a beneficial effect of ticagrelor on top of ASA at day 30 in reducing the rate of the composite of stroke or death in patients who have had an acute ischaemic stroke or TIA

(HR 0.83 [95% CI 0.71, 0.96], p = 0.015). This was primarily attributed to reduction in ischaemic stroke (HR 0.79 [95% CI 0.68, 0.93], p = 0.004, secondary endpoint), while a negative imbalance was found for the death component . Subgroup analyses were generally consistent with this observation. However, no beneficial effects on overall disability or patient-reported outcomes were found.

2.7. Clinical safety

2.7.1. Introduction

Ticagrelor is an approved product, and its safety profile has been documented in large clinical studies. Based on its mechanism of action bleeding is the main known adverse drug reaction of ticagrelor as described in the core prescribing information. The safety evaluation presented is based on data from the THALES study alone and does not include pooled analyses of data from other ticagrelor studies.

2.7.2. Patient exposure

A total of 10976 patients (99.6% of randomised patients) received at least one dose of randomised IP: 5506 patients in the group randomised to ticagrelor and 5470 patients in the group randomised to placebo. Four patients received different IP from what they were randomised to; 3 patients in the placebo group received ticagrelor, and 1 patient in the ticagrelor group received placebo. Nearly all patients (99.5%) took ASA as background therapy during the treatment period, and differences between treatment groups are, therefore not attributed to ASA use.

Safety analyses were conducted for AEs occurring up to Visit 3 (the end of the treatment period, occurring on Day 30 to 34) and up to Visit 4 (the end of the follow-up period, occurring on Day 60 to 64). The analyses up to Visit 3 are considered the main safety analyses.

2.7.3. Adverse events

Adverse events that were not SAEs or DAEs were not required to be collected in this study. Any such event reported voluntarily or as per specific local requirements is therefore not included in the safety analyses but listed in appendix 16 of the clinical study report.

Table 21 summarises the number of patients with adverse events in any category up to visit 3 .

Table 21. Number of patients with adverse events in any category up to visit 3 (full analysis set)

	Number (%) of patients [a]	
AE category	Ticagrelor 90 mg bd (N=5523)	Placebo (N=5493)
Any AE with outcome of death	40 (0.7)	32 (0.6)
Any SAE (including events with outcome of death)	571 (10.3)	609 (11.1)
Any AE leading to premature permanent discontinuation of IP	535 (9.7)	415 (7.6)
Any bleeding SAE or bleeding AE leading to premature permanent discontinuation of IP	183 (3.3)	41 (0.7)

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.

2.7.4. Bleeding events

The occurrence of GUSTO Severe, GUSTO Moderate/Severe, ICH, fatal bleeding, and premature permanent discontinuation of IP due to bleeding at Visit 3/Day 30 are summarised in Table 22.

Table 22. Analysis of bleeding variables 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
GUSTO Severe [a]	28 (0.5)	0.5	7 (0.1)	0.1	3.99	(1.74, 9.14)	0.001
Intracranial haemorrhage or fatal bleeding	22 (0.4)	0.4	6 (0.1)	0.1	3.66	(1.48, 9.02)	0.005
Fatal bleeding	11 (0.2)		2 (0.0)				
Intracranial haemorrhage	20 (0.4)	0.4	6 (0.1)	0.1	3.33	(1.34, 8.28)	0.010
GUSTO Moderate/Severe [a]	36 (0.7)	0.6	11 (0.2)	0.2	3.27	(1.67, 6.43)	<.001
Premature permanent discontinuation of IP due to bleeding	152 (2.8)	2.9	32 (0.6)	0.6	4.80	(3.28, 7.02)	<.001

[a] Fulfilling SAE criteria.

GUSTO Severe

At Day 30, GUSTO Severe bleeding events were reported for 28 patients in the ticagrelor group and 7 patients in the placebo group (KM percentage 0.5% and 0.1% in the ticagrelor and placebo group,

respectively; HR 3.99 [95% CI 1.74, 9.14]) (see Figure 11). The most common GUSTO Severe bleeding events up to Visit 3 were in the SOC Nervous system disorders for both groups.

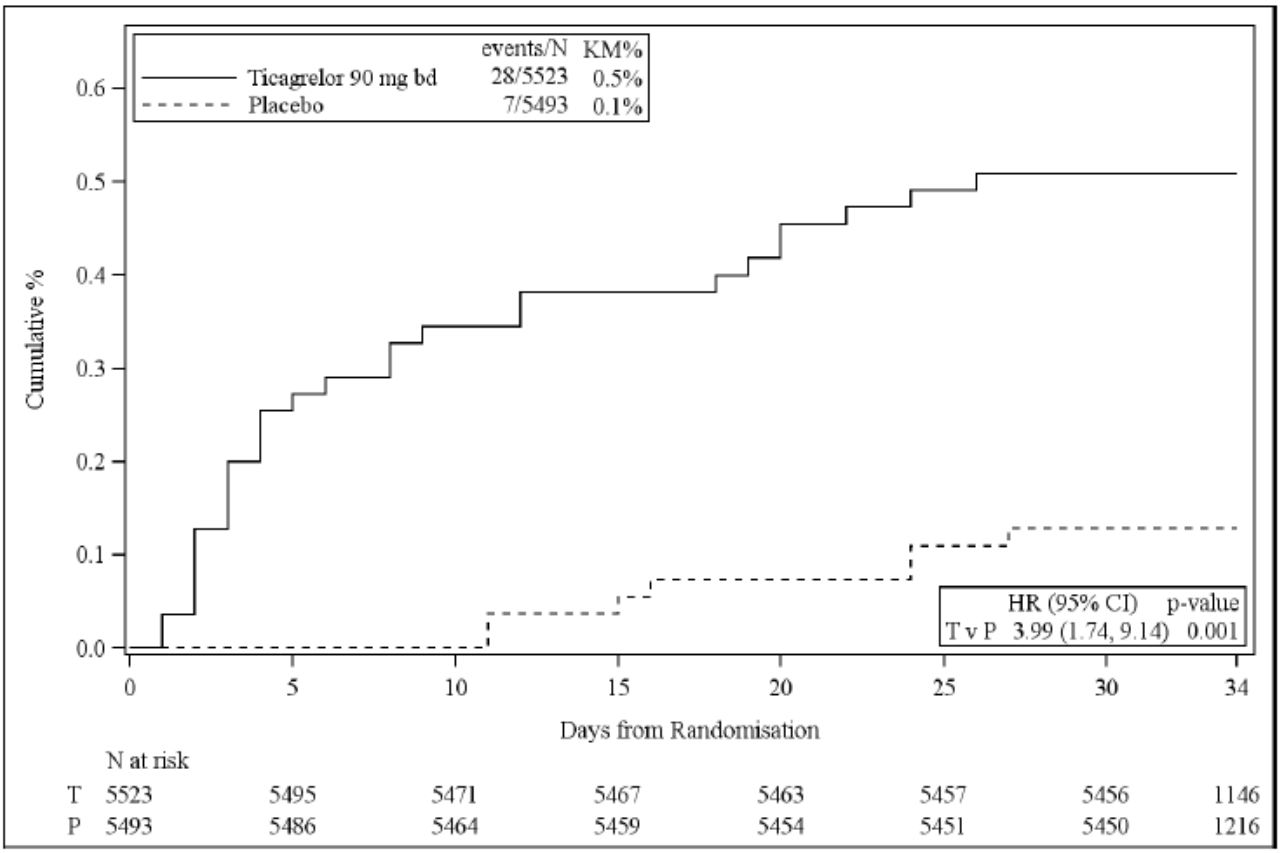


Figure 11. Kaplan-Meier plot of GUSTO severe bleeding events (full analysis set)

Pre-specified subgroup analyses were performed to evaluate whether there were any heterogeneities in the GUSTO Severe bleeding profile between subgroups. There were similar rates in all subgroups and no specific subgroup with an increased bleeding risk was identified. Considering the small number of patients with GUSTO Severe bleeding events, results for subgroups should be interpreted with caution.

Table 23. Analysis of GUSTO Severe bleeding events by subgroup (full analysis set)

