AstraZeneca

Clinical Study Protocol

Drug Substance	Ticagrelor
Study Code	D5134C00003
Version	3.0
Date	08 May 2019

A Randomised, Double-Blind, Placebo-Controlled, International, Multicentre, Phase III Study to Investigate the Efficacy and Safety of Ticagrelor and ASA Compared with ASA in the Prevention of Stroke and Death in Patients with Acute Ischaemic Stroke or Transient Ischaemic Attack

[THALES - Acute STroke or Transient IscHaemic Attack Treated with TicAgreLor and ASA for PrEvention of Stroke and Death]

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

VERSION HISTORY

Version 3.0, 08 May 2019

Changes to the protocol are summarised below.

Section Protocol Synopsis (International co-ordinating Investigator(s))**:** Contact details for Pierre Amarenco, MD were updated.

Section Protocol Synopsis (International co-ordinating Investigator(s))**:** Contact details for S. Claiborne Johnston, MD, PhD were updated.

Section Protocol Synopsis (Study site(s) and number of patients planned): Adjusted the total number of randomised patients to approximately 11000. Adjusted the required number of primary events to 647.

Section Protocol Synopsis (Statistical methods): Adjusted interim analysis to be conducted after approximately 70% of primary events have been collected. Adjusted significance level of the final analysis to 4.996%. Adjusted the primary endpoint hazard ratio (HR) at which the study may be stopped for futility to >0.933.

Section 1.1 (Background and rationale for conducting this study): Added description and reference to a relevant clinical study completed during the course of this study (Johnston et al 2018).

Section 1.4 (Study design): Adjusted interim analysis to be conducted after approximately 70% of primary events have been collected. Adjusted sample size to approximately 11 000.

Section 9.2 (Sample size estimate): Adjusted the assumed primary endpoint HR to 0.775. Adjusted the power to show an effect on the primary endpoint to 90%. Adjusted the required number of primary endpoint events to 647. Adjusted significance level of the final analysis to 4.996%. Adjusted critical value for the final analysis to 0.857. Adjusted the total number of randomised patients to approximately 11000. Adjusted interim analysis to be conducted after approximately 70% of primary events have been collected.

Section 9.5.1 (Analysis of the primary variable): Adjusted significance level of the primary endpoint analysis to 4.996%.

Section 9.5.2 (Analysis of the secondary variables): Adjusted significance level of the primary and secondary endpoint analyses to 4.996%.

Section 9.5.6 (Interim analysis): Adjusted interim analysis to be conducted after approximately 70% of primary events (453 events) have been collected. Adjusted critical value for interim analysis to 0.734. Adjusted significance level of the final analysis to 4.996%. Adjusted the primary endpoint HR at which the study may be stopped for futility to >0.933.

Section 12 (List of references): Added reference to Johnston et al 2018.

Version 2.1, 05 February 2019

Changes to the protocol are summarised below.

Section Version History. Date of Version 1 was updated on page 3 from 15 October 2018 to 08 February 2017.

Version 2, 15 October 2018

Changes to the protocol are summarised below,

Section Protocol Synopsis (International co-ordinating Investigator(s)): Postal address of the international co-ordinating investigator S. Claiborne Johnston was updated.

Section Protocol Synopsis (Study site(s) and number of patients planned): Adjusted total number of the required primary events to 764.

Section Protocol Synopsis (Study period): Amended study period to the first patient in Q1 2018 and to the last patient in Q4 2019, to align with the most current study plan.

Section Protocol Synopsis (Statistical methods): An update to the stopping boundary at the interim, which is a 2-sided p-value of <0.001. Increase in value of significance level to 4.988%. Futility analysis has been added.

Section 1.2 (Rationale for study design, doses, and control groups): Added annotation of the terms “stroke” and “death”.

Section 1.4 (Study design): The Visit’s 4 name adjusted to ‘end of follow-up period’, to standardise with the collective understanding of study timelines vs follow up period. Clarification on the IP availability at the time of randomisation.

Section 3 (Patient selection, enrolment, randomisation, restrictions, discontinuation, and withdrawal): Added annotation of the $ABCD^2$ score.

Section 3.4 (Procedures for handling incorrectly enrolled or randomised patients): Additional information about collecting a patient vital status at the end of study follow up (V4) consistent with the intention-to-treat principle.

Section 4.1 (Visit 1, enrolment/randomisation (Day 1)): Administrative update about availability of IP at the time of randomisation.

Section 4.4 (Visit 4 end of study (Day 60 +4 days)): Changes stated in above Section 1.4

Section 5.3.4 (Cerebrovascular atherosclerosis phenotyping): The Figure 2 Cerebrovascular atherosclerosis phenotyping was updated to align stenosis percentage values of the artery with CRF guidance.

Section 5.3.5 (mRS score): The Figure 3: Simplified modified Rankin Scale questionnaire was added.

Section 6.4.1 (Reporting of SAEs that are also endpoints in the study): Clarification on SAE reporting process for events that are also endpoints.

Section 8.5 (Compliance): Clarification on responsibilities of AZ representative regarding verification of the amount of returned IP for each patient.

Section 8.7 (Concomitant medications and other treatments): Added information on recording of concomitant medications including all changes within 30 days prior to randomization.

Section 9 (Statistical analyses by AstraZeneca) Sub-Sections (9.2), (9.5.1), (9.5.2), (9.5.6): Changes already stated above in Section Protocol Synopsis.

Section 10.3 (Study timetable and end of study): Amended study period to the first patient in Q1 2018 and to the last patient in Q4 2019, to align with the most current study plan.

Section 12 (List of references): Updated Amarenco et al 2017, Bruno et al 2011 was added.

Version 1, 08 February 2017

Initial creation.

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PROTOCOL SYNOPSIS

A Randomised, Double-Blind, Placebo-Controlled, International, Multicentre, Phase III Study to Investigate the Efficacy and Safety of Ticagrelor and ASA Compared with ASA in the Prevention of Stroke and Death in Patients with Acute Ischaemic Stroke or Transient Ischaemic Attack

International co-ordinating Investigator(s)

S. Claiborne Johnston, MD, PhD; Dean, Dell Medical School; [redacted]

Pierre Amarenco, MD, Paris University, Paris, [redacted]

Study site(s) and number of patients planned

This study will be conducted in approximately 450 study sites in approximately 30 countries worldwide. It is expected that approximately 11 000 patients will be randomised. The study is event-driven and the true event rate will determine the number of patients who need to be randomised to collect the required 647 primary events.

Study period

Enrolment of the first patient is expected to occur in Q1 2018, and completion of the study by the last patient is expected to occur in Q4 2019.

Study design

This is a randomised, placebo-controlled, double-blind, parallel-group, international, multicentre Phase III study to test the hypothesis that ticagrelor and acetylsalicylic acid (ASA) is superior to ASA in preventing stroke and death in patients with acute ischaemic stroke (AIS) or transient ischaemic attack (TIA).

Primary, secondary, and safety objectives

Primary objective	Variable
To demonstrate superior efficacy of ticagrelor and ASA compared with placebo and ASA in AIS/TIA patients in the prevention of the composite of stroke and death at 30 days	Time from randomisation to first subsequent stroke or death

Secondary objectives	**Variables**
To demonstrate superior efficacy of ticagrelor and ASA compared with placebo and ASA in AIS/TIA patients in the prevention of ischaemic stroke at 30 days	Time from randomisation to first subsequent ischaemic stroke
To demonstrate superior efficacy of ticagrelor and ASA compared with placebo and ASA in AIS/TIA patients in reducing overall disability at 30 days	mRS score >1 at Visit 3
Safety objective	**Variables**
To assess the safety of ticagrelor and ASA compared with that of placebo and ASA in AIS/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

AIS acute ischaemic stroke; ASA acetylsalicylic acid; DAE premature permanent discontinuation of investigational product due to adverse event; ICH intracranial haemorrhage; TIA transient ischaemic attack; SAE serious adverse event

Target patient population

Patients ≥40 years of age with non-cardioembolic AIS 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) will be randomised within 24 hours of symptom onset.