		Ticagrelor 90 mg bd (N=5523)			Placebo (N=5493)						
Characteristic	Group	n	Patients with events (%)	KM%	n	Patients with events (%)	KM%	Hazard ratio	95% CI	p-value	p-value interaction
Age (years)	<65	2676	10 (0.4)		2632	3 (0.1)					
	65-75	1749	8 (0.5)		1809	2 (0.1)					
	>75	1098	10 (0.9)		1052	2 (0.2)					
Sex	Male	3415	18 (0.5)	0.5	3322	6 (0.2)	0.2	2.93	(1.16, 7.37)	0.023	
	Female	2108	10 (0.5)		2171	1 (0.0)					
Race	White	2973	11 (0.4)		2948	2 (0.1)					
	Black or African American	21	0 (0.0)		32	0 (0.0)					
	Asian	2353	15 (0.6)	0.6	2339	5 (0.2)	0.2	3.00	(1.09, 8.24)	0.034	
	Other	176	2 (1.1)		174	0 (0.0)					
Weight (kg)	<70	2324	15 (0.6)	0.6	2388	3 (0.1)	0.1	5.17	(1.50, 17.85)	0.009	0.562
	≥70	3174	13 (0.4)	0.4	3073	4 (0.1)	0.1	3.15	(1.03, 9.66)	0.045	
BMI (kg/m²)	<30	4446	27 (0.6)	0.6	4429	6 (0.1)	0.1	4.50	(1.86, 10.89)	<.001	
	≥30	1047	1 (0.1)		1026	1 (0.1)					
Geographic region	Asia and Australia	2373	15 (0.6)	0.6	2356	5 (0.2)	0.2	2.99	(1.09, 8.23)	0.034	
	Europe	2814	9 (0.3)		2803	2 (0.1)					
	North America	12	1 (8.3)		11	0 (0.0)					
	Central and South America	324	3 (0.9)		323	0 (0.0)					
Diagnosis of index event	Stroke NIHSS score ≤3	3359	16 (0.5)	0.5	3312	3 (0.1)	0.1	5.28	(1.54, 18.10)	0.008	
	Stroke NIHSS score >3	1673	8 (0.5)		1641	4 (0.2)					
	TIA	491	4 (0.8)		540	0 (0.0)					
Time from index event to randomisation (hours)	<12	1812	9 (0.5)		1776	1 (0.1)					
	≥12	3711	19 (0.5)	0.5	3717	6 (0.2)	0.2	3.18	(1.27, 7.96)	0.014	
Time from index event to loading dose (hours)	<12	1655	8 (0.5)		1659	0 (0.0)					
	≥12	3823	20 (0.5)	0.5	3787	7 (0.2)	0.2	2.83	(1.20, 6.70)	0.018	
Diabetes mellitus	Yes	1589	8 (0.5)		1557	4 (0.3)					
	No	3934	20 (0.5)	0.5	3936	3 (0.1)	0.1	6.69	(1.99, 22.52)	0.002	
Hypertension	Yes	4298	21 (0.5)	0.5	4222	4 (0.1)	0.1	5.17	(1.77, 15.05)	0.003	
	No	1225	7 (0.6)		1271	3 (0.2)					

Prior ischaemic stroke or TIA	Yes	1122	6 (0.5)		1101	3 (0.3)				
	No	4401	22 (0.5)	0.5	4392	4 (0.1)	0.1	5.51	(1.90, 15.99)	0.002
Prior ischaemic heart disease[a]	Yes	532	2 (0.4)		533	1 (0.2)				
	No	4991	26 (0.5)	0.5	4960	6 (0.1)	0.1	4.32	(1.78, 10.50)	0.001
Prior ASA[b]	Yes	754	5 (0.7)		679	1 (0.1)				
	No	4769	23 (0.5)	0.5	4814	6 (0.1)	0.1	3.88	(1.58, 9.53)	0.003
Prior statin treatment[b]	Yes	865	2 (0.2)		879	1 (0.1)				
	No	4658	26 (0.6)	0.6	4614	6 (0.1)	0.1	4.30	(1.77, 10.46)	0.001
Smoking status	Current	1504	6 (0.4)		1428	1 (0.1)				
	Former	980	6 (0.6)		925	2 (0.2)				
	Never	3038	16 (0.5)	0.5	3140	4 (0.1)	0.1	4.15	(1.39, 12.41)	0.011

a Coronary artery bypass grafting, myocardial infarction, percutaneous coronary intervention, or coronary artery disease. b At least one dose taken within 2-7 days prior to randomisation.

GUSTO Severe bleeding events categorised as Intracranial Haemorrhage or fatal bleeding

GUSTO Severe bleeding events categorised as ICH or fatal bleeding were reported in 22 patients in the ticagrelor group and 6 patients in the placebo group during the treatment period (KM percentage 0.4% and 0.1% in the ticagrelor and placebo group, respectively; HR 3.66 [95% CI 1.48, 9.02]) (see Figure 12).

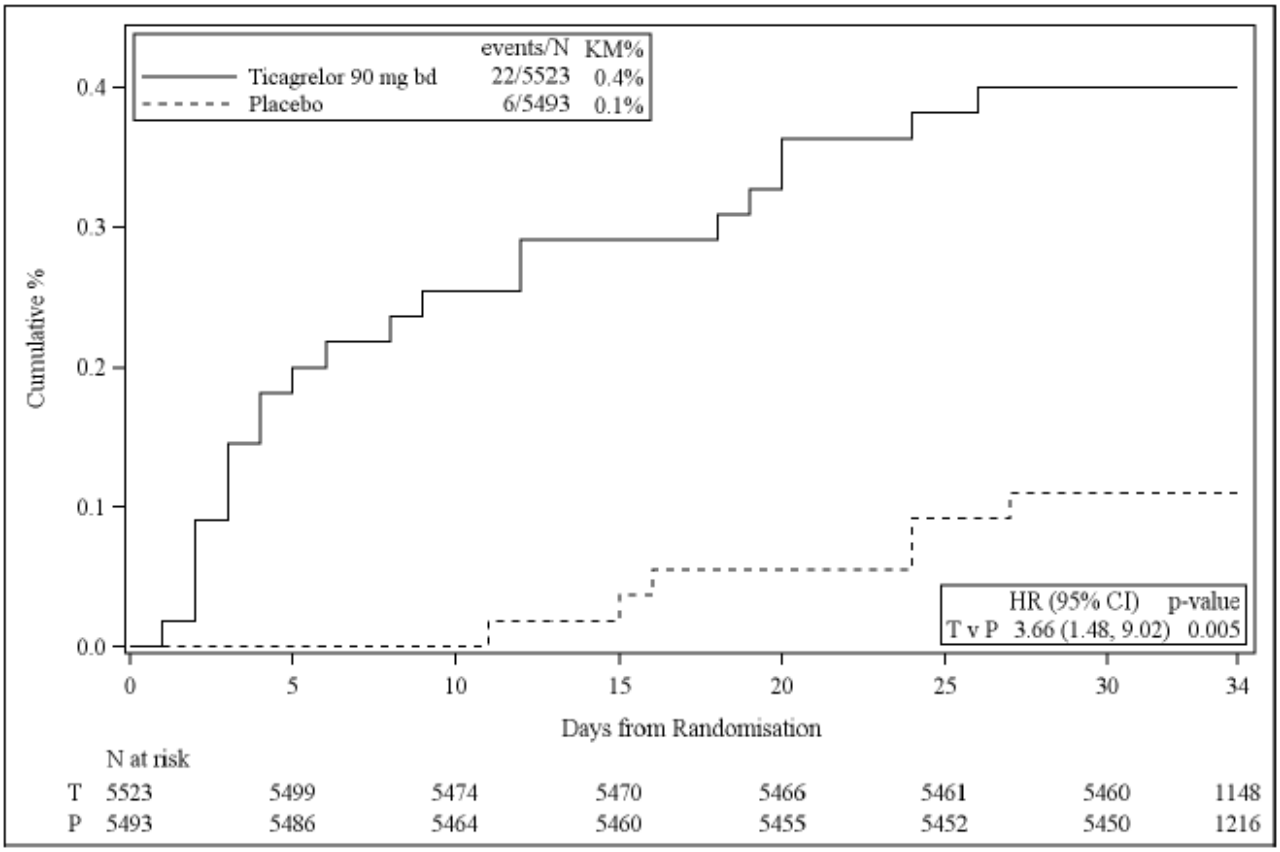


Figure 12. Kaplan-Meier plot of intracranial haemorrhage and fatal bleeding events (full analysis set)

Intracranial haemorrhage

During the treatment period (ie, up to Visit 3), ICH was reported in 20 patients in the ticagrelor group and 6 patients in the placebo group, corresponding to KM percentages of 0.4% and 0.1%, respectively. Two events in the placebo group and 1 in the ticagrelor group were provoked by trauma and 1 in each treatment group was provoked by surgical procedure. One additional haemorrhagic stroke with fatal outcome (patient E4905003) in the ticagrelor group was reported as GUSTO Severe fatal bleeding but was not captured in the ICH category.

Table 24. Number of patients with GUSTO severe bleeding categorised as intracranial haemorrhage by preferred term (full analysis set)

	Number (%) of patients [a]	
Preferred term	**Ticagrelor 90 mg bd (N=5523)**	**Placebo (N=5493)**
Patients with any intracranial haemorrhage	20 (0.4)	6 (0.1)
Haemorrhagic stroke	6 (0.1)	0 (0.0)
Cerebral haemorrhage	4 (0.1)	3 (0.1)
Haemorrhagic transformation stroke	4 (0.1)	2 (0.0)
Haemorrhage intracranial	2 (0.0)	0 (0.0)
Subarachnoid haemorrhage	2 (0.0)	0 (0.0)
Basal ganglia haemorrhage	1 (0.0)	0 (0.0)
Subdural haematoma	1 (0.0)	0 (0.0)
Traumatic intracranial haemorrhage	0 (0.0)	1 (0.0)

[a] Number (%) of patients with a GUSTO intracranial bleeding, sorted in decreasing frequency for preferred term (sorted by ticagrelor group)
Include adverse events occurring during the treatment period.

Fatal bleeding events

During the treatment period (i.e., up to Visit 3), fatal bleeding events were reported in 11 patients in the ticagrelor group and 2 patients in the placebo group (Table 25). One event in the placebo group was provoked by trauma, and 1 in the ticagrelor group was provoked by a surgical procedure.

Table 25. Number of patients with GUSTO severe bleeding categorised as fatal by preferred term (full analysis set)

	Number (%) of patients [a]	
Preferred term	**Ticagrelor 90 mg bd (N=5523)**	**Placebo (N=5493)**
Patients with any fatal bleeding	11 (0.2)	2 (0.0)
Haemorrhagic stroke	6 (0.1)	0 (0.0)
Cerebral haemorrhage	4 (0.1)	2 (0.0)
Gastrointestinal haemorrhage	1 (0.0)	0 (0.0)

[b] Number (%) of patients with a fatal bleeding, sorted in decreasing frequency for preferred term (sorted by ticagrelor group).
Include adverse events occurring during the treatment period.

GUSTO Severe – Haemodynamic compromise

During the treatment period (i.e., up to Visit 3), bleeding events categorised as GUSTO Severe due to haemodynamic compromise were reported in 7 patients in the ticagrelor group (gastrointestinal haemorrhage [2 patients], gastric cancer, aortic intramural haematoma, cerebral haemorrhage, small intestinal haemorrhage and respiratory tract haemorrhage) and 1 patient in the placebo group (gastrointestinal haemorrhage). The event of cerebral haemorrhage in the ticagrelor group was fatal and is therefore captured also in both the ICH and Fatal category.

GUSTO Moderate/Severe

Consistent with the GUSTO Severe results, analyses of GUSTO Moderate/Severe bleeding events indicated a higher rate of events for the ticagrelor group compared with the placebo group up to Day 30 (KM percentage 0.6% and 0.2% in the ticagrelor and placebo group, respectively; HR 3.27 [95% CI 1.67, 6.43]) (see Figure 13).

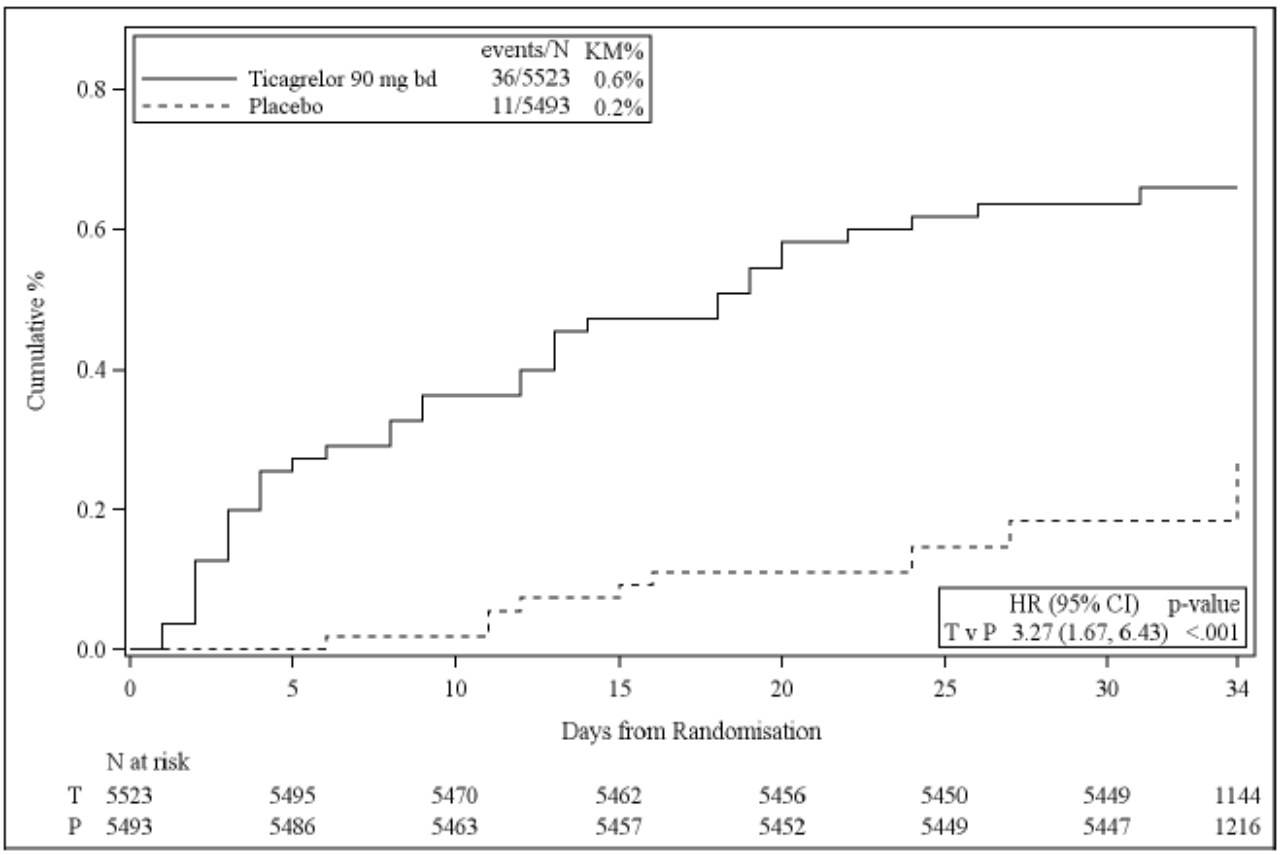


Figure 13. Kaplan-Meier plot of GUSTO moderate/severe bleeding events (full analysis set)

2.7.5. Death

Strokes and deaths were efficacy endpoints and were also recorded as SAEs/DAEs as applicable. During the treatment period (i.e., up to Visit 3), 40 (0.7%) patients in the ticagrelor group and 32 (0.6%) patients in the placebo group had an AE with the outcome of death (Table 26). The number of patients with AEs with the outcome of death, excluding fatal bleeding events, was similar between treatment groups. The most common AEs with the outcome of death, by SOC, was Nervous system disorders, with Ischaemic stroke the most common PT in both treatment groups. On-treatment, AEs

with the outcome of death were reported for 38 (0.7%) patients in the ticagrelor group and 31 (0.6%) patients in the placebo group. For data on fatal bleedings, see Table 25.

During the treatment and follow-up period (i.e., up to visit 4), 47 patients in the ticagrelor group and 43 patients in the placebo group had an AE with the outcome of death compared with the placebo group.

Table 26. Number of patients with adverse events with outcome of death by system organ class and preferred term up to visit 3 (full analysis set)

	Number (%) of patients [a]	
System organ class / Preferred term	**Ticagrelor 90 mg bd (N=5523)**	**Placebo (N=5493)**
Patients with AE with outcome of death	40 (0.7)	32 (0.6)
Infections and infestations	3 (0.1)	8 (0.1)
Clostridium colitis	0 (0.0)	1 (0.0)
Endocarditis	1 (0.0)	0 (0.0)
Gastroenteritis	0 (0.0)	1 (0.0)
Pneumonia	2 (0.0)	4 (0.1)
Respiratory tract infection	0 (0.0)	1 (0.0)
Sepsis	2 (0.0)	1 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.0)	3 (0.1)
Gastric cancer	1 (0.0)	0 (0.0)
Hepatic cancer	0 (0.0)	1 (0.0)
Lung neoplasm malignant	0 (0.0)	1 (0.0)
Ovarian neoplasm	1 (0.0)	0 (0.0)
Uterine cancer	0 (0.0)	1 (0.0)
Psychiatric disorders	1 (0.0)	0 (0.0)
Completed suicide	1 (0.0)	0 (0.0)
Nervous system disorders	23 (0.4)	11 (0.2)
Brain oedema	3 (0.1)	1 (0.0)
Cerebellar infarction	1 (0.0)	0 (0.0)
Cerebral haemorrhage	4 (0.1)	2 (0.0)
Cerebrovascular disorder	0 (0.0)	1 (0.0)

	Number (%) of patients [a]	
System organ class / Preferred term	Ticagrelor 90 mg bd (N=5523)	Placebo (N=5493)
Guillain-Barre syndrome	1 (0.0)	0 (0.0)
Haemorrhagic stroke	6 (0.1)	0 (0.0)
Ischaemic stroke	8 (0.1)	7 (0.1)
Status epilepticus	1 (0.0)	0 (0.0)
Cardiac disorders	5 (0.1)	3 (0.1)
Acute left ventricular failure	1 (0.0)	0 (0.0)
Acute myocardial infarction	2 (0.0)	0 (0.0)
Atrial fibrillation	1 (0.0)	0 (0.0)
Cardiac failure	0 (0.0)	1 (0.0)
Cardiac failure chronic	1 (0.0)	0 (0.0)
Cardio-respiratory arrest	0 (0.0)	1 (0.0)
Right ventricular failure	0 (0.0)	1 (0.0)
Vascular disorders	1 (0.0)	0 (0.0)
Aortic intramural haematoma	1 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	4 (0.1)	3 (0.1)
Acute respiratory failure	1 (0.0)	1 (0.0)
Bronchitis chronic	1 (0.0)	0 (0.0)
Pneumonia aspiration	0 (0.0)	1 (0.0)
Pneumonitis	1 (0.0)	0 (0.0)
Pulmonary embolism	1 (0.0)	1 (0.0)
Gastrointestinal disorders	1 (0.0)	0 (0.0)
Gastrointestinal haemorrhage	1 (0.0)	0 (0.0)
Renal and urinary disorders	1 (0.0)	0 (0.0)
Chronic kidney disease	1 (0.0)	0 (0.0)
General disorders and administration site conditions	4 (0.1)	5 (0.1)
Death	4 (0.1)	4 (0.1)
Sudden cardiac death	0 (0.0)	1 (0.0)

2.7.6. Serious adverse events

During the treatment period, numerically fewer patients had SAEs in the ticagrelor group compared with the placebo group during the treatment period: 571 (10.3%) and 609 (11.1%), respectively. The most commonly reported SAE, by PT, was Ischaemic stroke in both treatment groups. There were numerically fewer SAEs of Ischaemic stroke in the ticagrelor group compared with the placebo group,

reflecting the efficacy analyses. The most commonly reported non-endpoint SAEs were Pneumonia, Atrial fibrillation, and TIA in both treatment groups.