Duration of treatment and follow-up

Patients will be treated for 30 days, and thereafter followed for an additional 30 days during which they will receive standard-of-care treatment.

Investigational product, dosage, and mode of administration

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

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

Concomitant ASA treatment

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

Statistical methods

All analyses will be based on the intention-to-treat principle using the full analysis set including all randomised patients. The primary and secondary variables are included in the confirmatory analyses and will be tested in sequential order; the secondary variables will only be tested in a confirmatory sense if the primary comparison is significant. The time-to-event variables will be analysed using the Cox proportional hazards model with a factor for treatment group. The hazard ratio, 95% confidence interval, and p-value will be reported.

One interim analysis will be conducted after approximately 70% of the primary events have been collected. The stopping boundary at the interim is a 2-sided p-value of <0.001. The final analysis will be conducted at a significance level of 4.996% with the family-wise error rate controlled at 5.00%.The study may be stopped for futility if the observed HR for the primary endpoint is >0.933, corresponding to a predictive power of 5%.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or special term	Explanation
AE	Adverse event
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)
AIS	Acute ischaemic stroke
ASA	Acetylsalicylic acid
(e)CRF	(electronic) Case Report Form
CSA	Clinical Study Agreement
CSP	Clinical Study Protocol
CT	Computed tomography
DAE	Premature permanent discontinuation of IP due to adverse event
DMC	Data monitoring committee
EC	Executive committee
EQ-5D-5L	A questionnaire used to measure health outcomes
FAS	Full analysis set
GCP	Good Clinical Practice
GUSTO	Bleeding scale: Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries
HR	Hazard ratio
ICH	Intracranial haemorrhage
IRB/IEC	Institutional review board/independent ethics committee
International co-ordinating Investigator	The Investigator who co-ordinates Investigators and/or activities internationally.
IP	Investigational product
IxRS	Interactive Voice/Web Response System
MI	Myocardial infarction
MRI	Magnetic resonance imaging
mRS	Modified Rankin scale
NIHSS	National Institute of Health Stroke Scale
Principal Investigator	The Investigator at a site who is overall accountable for study procedures at the site. 'Investigator' refers to both Principal Investigators and co-Investigators.
SAE	Serious adverse event
TIA	Transient ischaemic attack
WBDC	Web Based Data Capture

1. INTRODUCTION

1.1 Background and rationale for conducting this study

Cerebrovascular disease is a leading cause of death and serious long-term disability worldwide. In 2013, there were an estimated 6.5 million stroke-related deaths, and 113 million disability-adjusted life-years (DALYs) were lost globally due to stroke. Of 10.3 million strokes, 6.9 million were ischaemic, with 3.3 million deaths and 47.4 million DALYs lost due to ischaemic stroke (Feigin et al 2015). The prevalence/incidence of transient ischaemic attack (TIA) is difficult to determine due to diagnostic challenges and underreporting, but estimates of the incidence rate of TIA range from 0.37 to 1.1 per 1000 person-years (AHA/ASA 2009).

Antiplatelet drugs are central to the management of ischaemic stroke and TIA. In the acute setting of non-cardioembolic cerebral ischaemic events, the cyclo-oxygenase inhibitor acetylsalicylic acid (ASA) is the antiplatelet therapy that has been most extensively studied. Current treatment guidelines recommend ASA to reduce the risk of death or subsequent stroke after acute ischaemic stroke (AIS)/TIA (Class I, Level of Evidence A) (AHA/ASA 2013, AHA/ASA 2014, ESO 2008).

The results of 3 studies, (1 in Canada and 1 in China and 1 primarily in the US), on the antiplatelet agent clopidogrel in combination with ASA suggest that dual antiplatelet therapy may improve outcomes in stroke/TIA patients when initiated in the acute setting (Kennedy et al 2007, Wang et al 2013, Johnston et al 2018). The latter was completed while this trial was ongoing. The combination of clopidogrel and ASA for treatment within 24 hours of a minor ischaemic stroke/TIA is also included in US treatment guidelines (Class IIb, Level of Evidence B) (AHA/ASA 2014), although there is no approved indication for clopidogrel in patients with AIS/TIA in the acute setting.

The efficacy and safety of ticagrelor monotherapy compared with ASA in preventing major vascular events in patients with AIS or TIA were evaluated in the AstraZeneca-sponsored SOCRATES study (Johnston et al 2016). Treatment was initiated within 24 hours of symptom onset and was continued for 90 days. There were numerically fewer primary endpoint events (stroke, myocardial infarction [MI], and death) in the ticagrelor group compared with the ASA group. However, the difference was not statistically significant. The majority of the primary endpoint events were strokes, and there were fewer strokes overall and ischaemic strokes in the ticagrelor group compared with the ASA group. A subgroup analysis indicated that the benefit of ticagrelor was greater in patients who received ASA within 7 days of randomisation, including those who received a single dose on Day 1. These patients would effectively have received dual antiplatelet therapy during the first days of the study.

Thus, while the SOCRATES study did not show ticagrelor monotherapy to be superior to ASA, these data suggest that dual antiplatelet therapy with ticagrelor and ASA could be a

promising treatment to prevent subsequent stroke events in patients with acute cerebral ischaemia.

Further information regarding the pharmacological class, mechanism of action, and clinical development programme of ticagrelor can be found in the Investigator's Brochure.

1.2 Rationale for study design, doses, and control groups

The study will be randomised, double-blind, placebo-controlled, and have a parallel-group design. Randomisation and double blinding will minimise potential bias. The study will be multicentre and conducted in numerous geographic regions, ensuring that a variety of nationalities, ethnicities, and races are represented and that the results of the study are widely applicable. Advice from the US Food and Drug Administration, European Medicines Agency, and China Food and Drug Administration was sought and taken into consideration during the design of the study.

Rationale for choice of study population

The target population will include patients ≥40 years of age with non-cardioembolic AIS or high-risk TIA randomised within 24 hours of symptom onset. The ≥40-year age cut-off was selected to minimise the number of patients with events stemming from rare causes (eg, dissection, coagulation disorders, and other inherited disorders), who are less likely to benefit from antiplatelet therapy.

To be eligible, patients with AIS must have a neurological deficit of acute onset indicative of focal ischaemia and a National Institute of Health Stroke Scale (NIHSS) score ≤5. The NIHSS is widely accepted, used both in clinical studies and in clinical practice, and a reliable and non-invasive way to measure stroke-related neurological deficits quantitatively, evaluate acuity of stroke patients, determine appropriate treatment, and predict functional outcome. The ≤5 NIHSS score cut-off was chosen as these patients have a substantial short-term risk of new ischaemic events and limited risk of intracranial haemorrhage (ICH).

To be eligible, patients with TIA must have a neurological deficit of acute onset attributed to focal ischaemia of the brain by history or examination with complete resolution of the deficit, and either an $ABCD^2$ score ≥6 or large-vessel occlusive arterial disease, ie, ipsilateral stenosis ≥50% of an extra- or intracranial artery.

The $ABCD^2$ score predicts the early risk of stroke after TIA, and is recommended by the American Stroke Association (AHA/ASA 2009). The score is reliable in predicting the risk of subsequent stroke within 2, 30, and 90 days after a TIA. The $ABCD^2$ score cut-off of ≥6 is different from that used in the SOCRATES study ($ABCD^2$ score ≥4). The cut-off of ≥6 was chosen to risk-enrich the TIA population further, as TIA patients with $ABCD^2$ scores ≥6 may be at particularly high risk for subsequent stroke events (Amarenco et al 2016). The higher cut-off may also reduce the risk of including TIA mimics, ie, patients later determined not to have had a true TIA (Josephson et al 2008).