Table 27. Number of patients with Serious Adverse Events (⩾ 5 in either treatment group) by preferred term up to visit 3 (full analysis set)

	Number (%) of patients [a]	
Preferred term	**Ticagrelor 90 mg bd (N=5523)**	**Placebo (N=5493)**
Patients with any SAE	**571 (10.3)**	**609 (11.1)**
Ischaemic stroke	254 (4.6)	324 (5.9)
Pneumonia	25 (0.5)	28 (0.5)
Atrial fibrillation	18 (0.3)	15 (0.3)
Transient ischaemic attack	12 (0.2)	30 (0.5)
Pulmonary embolism	9 (0.2)	5 (0.1)
Carotid artery stenosis	8 (0.1)	7 (0.1)
Haemorrhagic transformation stroke	8 (0.1)	6 (0.1)
Haematuria	8 (0.1)	1 (0.0)
Haemorrhagic stroke	7 (0.1)	0 (0.0)
Cerebral infarction	6 (0.1)	8 (0.1)
Cerebrovascular accident	6 (0.1)	7 (0.1)
Urinary tract infection	6 (0.1)	7 (0.1)
Gastrointestinal haemorrhage	6 (0.1)	6 (0.1)
Epistaxis	6 (0.1)	0 (0.0)
Hypertension	5 (0.1)	5 (0.1)
Epilepsy	5 (0.1)	3 (0.1)
Upper gastrointestinal haemorrhage	5 (0.1)	1 (0.0)
Ischaemic cerebral infarction	4 (0.1)	6 (0.1)
Acute myocardial infarction	4 (0.1)	5 (0.1)
Sepsis	3 (0.1)	5 (0.1)

[a] Number (%) of patients with an SAE, sorted in decreasing frequency for preferred term by ticagrelor group.

2.7.7. Laboratory findings

No clinical laboratory evaluations were performed as part of this study; however, if a patient had a clinically important deterioration in a laboratory test performed as part of standard clinical practice that qualified as an SAE/DAE, it was reported as such. No AEs, associated with a combination of ALT ≥ 3×ULN or AST ≥ 3×ULN and total bilirubin ≥ 2×ULN, were reported.

2.7.8. Discontinuation due to adverse events

The number of patients with DAEs was higher in the ticagrelor group compared with the placebo group; 535 (9.7%) and 415 (7.6%), respectively. The difference was mainly driven by higher numbers of bleeding events and dyspnoea, which is aligned with the bleeding and dyspnoea data presented in the current ticagrelor prescribing information.

In total, 140 patients had a DAE of atrial fibrillation (Table 28). History of atrial fibrillation was an exclusion criterion in the study, and patients who were diagnosed with atrial fibrillation for which they should start anticoagulation therapy were required to discontinue IP.

Table 28. Number of patients with adverse events leading to discontinuation of IP (≥ 5 in either treatment group), by preferred term (full analysis set)

	Number (%) of patients [a]	
Preferred term	**Ticagrelor 90 mg bd (N=5523)**	**Placebo (N=5493)**
Patients with any AE leading to premature permanent discontinuation of IP	**535 (9.7)**	**415 (7.6)**
Ischaemic stroke	84 (1.5)	126 (2.3)
Atrial fibrillation	70 (1.3)	70 (1.3)
Dyspnoea	57 (1.0)	10 (0.2)
Ecchymosis	24 (0.4)	2 (0.0)
Epistaxis	19 (0.3)	1 (0.0)
Haematuria	15 (0.3)	3 (0.1)
Haemorrhagic transformation stroke	12 (0.2)	8 (0.1)
Transient ischaemic attack	7 (0.1)	9 (0.2)
Pulmonary embolism	7 (0.1)	4 (0.1)
Gingival bleeding	7 (0.1)	1 (0.0)
Increased tendency to bruise	7 (0.1)	0 (0.0)
Spontaneous haematoma	7 (0.1)	0 (0.0)
Carotid artery stenosis	6 (0.1)	4 (0.1)
Dizziness	6 (0.1)	4 (0.1)
Gastrointestinal haemorrhage	6 (0.1)	2 (0.0)
Palpitations	6 (0.1)	0 (0.0)
Rectal haemorrhage	5 (0.1)	3 (0.1)
Cerebral infarction	5 (0.1)	2 (0.0)
Chest discomfort	5 (0.1)	1 (0.0)
Haematoma	5 (0.1)	1 (0.0)
Spontaneous haemorrhage	5 (0.1)	0 (0.0)
Diarrhoea	4 (0.1)	7 (0.1)
Rash	3 (0.1)	5 (0.1)
Deep vein thrombosis	1 (0.0)	5 (0.1)
Nausea	1 (0.0)	5 (0.1)

Discontinuation due to bleeding events

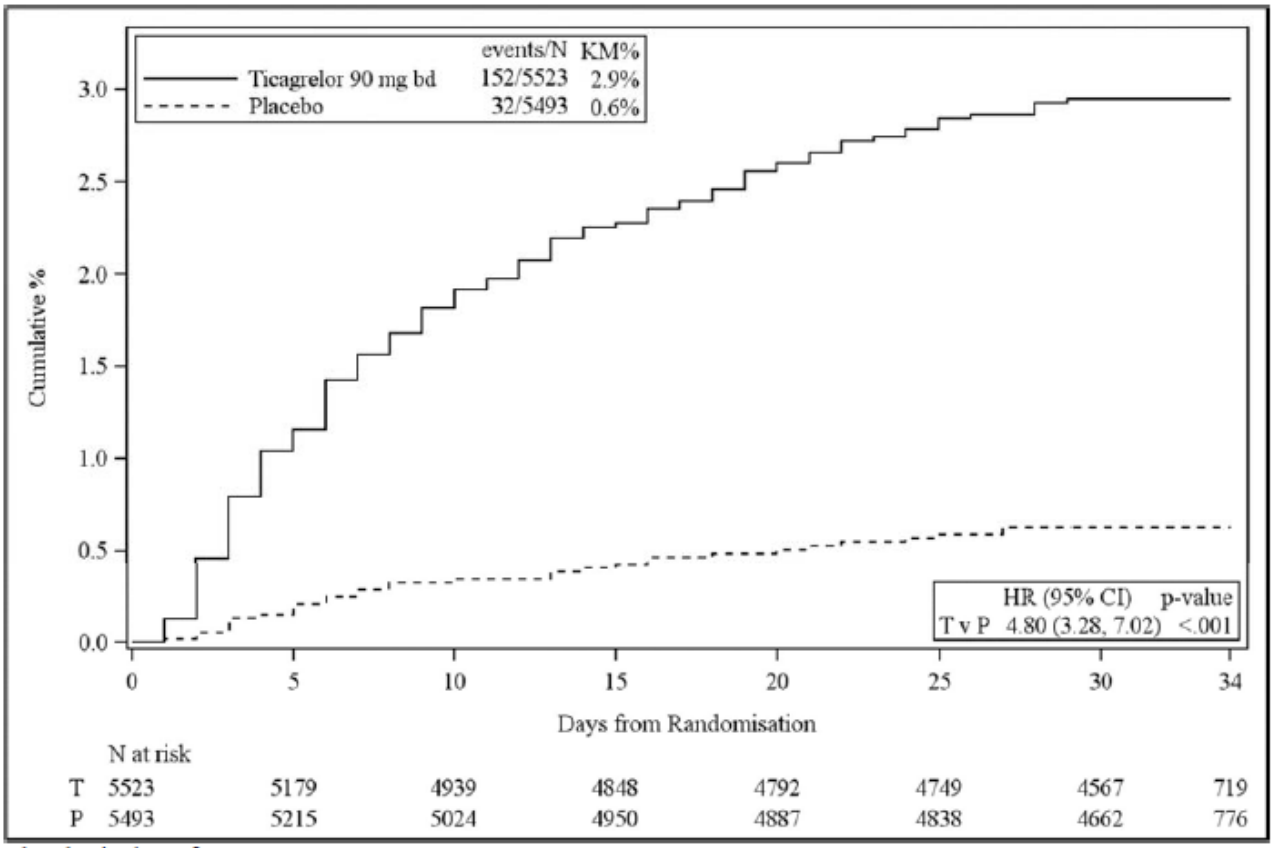
More patients prematurely and permanently discontinued IP due to a bleeding event in the ticagrelor group compared with the placebo group (Figure 14 and see Table 29). The KM percentages at Day 30 were 2.9% in the ticagrelor group and 0.6% in the placebo group.

Most of the discontinuations in both treatment groups were due to GUSTO Mild bleeding events.