Patients with ipsilateral stenosis (ie, extracranial or intracranial stenosis of a vessel supplying the ischaemic field) are at high risk of stroke (Amarenco et al 2016). Subgroup analyses of such patients in the SOCRATES study showed high stroke rates and suggested that these patients would benefit from ticagrelor treatment (Amarenco et al 2017).

The use of the NIHSS score ≤5 criterion for stroke patients and the $ABCD^2$ score ≥6 and ipsilateral stenosis criteria for TIA patients allows inclusion of a clinically well-defined study population of patients with similar and well-characterised risk levels.

Rationale for choice of dosing and control treatment

The investigational products (IP) are ticagrelor and placebo. Additionally, both treatment groups will be taking open-label ASA as a concomitant medication during the treatment period. Placebo with concomitant ASA treatment was chosen as the control treatment because ASA is the only antiplatelet therapy approved and recommended for use in patients for the acute management of ischaemic stroke, and is the standard-of-care treatment.

The 180 mg ticagrelor loading dose results in a rapid, high degree of inhibition of platelet activation (IPA) and the 90 mg twice daily maintenance dose showed high and consistent levels of IPA (Gurbel et al 2009). The ticagrelor dose is the same as that used in the target population of patients with ischaemic stroke or TIA in the SOCRATES study, in which it was well-tolerated and had a similar safety profile as ASA with respect to major bleedings. The same ticagrelor dose was effective and had an acceptable safety profile when administered concomitantly with ASA in the acute setting in patients with acute coronary syndrome in the PLATO study (Wallentin et al 2009).

Both treatment groups should be treated with ASA, with a 300 to 325 mg ASA loading dose followed by a 75 to 100 mg once daily maintenance dose recommended. Treatment guidelines recommend an ASA maintenance dose of 50 to 325 mg/day after a TIA or ischaemic stroke to prevent future strokes (AHA/ASA 2013, AHA/ASA 2014). Current US and EU prescribing information for the approved indications for ticagrelor recommend an ASA dose no higher than 100 mg (US) or 150 mg (EU) when treating with both ticagrelor and ASA. The ASA maintenance doses in this study align with the treatment guidelines and was considered optimal to maximise efficacy while minimising the risk for gastrointestinal toxicity and bleeding events.

Rationale for choice of treatment duration

Individuals who survive an ischaemic stroke or experience a TIA are at high risk for a subsequent ischaemic event in the early period after the initial event (Coull et al 2004, AHA/ASA 2009). In the SOCRATES study, most of the primary endpoint events (stroke, MI, and death) occurred during the first 30 days of the study (728 of 939 events). The 30-day treatment duration in this study therefore corresponds to the period during which the largest number of vascular events (eg, strokes) occur in this population. The early randomisation (within 24 hours of index event) will enable an assessment of treatment effect immediately after the initial event, when patients are the most vulnerable to subsequent events and may

benefit the most from dual antiplatelet therapy. Few other therapies are approved or have been investigated in large outcome trials during this early period.

Rationale for choice of endpoints

The primary endpoint (the composite of stroke and death[1]) was chosen as stroke is the most relevant outcome in this patient population, and as death is a competing risk to stroke. Patients with acute cerebral ischaemic events have a higher risk of stroke than of any other vascular outcome during the initial months after the event (Albers 2000, Petty et al 1998, AHA/ASA 2009). This was also true in the SOCRATES study, where 836 of 939 primary endpoint events (stroke, MI, and death) occurring during the 90-day treatment period were strokes (Johnston et al 2016). Stroke can be objectively and consistently assessed and represents a clinically meaningful event causing irreversible loss of organ function with important medical consequences.

Antiplatelet therapy may reduce subsequent ischaemic strokes in patients with AIS or TIA. However, because antiplatelet drugs increase the risk of bleeding, they could potentially increase the rate of haemorrhagic events. Inclusion of all strokes, including haemorrhagic strokes, in the primary endpoint therefore ensures that the net benefit of treatment with ticagrelor in preventing strokes is adequately captured. Additionally, bleedings classified as GUSTO Severe are included as a key safety endpoint. The GUSTO bleeding scale was chosen because it captures clinically relevant events, is widely used, and is easily applied.

The first secondary endpoint (ischaemic stroke) was chosen because prevention of ischaemic stroke is expected to be the main benefit of ticagrelor treatment. The second secondary endpoint (modified Rankin Scale [mRS] score >1) was chosen to assess potential differences in disability as a result of study treatment.

1.3 Benefit/risk and ethical assessment

Patients who experience ischaemic stroke or TIA are at high risk for subsequent stroke events even when treated with ASA, the current standard of care. Because the risk for a new stroke is highest soon after the initial event, urgent initiation of treatment is warranted. However, treatment options are limited, particularly in the acute time-frame after the initial event.

Major bleeding is the most important risk for all antiplatelet agents, and the risk for intracerebral bleeding is particularly important to consider in patients with AIS. The risk for intracerebral bleeding is mitigated in this study by including patients with non-severe AIS (NIHSS ≤5) and excluding patients with acute or previous intracerebral haemorrhage.

In the recent SOCRATES study, ticagrelor and ASA monotherapy were compared in a similar population to that of the current study. Although the primary endpoint of the SOCRATES study was not statistically significant, the results indicated a positive benefit-risk profile when

[1] The term “stroke” in this document refers to all-cause stroke (ischaemic and haemorrhagic), and the term “death” refers to all-cause death.

analysing the number of subsequent strokes prevented in relation to the occurrence of ICH and fatal bleeding events.

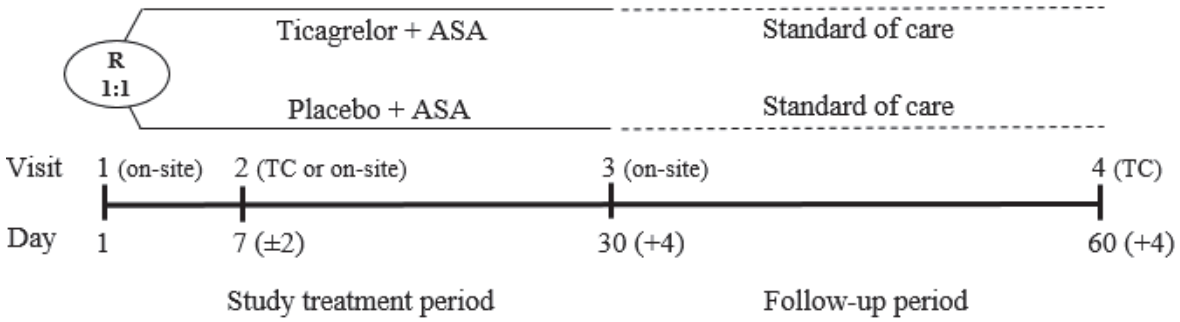
The available data suggest a positive benefit-risk profile for dual antiplatelet treatment with ticagrelor and ASA in patients with AIS or high-risk TIA, and the efficacy of the treatment in preventing stroke events is expected to be greater compared with that of ASA, the current standard of care. However, this treatment could only be made available to patients if proven to be statistically significantly superior to ASA in a randomised controlled trial. AstraZeneca therefore considers the proposed study justified from an ethical standpoint.