Table 29. Number of patients with bleeding adverse events leading to discontinuation of investigational product by system organ class and preferred term (full analysis set)

	Number (%) of patients[a]	
System organ class / Preferred term	Ticagrelor 90 mg bd (N=5523)	Placebo (N=5493)
Patients with any bleeding AE leading to premature permanent discontinuation of IP	152 (2.8)	32 (0.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (0.1)	0 (0.0)
Blood and lymphatic system disorders	19 (0.3)	0 (0.0)
Nervous system disorders	20 (0.4)	10 (0.2)
Eye disorders	1 (0.0)	1 (0.0)
Vascular disorders	5 (0.1)	1 (0.0)
Respiratory, thoracic and mediastinal disorders	20 (0.4)	2 (0.0)
Gastrointestinal disorders	34 (0.6)	8 (0.1)
Skin and subcutaneous tissue disorders	28 (0.5)	2 (0.0)
Renal and urinary disorders	19 (0.3)	3 (0.1)
Reproductive system and breast disorders - Uterine haemorrhage	0 (0.0)	1 (0.0)
Investigations - Blood urine, Occult blood positive	1 (0.0)	2 (0.0)
Injury, poisoning and procedural complications	6 (0.1)	3 (0.1)

[a] *Number (%) of patients with an AE leading to discontinuation of IP, sorted by international order for system organ class and alphabetically for preferred term.*



Placebo is the reference treatment.

Figure 14. Kaplan-Meier plot of premature permanent discontinuation of IP due to bleeding events (full analysis set)

2.7.9. Post marketing experience

No post-marketing experience is available for the indication sought in patients with acute ischaemic stroke or TIA. Post-marketing experience in the currently approved indications is available from approximately 6.3 million patient-years of treatment, and concluded that a comprehensive review of clinical studies and post-marketing experience revealed no new information during the reporting period that alters the overall positive benefit-risk profile for ticagrelor in the approved indication.

2.7.10. Discussion on clinical safety

Extensive safety information on ticagrelor is already known. Based on its mechanism of action, bleeding is the main known adverse drug reaction of ticagrelor as also described in the SmPC. In the THALES study, a high number of randomised patients (99.6%) received at least one dose of randomised IP. The mean duration of exposure to IP was similar between treatment groups.

The THALES study assessed the safety of ticagrelor and ASA compared with that of placebo and ASA in acute ischaemic stroke/TIA patients, in particular with respect to major bleeding events and showed GUSTO Severe bleeding events were reported more often for patients in the ticagrelor group compared to patients in the placebo group at day 30 (KM percentage 0.5% and 0.1% in the ticagrelor and

placebo group, respectively; HR 3.99 [95% CI 1.74, 9.14], p = 0.001). GUSTO Severe bleeding events categorised as ICH or fatal bleeding were reported in 22 patients in the ticagrelor group and 6 patients in the placebo group during the treatment period (KM percentage 0.4% and 0.1% in the ticagrelor and placebo group, respectively; HR 3.66 [95% CI 1.48, 9.02], p = 0.005). Of these, 11 patients in the ticagrelor group and 2 patients in the placebo group were fatal. ICH was reported in 20 patients in the ticagrelor group and 6 patients in the placebo group up to Day 30. Also, GUSTO Moderate/Severe bleeding events were reported at increased incidence for ticagrelor with 36 patients in the ticagrelor group and 11 patients in the placebo group (KM percentage 0.6% and 0.2% in the ticagrelor and placebo group, respectively; HR 3.27 [95% CI 1.67, 6.43], p < 0.001).

The observed increase in severe bleeding, in particular ICH and fatal bleeding is found particularly worrisome given that the studied population was at expected low risk of bleeding. Based on further request, no subgroups could be identified in whom the B/R could be deemed more positive, and additional SmPC amendments could only restrict the intended treatment population to a population similar to the THALES study in which the risk of bleeding is deemed unacceptable, resulting in that the risk of ICH and fatal bleeding appears not to outweigh the expected benefit (MO).

Numerically fewer patients had SAEs in the ticagrelor group compared with the placebo group during the treatment period: 571 (10.3%) and 609 (11.1%), respectively. The most commonly reported SAE, by PT, was Ischaemic stroke in both treatment groups.

The rate of non-serious AEs cannot be assessed in the TIA/stroke population as selective safety data collection was applied.

The number of patients who discontinued due to an AE was higher in the ticagrelor group compared with the placebo group; 535 (9.7%) and 415 (7.6%), respectively. The difference was mainly driven by higher numbers of bleeding events and dyspnoea. More patients prematurely and permanently discontinued IP due to a bleeding event in the ticagrelor group compared with the placebo group: 152 and 32, respectively. The KM percentages at Day 30 were 2.9% in the ticagrelor group and 0.6% in the placebo group (p < 0.001).

2.7.11. Conclusions on clinical safety

The THALES study assessed the safety of ticagrelor and ASA compared with that of placebo and ASA in acute ischaemic stroke/TIA patients, in particular with respect to major bleeding events. The use of ticagrelor and ASA was associated with an increased risk of bleeding, including ICH.

2.7.12. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

3. Risk management plan

The MAH submitted an updated RMP version (version 13, with data lock point 16 January 2020) with this application. The (main) proposed RMP changes were the following: The RMP is updated to version 13 to include a new target indication and dose recommendations supported by data from the Phase III study D5134C00003 (THALES - Acute STroke or Transient IscHaemic Attack Treated with TicAgreLor

and ASA for PrEvention of Stroke and Death) in patients with acute ischaemic stroke or transient ischaemic attack (TIA). In addition, the remaining important identified risk of bleeding has been removed from the list of identified safety concerns.

Other RMP versions under evaluation:
Version Number: 12
Submitted: 24 March 2020
Procedure number: EMEA/H/C/001241/II/0047/G

Part I Product Overview
Addition of BRILIQUE indication in patients with CAD and T2DM who have undergone percutaneous coronary intervention (PCI) and proposed dosing regimen for these patients.

Addition of BRILIQUE indication in patients with acute ischaemic stroke or TIA and proposed dosing regimen for these patients.

Part II Module SI Epidemiology and of the indication(S) and target population
Addition of new section, 'Part II: 1.4' for CAD and T2DM epidemiology.
Addition of new section, 'Part II: 1.4' for ischaemic stroke and TIA epidemiology.

Part II Module SIII Clinical trial exposure
Clinical trial exposure data updated.

Part II: Module SIV: Populations not studied in clinical trials
Number of patients exposed to ticagrelor in completed clinical studies updated.

Part II Module SV: Post Authorisation Experience
Cumulative marketed exposure data updated

Part II Module SVII: Identified and potential risks

- Removal of text describing safety concerns reclassified based on the update to the Good Pharmacovigilance Practices (GVP) Module V – Risk management systems (Revision 2), implemented in the previous update (to Version 11).

- Addition of rationale for removal of "increased risk of bleeding" as an important identified risk: The MAH has reviewed the summary of safety concerns based on the cumulative experience with ticagrelor including data from the recently finalised THALES study, which is the last outcome study within the ticagrelor development programme. As a result, the remaining important identified risk of bleeding is no longer considered relevant for inclusion in the RMP. A rationale for the removal of the risk is presented below:
    - Bleeding is an expected side effect of antiplatelet therapy, including ticagrelor, inherent to their PD effects. Increased risk of bleeding is an identified and well-characterised adverse drug reaction (ADR) of ticagrelor that has been thoroughly investigated and documented in the ticagrelor development programme, including 6 large CV outcome studies across different populations.
      Data from the outcome studies show that the majority of bleeding events in patients treated with ticagrelor were less severe (eg, epistaxis, bruising and haematomas). The number of fatal bleeding events has been low and with similar frequency for ticagrelor and comparators (clopidogrel, placebo [on top of ASA] and ASA). In addition, the proportion of patients experiencing intracranial bleeding has been low for both ticagrelor and comparators given the significant comorbidity and CV risk factors of the

populations studied (ACS, previous MI, acute ischaemic stroke or TIA, patients with symptomatic PAD and CAD in patients with T2DM). Discontinuation of treatment due to bleeding events has been more common with ticagrelor than with comparators.

- The SmPC (Section 4.4) and Patient Information Leaflet contain warnings and precautions to remind health care professionals and patients that ticagrelor should be used with caution in patients at known increased risk of bleeding, including patients with a propensity to bleed (eg, due to recent trauma, recent surgery, coagulation disorders, active or recent gastrointestinal bleeding or who are at increased risk of trauma) and patients with concomitant administration of medicinal products that may increase the risk of bleeding (eg, NSAIDs, oral anticoagulants and/or fibrinolytics within 24 hours of ticagrelor dosing). In addition, the SmPC includes contraindications for patients with active pathological bleeding, history of ICH, and severe hepatic impairment.
- The established benefit-risk balance, which is based on the extensive clinical development programme including 58750 patients who have received ticagrelor, is not expected to shift. There are currently no additional activities in the pharmacovigilance (PV) plan, no additional risk minimisation measures (RMM), and no clinical measures related to this risk.

Part II: Module SVIII: Summary of safety concerns

The MAH made the following changes to the summary of safety concerns (new text underlined and in bold, deleted text ~~strike through~~):

Summary of safety concerns	
Important identified risks	~~Increased risk of bleeding~~ None
Important potential risks	None
Missing information	Long term use in patients with prior ischaemic stroke

Part V: Risk minimisation measures

- Addition of 'Long-term use in patients with prior ischaemic stroke' to Tables V-1 and V-2, which was inadvertently left out of the tables upon resolution of the last approval procedure (EMEA/H/C/001241/II/0042), approval date 15 November 2018.
- Removal of increased risk of bleeding from Table V-1: Description of Routine Risk Minimisation Measures by Safety Concern, the summary Table of PV Activities and Risk Minimisation Activities by Safety Concern and from table V-2.

Part VI: Summary of the risk management plan

- Addition of Brilique indication in patients with CAD and T2DM who have undergone PCI.
- Addition of Brilique indication in patients with acute ischaemic stroke or TIA.
- Removal of increased risk of bleeding from Table VI-1; List of Important Risks and Missing Information
- Removal of Table VI-2; Important Identified Risk – Increased Risk of Bleeding

Annex 2

Change of non-interventional database study D5130R00027 from ongoing to completed and addition of completed study D5130L00067, which provided missing information on use in renal failure/dialysis.

Annex 8
Update of summary of changes to RMP over time to reflect this update.

3.1. Overall conclusion on the RMP

The changes to the RMP could be acceptable provided an updated RMP and satisfactory responses to the request for supplementary information in section 5 are submitted.

4. Changes to the Product Information

As a result of this variation, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC have been proposed to be updated. No changes to the Package Leaflet (PL) have been proposed by the applicant.

Please refer to the separately attached document which includes all proposed changes to the Product Information and the assessment thereof.

4.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

The wording in the PL is consistent with the style tested previously during the MA applications. Therefore, it is justified to consider the Package Leaflet User Testing reports provided during review of MA application procedures as relevant for this application, and that no updated document is needed for this submission.

5. Benefit-Risk Balance

5.1. Therapeutic Context

5.1.1. Disease or condition

Cerebrovascular disease is a leading cause of death and serious long-term disability worldwide. In 2017, there were globally an estimated 6.2 million stroke-related deaths and 132 million DALYs due to stroke, from which 2.7 million deaths and 55.1 million DALYs were due to ischaemic stroke (GBD 2017 Causes of Death Collaborators 2018, GBD 2017 DALYs and HALE Collaborators 2018).

Individuals who experience an ischaemic stroke or TIA are at high risk for a subsequent stroke. In recent clinical studies, the risk of a subsequent event was approximately 5% to 10% during the first month (Wang et al. 2013, Johnston et al. 2018, Johnston et al., 2016).

The aim of treatment for patients who have had an acute ischaemic stroke or TIA is to minimise disability from the initial event and prevent subsequent strokes. Optimal management of stroke and TIA patients should include secondary preventive measures to improve outcomes. Interventions to

prevent subsequent events include pharmacological and non-pharmacological treatment of risk factors (e.g., hypertension, diabetes mellitus, hypercholesterolaemia, and smoking) (AHA/ASA 2018, ESO 2008, Wang et al. 2017). Platelets play a major role in thrombotic complications of atherosclerotic disease, and the use of antiplatelet agents is recommended to reduce the risk of recurrent stroke and other CV events in patients with non-cardioembolic acute ischaemic stroke.

Ticagrelor is an oral, direct-acting, selective, and reversibly binding P2Y12 receptor antagonist that prevents ADP-mediated platelet activation and aggregation without requiring metabolic activation.

Ticagrelor, co-administered with acetylsalicylic acid (ASA), is currently indicated for the prevention of atherothrombotic events in adult patients with

- acute coronary syndromes (ACS) or
- a history of myocardial infarction (MI) and a high risk of developing an atherothrombotic event.

The applicant proposed the following additional indication:

“Brilique, co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of stroke in adult patients with non-cardioembolic acute ischaemic stroke (NIHSS ≤5) or high-risk transient ischaemic attack (TIA) (ABCD^2 score ≥ 6 or ipsilateral atherosclerotic stenosis ≥ 50%)”.

This indication was amended to the following during the procedure to better reflect the included population:

“Brilique, co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of stroke in adult patients with non-cardioembolic acute ischaemic stroke (NIHSS ≤5) or high-risk transient ischaemic attack (TIA) (ABCD^2 score ≥ 6 or ipsilateral atherosclerotic stenosis ≥ 50%)”.

Inclusion of ipsilateral atherosclerotic stenosis in the indication next to the ABCD may reflect the studied population more accurately. However, this criterion is unfamiliar in the regulatory field. Based on further request to analyse any further fine-tuning on the indication was not discussed considering the overall negative benefit-risk assessment.

5.1.2. Available therapies and unmet medical need

ASA is the global standard-of-care treatment for patients with an acute ischaemic stroke or TIA. However, even with ASA treatment, the risk of recurrent stroke remains high. For the secondary prevention after a stroke or TIA in the non-acute phase, American and European guidelines recommend clopidogrel monotherapy or ASA in combination with dipyridamole (Kernan et al. 2014, European Stroke Organisation 2008).

Previous studies of clopidogrel, in combination with ASA, suggest that more intensive antiplatelet therapy with DAPT may improve outcomes in stroke/TIA patients when initiated in the acute setting. Early initiation and short term (21 days) DAPT therapy for patients with an acute minor ischaemic stroke (NIHSS ≤ 3) or TIA (ABCD^2 ≥4) resulted in a reduced rate of ischaemic stroke (HR 0.68; 95% CI 0.57 to 0.81; P<0.001) (Wang et a. 2013). Several guidelines, therefore, advise early initiation and short-term (21 days) DAPT using ASA plus clopidogrel (300 mg loading dose, followed by 75 mg daily) for 21 days rather than ASA monotherapy for patients with acute high-risk TIA or minor ischemic stroke who do not have a known cardiac source (Wang et al. 2013, Up to date 2020, as well as Dutch guidelines). In the SOCRATES study, ticagrelor alone in patients with acute ischaemic stroke or TIA did

not show a benefit over ASA in preventing subsequent cardiovascular events (stroke, myocardial infarction, or death). However, subgroup analyses of the SOCRATES study on ticagrelor suggested that ticagrelor on background ASA therapy could be a promising treatment to prevent subsequent stroke events in patients with acute cerebral ischaemia (Wong et al. 2018). On 10 December 2020, the Committee for Medicinal Products for Human Use (CHMP) adopted an extension of the indication for clopidogrel to include adult patients with high risk Transient Ischemic Attack (TIA) ($ABCD^2$ score ≥4) or minor Ischemic Stroke (IS) (NIHSS ≤3) within 24 hours of either the TIA or IS event.

Regarding the current procedure it is important to notice that the European Stroke Organisation Guideline Board in preventing early recurrent ischaemic stroke strongly recommends the use of 21-days of dual antiplatelet therapy with aspirin and clopidogrel. However, a weak recommendation is made based on moderate quality evidence for 30-days of dual antiplatelet therapy with aspirin and ticagrelor in people with non-cardioembolic mild to moderate ischaemic stroke or high-risk TIA in the past 24 hours. (Dawson et al, European Stroke Journal, 2021).

5.1.3. Main clinical studies

The applicant submitted the results of the THALES study to support the indication "Ticagrelor, co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of stroke in adult patients with acute ischaemic stroke or transient ischaemic attack (TIA) ($ABCD^2$ score ≥ 6 or ipsilateral atherosclerotic stenosis ≥ 50%)". A randomised, placebo-controlled, double-blind study involving patients who had had a mild-to-moderate acute non-cardioembolic ischemic stroke, with a NIHSS score of 5 or less, or high-risk TIA and who were not undergoing thrombolysis or thrombectomy. The patients were assigned within 24 hours after symptom onset, in a 1:1 ratio, to receive a 30-day regimen of either ticagrelor (180-mg loading dose followed by 90 mg twice daily) plus ASA (300 to 325 mg on the first day followed by 75 to 100 mg daily) or matching placebo plus ASA.

Table 30. Description of the THALES study

Objective(s) of the study	Primary efficacy: To demonstrate superior efficacy of ticagrelor and ASA compared with placebo and ASA in acute ischaemic stroke/TIA patients in the prevention of the composite of stroke and death at 30 days Safety: To assess the safety of ticagrelor and ASA compared with that of placebo and ASA in acute ischaemic stroke/TIA patients, in particular with respect to major bleeding events.
Study design and control	Phase III, international, multicentre, parallel-group, event-driven, randomised, double-blind, placebo controlled study
Dosing	Ticagrelor: Loading dose of oral ticagrelor was 180 mg (2 tablets 90 mg) on Day 1, followed by 90 mg twice daily OR Placebo: Loading dose of oral matching placebo was 180 mg (2 tablets 90 mg) on Day 1, followed by 90 mg oral twice daily Background therapy: ASA was provided to all patients as part of standard of care. The recommended loading dose on Day 1 was 300 to 325 mg and 75 to 100 mg once daily thereafter.
No. of subjects randomized /treated	Ticagrelor: 5523/5506 Placebo: 5493/5470
Study size	Male or female patients (≥ 40 years), noncardioembolic acute ischaemic stroke with NIHSS score ≤ 5 OR TIA with $ABCD^2$ score ≥ 6 or with large-vessel disease (ie, ipsilateral ≥ 50% stenosis of extra or intracranial artery) were randomized within 24 hours of symptom onset
Duration of treatment	30 days

5.2. Favourable effects

A superior efficacy of ticagrelor and ASA compared with placebo and ASA in acute ischaemic stroke/TIA patients in the prevention of the composite of stroke and death at 30 days (HR 0.83 [95% CI 0.71, 0.96], p = 0.015) (primary objective) was observed. This was primarily attributed to reduction in ischaemic stroke (HR 0.79 [95% CI 0.68, 0.93], p = 0.004, secondary endpoint). During the follow-up period, the treatment effect was maintained with numerically fewer primary events in the ticagrelor group compared with the placebo group up to Day 60 (HR 0.83 [95% CI 0.72, 0.96]). Subgroup analyses were consistent with the primary endpoint.