1.4 Study design

This is a randomised, placebo-controlled, double-blind, parallel-group, international, multicentre Phase III study to test the hypothesis that ticagrelor and ASA is superior to ASA in preventing stroke and death in patients with acute cerebral ischaemia. Patients with AIS or TIA before randomisation who fulfil all of the inclusion criteria (see Section 3.1) and none of the exclusion criteria (see Section 3.2) will be randomised within 24 hours of symptom onset in a 1:1 ratio to ticagrelor or placebo, with all patients receiving ASA. The study includes 4 visits: on Day 1 (enrolment/randomisation; Visit 1), on Day 5 to 9 (Visit 2), on Day 30 to 34 (end of treatment period; Visit 3), and on Day 60 to 64 (end of follow-up period; Visit 4) (Figure 1).

A loading dose of 180 mg ticagrelor or placebo will be given on Day 1 as soon as possible after randomisation. Therefore, IP should be available for dispensation at the time of randomisation. Thereafter, patients will receive either ticagrelor 90 mg twice daily or placebo twice daily. All patients should be treated with open-label ASA. Patients should receive an ASA loading dose on Day 1. The recommended loading dose is 300 to 325 mg ASA. Thereafter, patients should be treated with ASA 75 to 100 mg once daily. Additionally, patients should receive medical treatment and be counselled on lifestyle modifications for cerebrovascular risk factors according to local and global guidelines.

Figure 1 Study design



ASA (concomitant medication) = open-label. Loading dose at the Investigator's discretion (300 to 325 mg recommended) followed by 75 to 100 mg once daily.
Ticagrelor (investigational product) = 180 mg loading dose followed by 90 mg twice daily
ASA acetylsalicylic acid; R randomisation; TC telephone contact

Approximately 11 000 patients will be randomised at approximately 450 study sites. The study is event-driven and the final number of randomised patients will be determined based on blind data review.

A data monitoring committee (DMC) (see Section 7.1.3) will conduct an interim analysis for efficacy after approximately 70% of the primary events have been collected.

2. STUDY OBJECTIVES

2.1 Primary objective

Primary objective	Variables
To demonstrate superior efficacy of ticagrelor and ASA compared with placebo and ASA in AIS/TIA patients in the prevention of the composite of stroke and death at 30 days	Time from randomisation to first subsequent stroke or death

2.2 Secondary objectives

Secondary objective	Variables
To demonstrate superior efficacy of ticagrelor and ASA compared with placebo and ASA in AIS/TIA patients in the prevention of ischaemic stroke at 30 days	Time from randomisation to first subsequent ischaemic stroke
To demonstrate superior efficacy of ticagrelor and ASA compared with placebo and ASA in AIS/TIA patients in reducing overall disability at 30 days	mRS score >1 at Visit 3

2.3 Safety objective

Safety objective	Variables
To assess the safety of ticagrelor and ASA compared with that of placebo and ASA in AIS/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

2.4 Exploratory objectives

Exploratory objectives	Variables
To assess the efficacy of ticagrelor and ASA compared with placebo and ASA in AIS/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
To assess the efficacy of ticagrelor and ASA compared with placebo and ASA in AIS/TIA patients in reducing disabling stroke at 30 days	mRS score >2 at Visit 3 in patients with subsequent stroke
To describe health-related quality of life in AIS/TIA patients after treating with ticagrelor and ASA or placebo and ASA for 30 days	EQ-5D-5L profile

3. PATIENT SELECTION, ENROLMENT, RANDOMISATION, RESTRICTIONS, DISCONTINUATION, AND WITHDRAWAL

The study population is defined as patients ≥40 years of age who have experienced a non-cardioembolic AIS (NIHSS score ≤5) OR high-risk TIA (defined as ABCD^2 score[2] ≥6 or ipsilateral atherosclerotic stenosis ≥50% in an extra/intracranial artery) who could be randomised within 24 hours of symptom onset.

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

3.1 Inclusion criteria

For inclusion in the study, patients should fulfil the following criteria:

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) AIS with NIHSS ≤5. AIS is defined as acute onset of neurological deficit attributed to focal brain ischaemia, and either of the following:

[2] ABCD^2 score is a clinical score based on: age, blood pressure, clinical features, duration of TIA and diabetes.

- Persistent signs or symptoms of the ischaemic event at the time of randomisation, OR

- Acute ischaemic brain lesion documented before randomisation by computed tomography (CT) scan or magnetic resonance imaging (MRI) (diffusion-weighted imaging) and that could account for the clinical presentation

(b) High-risk TIA, defined as neurological deficit of acute onset attributed to focal ischaemia of the brain by history or examination with complete resolution of the deficit, and at least one of the following:

- $ABCD^2$ score ≥6 and TIA symptoms not limited to isolated numbness, isolated visual changes, or isolated dizziness/vertigo

- Symptomatic intracranial arterial occlusive disease that could account for the clinical presentation, documented by transcranial Doppler or vascular imaging and defined as at least 50% narrowing in the diameter of the vessel lumen

- Internal carotid arterial occlusive disease that could account for the clinical presentation, documented by Doppler, ultrasound, or vascular imaging and defined as at least 50% narrowing in diameter of the vessel lumen

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

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

3.2 Exclusion criteria

Patients fulfilling any of the exclusion criteria must not be randomised.

1. Need for or an anticipated need for any of the following:

(a) Dual antiplatelet therapy with ASA and $P2Y_{12}$ 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 investigational product within 3 days of randomisation or is expected to require unblinding of investigational product (planned carotid endarterectomy is in itself not an exclusion criterion)

5. History of previous intracranial haemorrhage 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 3A (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 investigational product at any time during the 30 days prior to randomisation (regardless of when treatment with the investigational product was discontinued)

3.3 Patient enrolment and randomisation

Investigator(s) should keep a record, the patient screening log, of patients who entered pre-study screening. The Investigator(s) will:

1. Obtain signed informed consent from the patient and/or legal representative before any study specific procedures are performed

2. Assign (using the Interactive Voice/Web Response System [IxRS], see Section 3.5) each patient a unique enrolment number, beginning with 'E#'

3. Determine patient eligibility (see Section 3.1 and 3.2)

4. Obtain unique randomisation code (patient number) for each eligible patient from IxRS (see Section 3.5)

If a patient withdraws from participation in the study, then his/her enrolment/randomisation code cannot be reused. Only the enrolment number will be used for patient identification in the eCRF.

3.4 Procedures for handling incorrectly enrolled or randomised patients

Patients who are enrolled but subsequently found not to be eligible (eg, not meeting all of the inclusion criteria or fulfilling any of the exclusion criteria) must not be randomised or initiated on treatment.

If a patient is not eligible but is randomised in error, or incorrectly started on treatment, the Investigator should inform the AstraZeneca representative immediately, and a discussion should occur between the Investigator and the AstraZeneca study physician (usually via the AstraZeneca representative) regarding whether to continue or discontinue the patient from treatment. Treatment must be discontinued in all cases where continued treatment is deemed to pose a safety risk to the patient. The AstraZeneca study physician must ensure that all

decisions, including the rationale for continuing or discontinuing treatment, are appropriately documented.

Regardless of whether study treatment is discontinued, the patient should still remain in the study for follow-up in accordance with defined study procedures including follow-up of endpoints. The majority of patients will have their vital status collected at V4. For unforeseen potentially lost to follow-up patients, efforts will be made to collect the vital status until data base lock, which is consistent with the intention-to-treat principle.

3.5 Methods for assigning treatment groups

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

3.6 Methods for ensuring blinding

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

No member of the extended study delivery team at AstraZeneca, personnel at investigational centres, or any contract research organisation handling study data will have access to the randomisation scheme during the study. The AstraZeneca personnel or delegate generating the randomisation scheme and the Supply Chain Study Management department may be able to access the randomisation scheme.

3.7 Methods for unblinding

The treatment code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment allocation. Individual treatment codes, indicating the treatment allocation for each randomised patient, will be available to the Investigator(s) or pharmacists from the IxRS. Routines for unblinding will be described in the IxRS user manual that will be provided to each centre. The Investigator documents and reports the action and its rationale to AstraZeneca, without revealing the treatment given to the patient to the AstraZeneca staff.