Recurrent TIA was not included among the efficacy outcomes but was included in the safety assessment. Consistent with the efficacy results, there were less TIAs with ticagrelor than with placebo in the safety assessment of SAEs (12 vs 30).

5.2.1. Uncertainties and limitations about favourable effects

Inclusion/exclusion criteria in THALES were quite extensive, leading to a very selected study population with acute ischaemic stroke or TIA at high risk of (recurrent) stroke and low risk of bleeding. The effect of ticagrelor in the patient population that was not included in the THALES study (patients with an ischaemic stroke with a NIHSS score ≥ 6, patients with a TIA and $ABCD^2$ score < 6 and those with cardioembolic stroke) is not known. The applicant restricted the indication to the major inclusion and exclusion criteria of the Thales study. The applicant proposed to include ipsilateral atherosclerotic stenosis in the indication. The inclusion of ipsilateral atherosclerotic stenosis in the indication next to the ABCD may reflect the studied population more accurately, however, this criterion is unfamiliar in the regulatory field. At the time of the assessment it was questioned, and was pending resolution, if the expression “ipsilateral atherosclerotic stenosis” should appear in the text as it might not be distinguished in the clinical setting (MO).

The primary endpoint was not consistent for stroke and death. The endpoint was driven by prevention of ischaemic strokes, while the component “all-cause mortality” (including fatal intracranial haemorrhages) numerically favoured placebo (KM 0.6% in the ticagrelor group and 0.5% in the placebo group).

Despite a reduction in ischaemic stroke, and numerically fewer patients with a subsequent disabling stroke at Day 30 in the ticagrelor group compared with the placebo group (exploratory objective), there was no overall reduction in disability, rendering the clinical relevance of efficacy questionable. A 5 times more disability data than disability data associated with an event, and absence of baseline disability data causes by the index event, also make these data uncertain.

5.3. Unfavourable effects

The THALES study showed that ticagrelor treatment was associated with more *GUSTO Severe bleeding* events than placebo. At Day 30, *GUSTO Severe bleeding* events were reported for 28 patients in the ticagrelor group and 7 patients in the placebo group (KM percentage 0.5% and 0.1% in the ticagrelor and placebo group, respectively; HR 3.99 [95% CI 1.74, 9.14], p = 0.001).

GUSTO Severe bleeding events categorised as ICH or fatal bleeding were also reported more frequently in the ticagrelor group compared to the placebo group (KM percentage 0.4% and 0.1% in the ticagrelor and placebo group, respectively; HR 3.66 [95% CI 1.48, 9.02], p = 0.005). A similar

pattern was seen for *GUSTO Moderate/Severe bleeding* events (KM percentage 0.6% and 0.2% in the ticagrelor and placebo group, respectively; HR 3.27 [95% CI 1.67, 6.43], p < 0.001). More patients prematurely and permanently discontinued trial medication due to a bleeding event in the ticagrelor group compared with the placebo group: 152 and 32, respectively (KM percentages 2.9% in the ticagrelor group and 0.6% in the placebo group; HR 4.80 [95% CI 3.28, 7.02], p < 0.001).

The number of patients with AEs with the outcome of death was also numerically higher in the ticagrelor group (40 vs 32), mainly due to fatal bleedings (11 vs 2).

The number of patients with DAEs was higher in the ticagrelor group (535 patients; 9.7%) compared with the placebo group (415 patients; 7.6%); the difference was mainly driven by higher numbers of bleedings (152 vs 32) and dyspnoea events (57 vs 10).

5.3.1. Uncertainties and limitations about unfavourable effects

In particular, the observed increase in severe bleeding, ICH and fatal bleeding, is found particularly worrisome given that the studied population was at an expected low risk of bleeding.

The rate of non-serious AEs cannot be assessed in the TIA/stroke population as selective safety data collection was applied.

5.4. Effects table

Table 29 The effects table of ticagrelor in patients who have had an acute ischaemic stroke or TIA with background ASA therapy at day 30

Outcome	Unit	Ticagrelor (n=5523)	Placebo (n=5493)	Uncertainties / Strength of evidence	Ref
Favourable effects					
The composite of stroke and death[1)]	*KM% (n)*	*5.4 (303) (4.9, 6.1)*	*6.5 (362) (5.9, 7.2)*	*SoE: Primary endpoint: HR (95%CI): 0.83 (0.71, 0.96); p = 0.015, RD -1.08 (-1.97, -0.20), NNT 92*	THALES Study
Non-fatal ischemic stroke		4.8 (268) (4.3, 5.4)	6.1 (339) (5.5, 6.8)	SoE: HR (95%CI): 0.78 (0.67, 0.92) p = 0.003, RD -1.28 (-2.13, -0.43), NNT 78; non-fatal stroke 4.9 (270) vs 6.1 (340)	
Unfavourable effects					
All-cause mortality, including fatal stroke and fatal bleeding)	*KM% (n)*	0.6 (36) (0.4, 0.9)	0.5 (27) (0.3, 0.7)	Unc: HR (95%CI): 1.33 (0.81, 2.19); p = 0.264, RD 0.14 (-0.13, 0.42), NNH 700	THALES Study
• *Fatal stroke[1)]*		*0.3 (17) (0.2, 0.5)*	*0.1(8) (0.1, 0.3)*	*Unc: HR (95%CI): 2.12 (0.91, 4.90); p = 0.080, RD 0.16 (-0.02, 0.34), NNH 614*	
• *Fatal bleeding[1)]*		*0.2 (11) (0.1, 0.4)*	*0.0 (2)(0.0, 0.2)*	*SoE: HR (95%CI): 5.48 (1.21, 24.71), p = 0.027, RD 0.16 (0.03, 0.29), NNH 612*	
GUSTO severe (excluding fatal bleeding)		0.3 (17) (0.2, 0.5)	0.1 (5) (0.0, 0.2)	SoE: HR (95%CI): 3.39 (1.25, 9.19); p = 0.016, RD 0.22 (0.05, 0.38), NNH 460	
• *Intracranial haemorrhage[1)]*		*0.4 (20) (0.2, 0.6)*	*0.1 (6) (0.1, 0.3)*	*SoE: HR (95%CI): 3.33 (1.34, 8.28); p = 0.010, RD 0.25 (0.07, 0.44), NNH 394*	
GUSTO moderate		0.1 (8) (0.1, 0.3)	0.1(4) (0.0, 0,2)	Unc: HR (95%CI): 2.00 (0.60, 6.65); p = 0.257, RD 0.07 (-0.04, 0.19), NNH 1371	

Abbreviations: HR: hazard ratio, 95%CI: 95% confidence interval (in case p-values are not mentioned the 95%-CI should be considered being descriptive), Gusto severe: fatal, intracranial, bleeding that cause haemodynamic compromise requiring intervention, GUSTO moderate: bleeding requiring transfusion of whole blood or PRBCs without haemodynamic compromise. mRS: modified Rankin score, KM percentage is calculated at 30 days. Kaplan-Meier estimates, hazard ratios, and confidence intervals are calculated if at least 15 events have occurred within the category. *[1)] numbers are also reflected in other effects*

5.5. Benefit-risk assessment and discussion

5.5.1. Importance of favourable and unfavourable effects

Ticagrelor was superior to placebo in reducing the rate of the composite of stroke and death up to Day 30 [HR = 0.83; 95%CI = 0.71, 0.96]. This was off-set by an increase in GUSTO severe bleeding (HR 3.99 [95%CI 1.74, 9.14], p < 0.001).

However, the primary endpoint and secondary endpoints of the THALES study consisted of composite endpoints complicating an accurate and balanced benefit-risk assessment. The reasons are that components of the primary endpoint (stroke or death) demonstrate an imbalanced number of events for each component , have an effect in opposite directions and may have different clinical impact for the patient. The death component primarily acts as a competing risk for stroke in the primary composite. Moreover, the primary efficacy and safety endpoints have overlapping events (e.g. death is also a component of the GUSTO severe bleeding as fatal bleedings).

The general clinical objective to treat patients with a mild to moderate acute stroke or a high risk TIA (equivalent) with ticagrelor is to reduce the risk of a subsequent ischemic stroke being highest in the initial period after experiencing an acute stroke (or TIA) event, and to reduce disability. Focusing the discussion of the benefit-risk assessment on individual endpoints without overlapping effects instead of composite endpoints showed the benefit of ticagrelor and ASA compared with placebo and ASA in acute ischaemic stroke/TIA patients in the prevention of the composite of stroke and death at 30 days was mainly a result of the reduction of non-fatal ischemic stroke (HR 0.78 [95% CI 0.67,0.92], NNT 78). However, despite a higher efficacy of ticagrelor in preventing ischemic stroke, the risk was higher with ticagrelor compared with placebo for all-cause mortality (HR 1.33 [95% CI 0.81, 2.19)], NNH 700).

The numerical difference in all-cause mortality was reflected in a numerical increase in fatal strokes (HR 2.12 [95% CI 0.91, 4.90], NNH 614) and the same events were also reflected in the numerical increase in fatal bleedings (HR 5.48 [95% CI 1.21, 24.71], NNH 612).

The risk was also significantly higher with ticagrelor compared with placebo for GUSTO severe bleedings (excluding fatal bleeding) (HR 3.39 [95% CI 1.25, 9.19], NNH 460), (Table 29).