The number of individuals at the study site who become aware of the treatment status should be kept to an absolute minimum, including keeping the patient blinded if possible. Treatment with IP should be continued, or re-initiated if interrupted, if considered appropriate.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational product (IP) and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented.

Unblinding for data monitoring committee (DMC)

An independent DMC will review accumulating study data by treatment group in order to monitor patient safety and efficacy, ensure the validity and integrity of the study, and make a benefit/risk assessment. The DMC will have access to unblinded data. The personnel involved in the clinical study at AstraZeneca will have no knowledge of unblinded results presented to the DMC. For details, see the DMC Charter.

3.8 Restrictions

Patients should not donate blood or bone marrow at any time during the study period. Restrictions regarding concomitant medications are described in Section 8.7.

3.9 Discontinuation of investigational product

At any time, patients are free to discontinue IP without prejudice to further treatment. IP refers to ticagrelor or placebo.

3.9.1 Management of IP in case of dyspnoea or bleeding

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

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

Platelet transfusion did not reverse the antiplatelet effect of ticagrelor in healthy volunteers. There is currently no available antidote to reverse the effects of ticagrelor, and ticagrelor is not expected to be dialyzable. For further details, see the Investigator's Brochure.

3.9.2 Procedures for discontinuation of IP

The patient should contact the site before or at the time IP is stopped. A patient who decides to discontinue IP will always be asked about the reason(s) and the presence of any adverse events (AEs). The date of last intake of IP should be documented in the eCRF. All IP should

be returned by the patient at their next on-site study visit or unscheduled visit. Patients permanently discontinuing IP should be given standard-of-care therapy, at the discretion of the Investigator.

Premature discontinuation of IP, for any reason, does not impact on the patient's participation in the study. The patient should continue attending subsequent study visits and data collection should continue according to the Clinical Study Protocol (CSP). If the patient does not agree to continue in-person study visits, a modified follow-up must be arranged and documented in medical records to ensure the collection of endpoints and safety information. This could be a telephone contact with the patient at Visit 3 and 4, a contact with a relative or treating physician, or information from medical records. A patient that agrees to modified follow-up is not considered to have withdrawn consent or to have withdrawn from the study.

3.9.3 Criteria for temporary discontinuation of IP

If IP must be temporarily discontinued, it should be restarted as soon as possible. Reasons for temporary discontinuation of IP include:

- Severe thrombocytopenia (platelet count <50,000/uL). Patients may restart IP once the severe thrombocytopenia resolves
- Major bleeding, see Section 3.9.1
- Surgery or procedures associated with major haemorrhage, see Section 8.7.2
- Need for treatment with prohibited concomitant medications, see Section 8.7.1

IP may be continued or interrupted temporarily for other surgery or invasive procedures at the discretion of the Investigator (see Section 8.7.2).

3.9.4 Criteria for permanent discontinuation of IP

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment
- Investigator's decision, including but not limited to these examples:
  - Incorrectly randomised patient in whom the inclusion/exclusion criteria violation would put the patient at undue risk
  - AE for which the Investigator thinks continued treatment may put the patient at undue risk, regardless of whether the AE is thought to be related to IP
  - Severe non-compliance to protocol
  - Pregnancy
  - Atrial fibrillation for which the patient receives anticoagulation therapy

3.10 Withdrawal of consent

Patients who are enrolled but not randomised (eg, because they do not fulfil the eligibility criteria) are not considered to have withdrawn from the study. Patients who are enrolled but not randomised will be recorded as "screening failures" in the eCRF.

Patients are free to withdraw from the study at any time, without prejudice to further treatment. Discontinuation of IP is not a reason to withdraw from the study. A patient who considers withdrawing from the study must be informed by the Investigator about modified follow-up options (eg, telephone contact at Visit 3 and 4, a contact with a relative or treating physician, or information from medical records). Withdrawal of consent must be ascertained (ie, patient must have been informed of the option of modified follow-up and subsequently refused any type of follow-up) and documented by the Investigator in the medical records and recorded in the eCRF.

A patient who withdraws consent will always be asked about the reason(s) and the presence of any AE. The contact must be recorded in the eCRF as a scheduled/unscheduled visit. The Investigator will follow up serious AEs (SAEs)/premature permanent discontinuations of IP due to AEs (DAEs) outside of the clinical study. AstraZeneca or its delegate will request Investigators to collect information on patients' Day 60 vital status (dead or alive; date of death when applicable) from publicly available sources, in accordance with local regulations. Knowledge of the Day 60 vital status in all patients is crucial for the integrity of the study.

3.11 Termination of the study

The study may be terminated if, in the judgment of AstraZeneca, trial patients are placed at undue risk. The judgment may be based on recommendations from the DMC (see the DMC Charter for details). In terminating the study, AstraZeneca will ensure that adequate consideration is given to the protection of the patients' interests.

4. STUDY PLAN AND TIMING OF PROCEDURES

Table 1 Study plan

Visit	**1**	**2**	**3**	**4**	**For details see section:**
Day	**1**	**7 (±2 days)**	**30 (+4 days)**	**60 (+4 days)**	
Signed informed consent	√				
Eligibility criteria	√				3.1, 3.2
Specific medical and surgical history	√				
Smoking status	√				
Demographics	√				

Visit	1	2	3	4	For details see section:
Day	**1**	**7 (±2 days)**	**30 (+4 days)**	**60 (+4 days)**	
Weight and height	√				
BP and heart rate	√		√		
NIHSS score	√				Appendix A
ABCD^2 score for TIA patients	√				5.3.1
Cerebrovascular atherosclerosis phenotyping	√				5.3.4
EQ-5D-5L	√		√		Appendix B
Dispense IP	√				
Compliance reminder		√			8.5
mRS score			√		5.3.5
Return IP			√		
Compliance/drug accountability			√		8.5, 8.6
Concomitant medications	√	√	√	√	8.7
SAEs, DAEs, and endpoints[a]	√	√	√	√	5.1, 6

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

BP blood pressure; DAE premature permanent discontinuation of IP due to adverse event; IP investigational product; mRS modifed Rankin scale; NIHSS National Institute of Health Stroke Scale; rand randomisation, SAE serious adverse event, TIA transient ischaemic attack

4.1 Visit 1, enrolment/randomisation (Day 1)

Consenting patients are assessed to ensure they are eligible for the study (meet all inclusion criteria and none of the exclusion criteria), including by evaluation of ECG and CT/MRI or vessel imaging performed as standard of care. Patients who are not eligible must not be randomised in the study.

Patients should be enrolled/randomised as soon as possible and within 24 hours after onset of symptoms. For wake-up strokes (when the time of symptom onset is not known), patients should be randomised within 24 hours from the time point at which the patient was reported to be in their normal condition.

The following will occur during Visit 1, which is an on-site visit:

- Obtaining of signed informed consent before any study-related procedures
- Assignment of an E-code in IxRS to the patient
- Confirmation of patient eligibility
- For patients not eligible for randomisation:
  - Collection of data in CRF (visit date; date of informed consent; eligibility criteria; reason for non-randomisation; SAEs; demography). If the patient has an SAE, data on specific medical and surgical history and concomitant medications will also be collected.
- For patients eligible for randomisation:
  - Randomisation using IxRS
  - Dispense IP, and ensure the loading dose is available at the time of randomisation
  - Ensure patient has received loading dose of ASA and has been prescribed ASA
  - Collection of data in CRF (visit date; date of informed consent; eligibility criteria [including NIHSS score, $ABCD^2$ score for TIA patients, and the presence of ipsilateral stenosis at randomisation]; specific medical and surgical history; concomitant medications; endpoints, SAEs, and DAEs; demography; smoking status; weight and height; blood pressure and heart rate; cerebrovascular atherosclerosis phenotyping of index event; EQ-5D-5L)

4.2 Visit 2 (Day 7 ±2 days)

The following will occur during Visit 2, which can be a telephone contact or on-site visit:

- Collection of data in CRF (visit date; type of visit; endpoints, SAEs, and DAEs; concomitant medications)
- Remind the patient of the importance of compliance with IP and other medications, either by TC or during hospitalisation

If an SAE/DAE or endpoint is reported by telephone, an unscheduled visit to evaluate the patient may be needed (at the Investigator's discretion).