Further, despite a reduction in ischaemic stroke, there was no overall reduction in disability (mRS score >1), rendering the clinical relevance of efficacy questionable. This was also due to the fact that disability due to the index event could not be separated from disability change due to the treatment effect of ticagrelor.

To provide more context to the benefit risk balance, a weighted analysis was subsequently requested using the aforementioned individual endpoints without overlapping effects. As requested, the MAH made efforts to weigh these components by applying a quantitative approach based on multi-criteria decision analysis (MCDA). In MCDA, the performance of the different treatment options on the favourable and unfavourable effects are judged for their clinical relevance and all effects are weighted to create a common unit of preference value, typically expressed on a 0 to 1

utility scale. An overall utility is 0 is when the drug or treatment brings no extra measure of perceived value whereas an overall utility of a drug is 1 is when the drug reached the maximal level of perceived value. Comparing treatments in terms of their utility values allows for a more quantitative assessment of the benefit-risk balance.

The MCDA of the MAH was based on a weighted sum of 4 treatment effects, with weights derived from WHO disability scores aligned with the use of weighted mRS scores in recent stroke studies considering mRS based severity information. This analysis was complemented with additional weighted benefit-risk analyses using bleeding-related risk components that range from the worst and most restrictive (fatal bleeding) to most GUSTO Moderate/Severe categories.

As stipulated above, for the stroke-related outcomes, disability weights were generated for mRS scores to better reflect the perceived clinical impact of each mRS score as part of the WHO Global Burden of Disease Project (Hong and Saver 2009). The disability weights range from 0 (no disability, ie, mRS score 0) to 1 (death, ie, mRS score 6). This disability weighting was applied to the THALES data to assess the disability impact of ischaemic stroke. The relative weight of a non-fatal ischaemic stroke compared with a fatal event was 0.34, ie, the importance of a fatal bleeding was 2.9 (1/0.34) times higher than that of a non-fatal ischaemic stroke; this weighting was used in the MCDA. The disability weight of a non-fatal ICH was similar to that of a non-fatal ischaemic stroke. The same relative weight was used for all deaths regardless of cause. Utility decrements (ie, decreases in health utility) were used to calculate the weight of ischaemic stroke versus haemodynamic compromise (the remaining component of GUSTO severe bleeding) and GUSTO Moderate bleeding. The ratio of the utility decrement for GUSTO Moderate bleeding and recurrent stroke was 0.4; in other words, 1 GUSTO Moderate bleeding in THALES resulted in 0.4 times the utility decrement of 1 ischaemic stroke over 1 month.

The MCDA included non-fatal ischaemic stroke as the benefit and death, non-fatal GUSTO Severe bleeding, and GUSTO Moderate bleeding as the risks (step 2 in Table 19). Incidence rates were used to measure the performance of ticagrelor and placebo for each of the benefit and risks outcomes (step 3 in Table 19). Scoring alternatives and weighting criteria were defined in step 4 and step 5 in Table 19. Aggregate scores (utilities) were then calculated for the difference in value between ticagrelor and placebo for each of the weighted outcome alternatives, which were then summed to yield a total score (step 6 in Table 19). The aggregate score was negative for the risks (death, non-fatal GUSTO Severe bleeding, and GUSTO Moderate bleeding), indicating that placebo outperformed ticagrelor, and positive for the benefit (nonfatal ischaemic stroke), indicating that ticagrelor outperformed placebo. The total aggregate score was positive (0.13), demonstrating a benefit of ticagrelor over placebo when both the benefit and the risks were taken into account.

MCDA results by index event and age subgroups and sub-subgroups have also been presented (see Table 20). Positive values indicate a benefit of ticagrelor over placebo. In patients with TIA as the index event, the total difference in value between ticagrelor and placebo was negative; this difference was driven by a numerical difference in deaths in the small sub-subgroup of TIA patients aged > 75 years (4 of 135 in the ticagrelor group versus 0 of 172 in the placebo group).

Several comments to the assumptions of weighting as utilised by the company can be made:

- Using the WHO mRS score (as measured at visit 3 in the THALES study) for identifying the weight of death versus ischemic stroke could be questioned. Especially, this method appears unreliable as there is great uncertainty whether the mRS score was shifted based on the stroke or bleeding event or was already present due to the baseline index acute stroke (or TIA) event. In this respect, the latter is far more likely as the proportion of mRS > 1 scores overall (1282 vs 1284) was more than 5 times greater than the applied mRS scores > 1 in patients with an event (201 vs 245). Further, as baseline mRS scores are missing, any distinction between both appears challenging to establish. Also, deaths have been restricted to fatal bleedings and not to overall deaths. To consider the clinical impact of death as 2.9 times more important as an ischemic stroke could be disputed, both methodologically and intuitively, and is not well justified, and may be appreciated being too low.
- Using the WHO mRS score (as measured at visit 3) for identifying the weight of ICH versus ischemic stroke is estimated in a similar way as for death and therefore also not appropriate for similar reasons.
- Further, extrapolating to a one or 5 years period based on two observational studies to consider both equal in weight appears uncertain and may not be appropriate when events are compared within the current study period of 30 days, apart from that patient populations may be different between those studies and current study. Especially, the 2 mentioned registry studies identified a higher mortality impact of haemorrhagic stroke vs ischemic stroke within 30 days of follow-up. Therefore, non-fatal GUSTO severe bleedings are rated as being of comparative importance in the MCDA exercise although the clinical impact of the occurrence of an early severe (cerebral) bleeding event is, as clearly indicated in the responses, more serious on the health status of the patient than the occurrence of a non-ischemic stroke. Overall, applying weight to the treatment effect components based on different methods and assumptions by using either WHO or health utility assumptions may be questioned.

Apart from these limitations, the sensitivity of the conclusions of an apparent positive benefit risk balance based on the weight assumptions needs some further consideration:

- The company has presented the weight estimation of the components to consider the benefit risk balance to become neutral. As disputed in Table 19, if the equivalence change for death would be considered 7 times increased versus ischemic stroke rather than 2.9, the BR balance would be neutral. In other words, 1 death is accepted when 7 subsequent ischemic strokes following the initial stroke are prevented. However, based on current assumptions, if the impact of disability prevention with subsequent strokes (after the initial stroke) would be regarded as less important, the willingness to accept one death will dramatically reduce and the health dis-utility of a subsequent stroke is clearly overestimated at the beginning of the exercise and consequently the trade-off figure of 2.9 could be considered as being understated by start. In this context, it should once more be mentioned that no effect on disability could be demonstrated. These considerations could

question the robustness of the benefit-risk balance. This would be more so if assumptions to the other individual components would also be appreciated less favourable based on different assumptions following the comments as made above.

- The company has examined the impact of the uncertainty around the point estimate for current assumptions and found that ticagrelor was favoured in 81% vs 19% of the simulation cases. However, when possible less favourable weighting, which is very likely considering above mentioned issues, than this may also be heavily influenced and could still make the benefit-risk be questionable.
- Further, previous studies evaluating ticagrelor on top of ASA in different patients population does not allow to clearly extrapolate the findings from these studies to the observed effects in current study. As, apart from differences in population, dose and treatment period, findings on bleeding events were not consistent between those studies. In PEGASUS, bleeding risk was not increased for fatal bleedings while in the THEMIS study a (limited) increased risk was observed. For ICH, a limited increased risk was observed in both studies. For other studies, the relevance to the current THALES study may be considered of less relevance due to study design and/or included population.
- Therefore, with currently applied weighing (method) there is too much uncertainty that short-term treatment of ticagrelor on top of ASA in patients presenting with acute mild to moderate stroke or high risk TIA would provide convincing clinical benefit to these patients, and thus the overall benefit risk balance should be considered negative.

Considering the uncertainties and limitation as identified for the overall BR balance estimation, any further discussion on the BR balance in several subgroup may currently not be considered appropriate, without, first of all, resolving these issues for the overall BR estimation. Especially, reluctance should be applied considering the scenario of an overall questionable benefit risk for ticagrelor in treating this proposed patient population, as there is a risk for multiplicity and selection bias since these post-hoc evaluation will be drawn to the findings that are most extreme, as indicated in scenario 2 of the guideline on the investigation of subgroups in confirmatory trials (EMA/CHMP/539146/2013, scenario 2). Nevertheless, efforts made for presentation and discussion on the benefit risk balance by the company in several subgroups is appreciated. When the efficacy of ischemic stroke and the safety of GUSTO severe bleedings are considered separately, no interaction could be found for age as a continuous variable, and for subgroups of the index event, although a larger absolute risk reduction is shown in patients with NIHSS 4 to 5 due to the overall higher event rate in this subgroup. Using the MCDA (multicriteria decision analysis) with the assumptions as used for the overall data (see limitations as discussed above), the data may suggest some less clear effects for age > 75 and for TIA. Although these data should already be interpreted with caution (as discussed), some further subdividing suggest that especially the subgroup of subgroup of patients with age > 75 and TIA may suggest for a negative BR balance based on point estimates. However, as mentioned, drawing any conclusions will be problematic considering the issues on the overall effect currently pending.

5.5.2. Balance of benefits and risks

The overall B/R of ticagrelor in the proposed new indication is negative.

5.6. Conclusions

The overall B/R of ticagrelor 90 mg in the pursued new indication (for the prevention of stroke in patients with acute ischaemic stroke or transient ischaemic attack) is currently negative.

The extension of indication submitted under this C.I.6.a variation was withdrawn by the MAH in the final round of the procedure.