4.3 Visit 3, end of treatment period (Day 30 +4 days)

The following will occur during Visit 3, which is an on-site visit:

- Collection of data in CRF (visit date; type of visit; endpoints, SAEs, and DAEs; blood pressure and heart rate; mRS; return of IP; drug accountability; concomitant medications; EQ-5D-5L)
- Return of IP
- Initiation of standard-of-care therapy (treatment[s] at the Investigator's discretion)

4.4 Visit 4, end of follow-up period (Day 60 +4 days)

The following will occur during Visit 4, which is a telephone contact:

- Collection of data in CRF (visit date; type of visit; endpoints and SAEs; concomitant medications)

4.5 Unscheduled visits

An unscheduled visit may occur in-between scheduled visits, eg, to follow up on potential endpoint events, to initiate standard-of-care therapy after IP discontinuation, or to evaluate SAEs/DAEs.

5. STUDY ASSESSMENTS

The Rave Web Based Data Capture (WBDC) system will be used for data collection and query handling. The Investigator will ensure that data are recorded on the eCRF as specified in the CSP and in accordance with the instructions provided.

The Investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement (CSA). The Investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

Endpoints will be identified using standard questioning of the patient at each visit, or by information that the Investigator may receive as part of standard medical practice. It is essential that Investigators collect all relevant and required endpoint data as soon as possible. For each suspected endpoint, the Investigator will record information specific to that type of endpoint on the eCRF.

5.1 Efficacy assessments

5.1.1 Stroke

The definition for stroke is based on the standardised definitions for endpoints (Hicks et al 2015). All strokes occurring post-enrolment will be recorded as SAEs. All strokes occurring post-randomisation will be considered endpoints. Stroke is defined as an acute episode of focal or global neurological dysfunction caused by cerebral vascular injury as a result of infarction or haemorrhage not caused by trauma. Investigators will classify strokes into 1 of 3

mutually exclusive categories: ischaemic, haemorrhagic, or undetermined. Whenever possible, stroke diagnoses should be confirmed using neuroimaging (CT or MRI) to minimise the number of strokes classified as "undetermined".

5.1.1.1 Ischaemic stroke

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

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

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

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

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

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

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

5.1.1.2 Haemorrhagic stroke

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

5.1.1.3 Undetermined category of stroke

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

5.1.2 Death

All deaths occurring post-enrolment will be recorded as SAEs with fatal outcome. All deaths occurring post-randomisation will be considered endpoints.

5.2 Safety assessments

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

Table 2 GUSTO definitions

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

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

5.3 Other assessments

5.3.1 ABCD^2 score

The ABCD^2 score is a risk assessment tool designed to improve the prediction of short-term stroke risk after a TIA. The score is optimised to predict the risk of stroke within 2 days after a TIA, but also predicts stroke risk within 30 and 90 days. The ABCD^2 score is calculated by summing points for 5 independent factors (Table 3).

Table 3 ABCD^2 score

Risk Factor	Points
Age ≥60 yrs	1
BP ≥140/90 mmHg[a]	1
Clinical features	
speech disturbance without weakness	1
unilateral weakness	2
Duration of TIA	
10–59 minutes	1
≥60 minutes	2
Diabetes	1

[a] Systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg (first assessment after TIA)
BP blood pressure; TIA transient ischaemic attack

5.3.2 NIHSS score

NIHSS scores at the time of randomisation will be collected for all patients to verify patient eligibility. The scores will also be used in the analysis of the disability endpoint to adjust for baseline stroke severity. A patient with an index event of TIA may have a NIHSS score above 0 if the patient has remaining neurological deficit from a previous cerebrovascular event. See Appendix A for the NIHSS questionnaire.

5.3.3 Vessel imaging for assessment of symptomatic ipsilateral stenosis

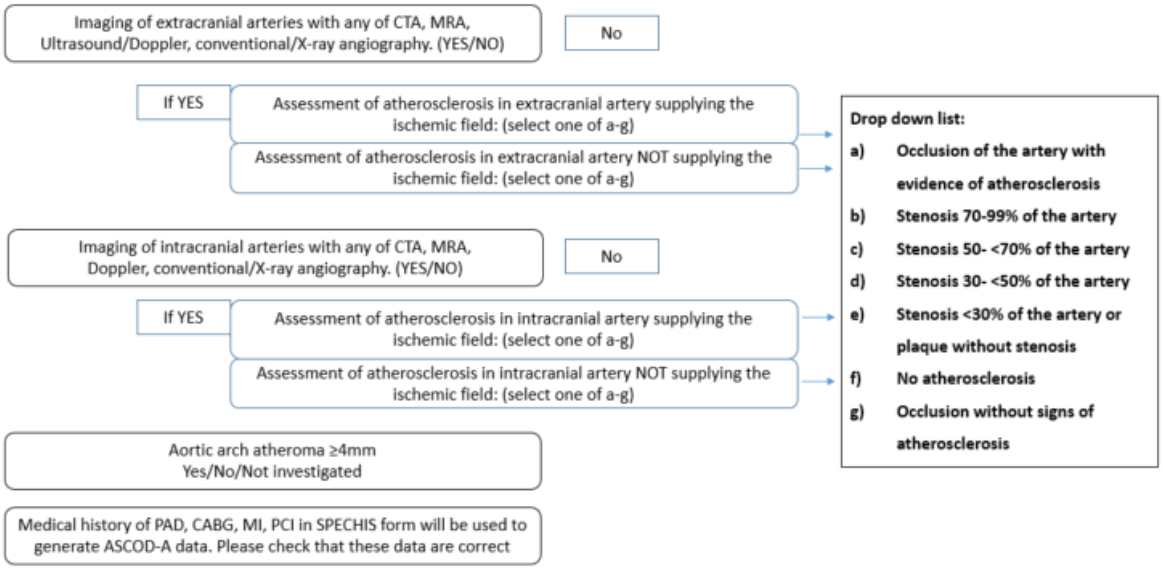
For TIA patients, the presence of symptomatic ipsilateral stenosis is a potential eligibility criterion. Presence of known symptomatic ipsilateral stenosis should be recorded for all patients at randomisation.

5.3.4 Cerebrovascular atherosclerosis phenotyping

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

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

Figure 2 Cerebrovascular atherosclerosis phenotyping



CABG coronary artery bypass grafting; CTA computed tomography angiography; MRA magnetic resonance angiography; PAD peripheral artery disease; PCI percutaneous coronary intervention

5.3.5 mRS score

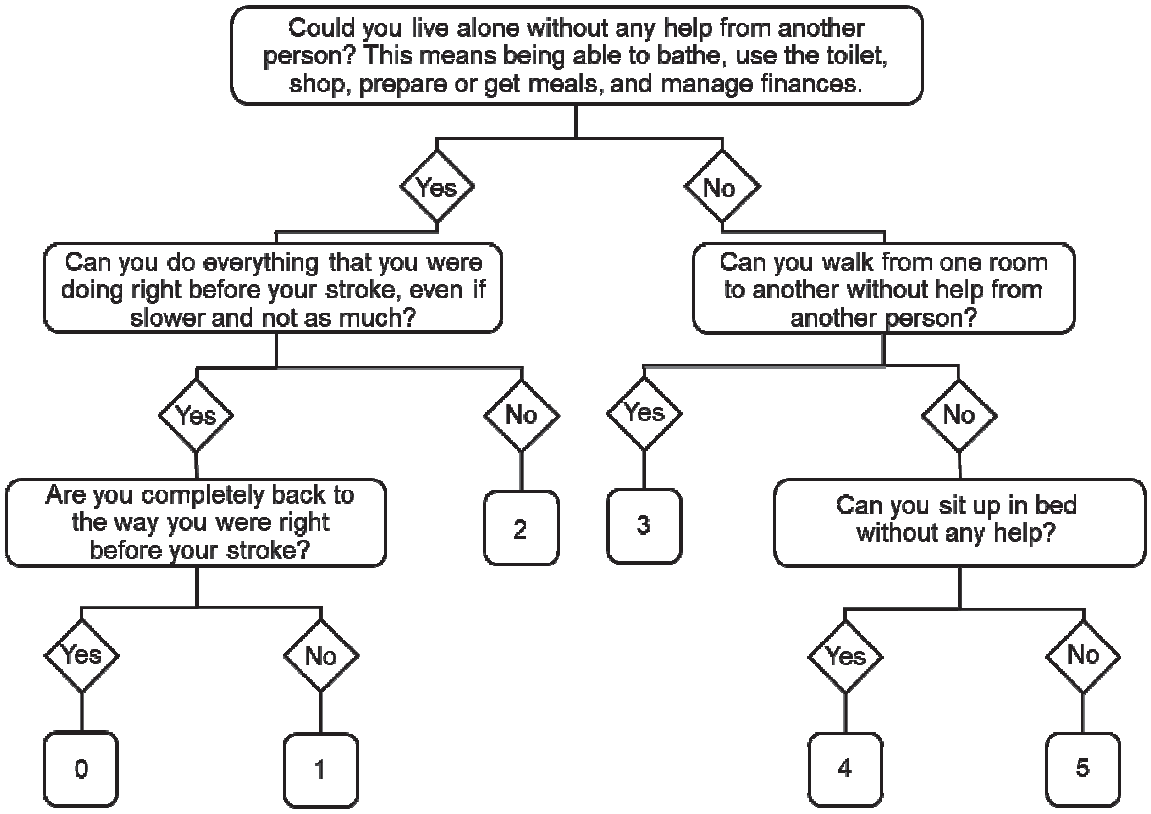
mRS scores will be collected for all patients at Visit 3. No mRS scores will be collected on Visit 1; NIHSS scores at Visit 1 will be used to adjust for baseline stroke severity. The following questionnaire will be used to determine the mRS score:

Table 4 mRS scores

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

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

Figure 3 Simplified modified Rankin Scale questionnaire



Derived from Bruno et al 2011

5.3.6 EQ-5D-5L

The EQ-5D-5L questionnaire, developed by the EuroQol Group, will be used to explore the impact of treatment and disease state (eg, the occurrence of stroke) on health state utility values. The EQ-5D-5L questionnaire will be filled in by the patients or, if needed, by a proxy (site personnel or family member). Study staff will transfer the responses into the eCRF. All patients will be asked to complete EQ-5D-5L questionnaire at Visit 1 and Visit 3. The questionnaire will only be administered in countries where an official language version is available. See Appendix B for an English version of the questionnaire.

The EQ-5D-5L profile will be converted into a weighted health state utility value, termed the EQ-5D-5L index, by applying a country-specific equation to the EQ-5D-5L profile that represents the comparative value of health states. This equation is based on national valuation sets elicited from the general population and the base case will be the UK perspective. The EQ-Visual Analogue Scale component of the questionnaire is reported separately. The EQ-5D-5L data will be combined with economic data and life expectancy data collected independently of the study for health economic analyses.

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

6.1 Definition of AE

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver), or the abnormal results of an investigation (eg, laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered. The term AE is used to include both serious and non-serious AEs.

In this study, serious AEs (SAEs) and premature permanent discontinuations of IP due to AEs (DAEs) will be collected.

6.2 Definition of SAE

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above.

For further details, see Appendix C.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria above. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria above. Conversely, it is possible for an event to be mild in intensity but still be considered an SAE if it fulfils the criteria above.

6.3 Recording of AEs

6.3.1 Time period for collection of AEs

SAEs will be recorded from the time of informed consent. DAEs will be recorded from the first intake of IP until Visit 3 (ie, the end of the treatment period).

6.3.2 Follow-up of unresolved AEs

Any AEs that are unresolved at the patient's last visit in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the CRF. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

6.3.3 Variables

The following variables will be collected for each AE fulfilling SAE or DAE critera:

- AE (verbatim)
- The date when the AE started and stopped
- Maximum intensity
- Whether the AE is serious or not
- Investigator causality rating against the IP (yes or no)
- Action taken with regard to IP
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date Investigator became aware of SAE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed

- Causality assessment in relation to study procedure(s)
- Causality assessment in relation to other medication
- Description of AE

In addition, the following variables will be collected for all bleedings fulfilling SAE/DAE criteria:

- GUSTO classification
- Provocation

6.3.4 Causality collection

The Investigator will assess causal relationship between IP (ticagrelor/placebo) and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

For SAEs, causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'. See Appendix C for a guide to the interpretation of the causality question.

6.3.5 AEs based on signs and symptoms

All SAEs and DAEs spontaneously reported by the patient or reported in response to the open question from the study personnel: 'Have you had any health problems since the previous visit?', or revealed by observation will be recorded in the CRF.

When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

6.3.6 AEs based on examinations and tests

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom should be reported as an AE, if fulfilling SAE or DAE criteria, and the associated laboratory result/vital sign will be considered as additional information. Whenever possible, the reporting Investigator uses the clinical rather than the laboratory term (eg, anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s), if fulfilling SAE or DAE criteria.

6.3.7 Bleedings

Bleedings should be recorded as SAEs/DAEs when appropriate. The Investigator should also classify the severity of the bleeding according to GUSTO bleeding definitions (see Section 5.2) and by provocation. Bleeding associated with procedures should only be reported as an

SAE/DAE if it exceeds what can be expected for the procedure. See Section 3.9.3 for management of IP in case of bleeding.

6.3.8 Myocardial infarctions

MIs are not endpoints in this study but should be recorded as SAEs (and DAEs when appropriate). The diagnosis of an MI should be made according to standard clinical practice but is expected to align with the criteria from Third Universal Definition of MI, ie, detection of a rise and/or fall of cardiac biomarkers such as troponin and at least one of the following: typical clinical symptoms, ischaemic ECG findings, imaging evidence of myocardial injury, or detection of an intracoronary thrombus by angiography or autopsy (Thygesen et al 2012). The diagnosis should be made by, or in consultation with, a cardiologist. The findings supporting the diagnosis should be documented in the description of the SAE in the eCRF.

6.4 Reporting of SAEs

All SAEs have to be reported to the appropriate AstraZeneca representative, whether or not considered causally related to the IP, or to the study procedure(s). All SAEs will be recorded in the CRF.

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate AstraZeneca representatives within 1 day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it. The designated AstraZeneca representative works with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within 1 calendar day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the WBDC system, an automated email alert is sent to the designated AstraZeneca representative. If the WBDC system is not available, then the Investigator or other study site personnel reports a SAE to the appropriate AstraZeneca representative by telephone. The AstraZeneca representative will advise the Investigator/study site personnel on how to proceed.

6.4.1 Reporting of SAEs that are also endpoints in the study

Efficacy endpoints should be reported by Investigator and AZ representatives according to same timelines as for all SAEs. Efficacy endpoints in the study (stroke, death) will not be reported to health authorities as SAEs by the Sponsor to avoid unnecessary unblinding of efficacy endpoints that are also SAEs.

6.5 Recording of cerebrovascular interventions

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

6.6 Overdose

An overdose is defined as an intake of greater than 4 tablets of IP (ticagrelor or placebo) per day. In the event of an overdose with ticagrelor, the Investigator must ascertain the time and extent of the overdose regardless of severity. The Investigator should determine the causative circumstance and whether haemorrhagic or toxic complications have occurred or are likely to do so. Depending on these facts, the Investigator must decide whether the patient should be hospitalised for observation or not. Bleeding is one of the most likely pharmacological effects of excessive ticagrelor dosing, and appropriate supportive measures such as volume replacement, local haemostatic measures, and decompression or drainage may be required depending on the extent of bleeding or volume of blood lost. Patients with overdose-related bleeding should be cautioned to avoid unnecessary activity, mechanical tissue stress, and minor trauma for at least 24 hours after the bleeding has stopped. For other symptoms that can be expected after an overdose of ticagrelor and additional information, see the Investigator's Brochure.

An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF, if SAE/DAE criteria are fulfilled, and on the Overdose CRF module. An overdose without associated symptoms is only reported on the Overdose CRF module.

If an overdose on an AstraZeneca IP occurs in the course of the study, then the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it. The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site. For overdoses associated with a SAE, the standard reporting timelines apply (see Section 6.4). For other overdoses, reporting must occur within 30 days.

6.7 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca. If a patient becomes pregnant during the course of the study, IP should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it. The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 6.4) and within 30 days for all other pregnancies. The same timelines apply when outcome information is available.

The PREGREP module in the CRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.

6.8 Medication error

For the purposes of this clinical study, a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study drug that either causes harm to the patient or has the potential to cause harm to the patient.

A medication error is not lack of efficacy of the drug, but rather a human or process-related failure while the drug is in control of the study site staff or patient.

Medication error includes situations where an error:

- occurred
- was identified and intercepted before the subject received the drug
- did not occur, but circumstances were recognized that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error, eg, medication prepared incorrectly, even if it was not actually given to the subject
- Drug not administered as indicated, eg, wrong route or wrong site of administration
- Drug not taken as indicated, eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed, eg, kept in the fridge when it should be at room temperature
- Wrong patient received the medication (excluding IxRS errors)
- Wrong drug administered to patient (excluding IxRS errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IxRS, including those which lead to one of the above listed events that would otherwise have been a medication error
- Subject accidentally missed drug dose(s), eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Patient failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard-of-care medication in open-label studies, even if an AstraZeneca product

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

If a medication error occurs during the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within 1 or 5 calendar days if there is an SAE associated with the medication error (see Section 6.4) and within 30 days for all other medication errors.

7. STUDY GOVERNANCE AND OVERSIGHT

7.1.1 Executive Committee

The Executive Committee (EC) will be responsible for the overall design, interpretation, supervision, and reporting (presenting at international congresses and publishing in peer-reviewed journals) of the study, including the development of the CSP and any CSP amendments. The EC will make recommendations to AstraZeneca with regard to early stopping or modifications of the study based on the information received from the DMC. The EC will be comprised of designated international academic leaders and non-voting AstraZeneca representatives, and will operate under a separate charter.

7.1.2 Steering Committee

The International Steering Committee is comprised of national lead investigators from each country where the study is conducted and will be supervised by the EC. Members of the committee will be responsible for providing clinical guidance on study implementation and conduct in their respective countries.

7.1.3 Data Monitoring Committee

An independent DMC will be appointed and will report to the EC. The DMC will be responsible for safeguarding the interests of the patients by assessing the benefit/risk profile of the intervention during the study, and for reviewing the overall conduct of the study. The

DMC will review all safety and efficacy data (endpoint data, SAEs, DAEs), overall and by region, on an ongoing basis. The DMC will have access to the individual treatment codes and will be able to merge these with the collected study data while the study is ongoing. If the DMC expresses safety concerns that suggest study conduct should be amended, information will be sent to the EC and regulatory authorities. The DMC will also conduct an interim analysis for efficacy (see Section 9.5.6). The DMC Charter details roles, responsibilities, and procedures to ensure maintenance of the blinding and integrity of the study.

8. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

At randomisation (Visit 1/Day 1), eligible patients will be randomly assigned to 1 of 2 treatments: ticagrelor or placebo (IP). In addition, all patients should be treated with open-label ASA, which will not be supplied by AstraZeneca. Treatments will be given orally with loading doses on Day 1 followed by maintenance treatment until Visit 3/Day 30.

8.1 Identity of investigational product

Investigational product	Dosage form and strength	Manufacturer
Ticagrelor 90 mg	Plain, round, yellow, film-coated tablet, 90 mg	AstraZeneca
Ticagrelor 90 mg placebo	Plain, round, yellow, film-coated tablet, placebo to match 90 mg	AstraZeneca

8.2 Dose and treatment regimens

8.2.1 Investigational product

Patients will be treated with:

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

8.2.2 Concomitant ASA treatment

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

8.2.3 Timing of loading doses and first maintenance doses

Randomisation and treatment pack assignment will be managed via the IxRS, and the first doses of IP and ASA (loading doses) should be taken on Day 1.

Ticagrelor/placebo

Patients should be randomised as soon as possible after symptom onset, and the loading dose of ticagrelor/placebo should be given immediately after randomisation.

The first maintenance dose should be given >6 to ≤12 hours after the loading dose. The second maintenance dose should 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 should be taken morning and evening at approximately 12-hour intervals for the remainder of the treatment period.

ASA

The ASA loading dose should be given on Day 1 (as directed in Section 8.2.2) and the first maintenance dose of ASA should be taken in the morning of Day 2.

8.3 Labelling

Labels will be prepared in accordance with Good Manufacturing Practice and local regulatory guidelines. The labels will fulfil Good Manufacturing Practice Annex 13 requirements for labelling. Label text will be translated into local language.

8.4 Storage

All IPs should be kept in a secure place under appropriate storage conditions. The IP label specifies the appropriate storage.

8.5 Compliance

At Visit 1, patients will receive enough IP to last until Visit 3. The administration of all IPs should be recorded in the appropriate sections of the eCRF. At Visit 2, any patient found to be non-compliant will be counselled on the importance of taking their IP as prescribed. Patients will be asked to return all unused IP and empty packages to the clinic at Visit 3. The amount of returned tablets for each patient should be verified by an AstraZeneca representative.

8.6 Accountability

The IP provided for this study will be used only as directed in the CSP. The study personnel will account for all IP dispensed to and returned from the patient.

The eCRF includes information regarding identification of the person to whom the drug is dispensed, the quantity dispensed, the date of dispensing, the quantity returned, and the date returned. Any IP deliberately or accidentally destroyed must be recorded. Any discrepancy between dispensed and returned IP should be explained.

Patients will be asked to return all unused IPs and empty packages to the clinic at Visit 3. The Investigator will retain the returned medication, along with any medication not dispensed, until the trial monitor or delegate collects it. The monitor or delegate is responsible for

confirming that the quantities of returned and unused tablets for each patient has been recorded before the medication is destroyed. Unused IP (including empty bottles) will be destroyed according to local procedure at an authorised site. Certificates of delivery, return, and destruction must be signed by an AstraZeneca representative.

8.7 Concomitant medications and other treatments

Recording of concomitant medications will be made at all visits, including all changes within 30 days prior to randomization and during study treatment and follow-up period. Particular attention should be given to antithrombotic medications, antihypertensives, lipid-lowering drugs including statins, insulin, and oral glucose-lowering drugs.

Prohibited medications are medications that cannot be given concomitantly with IP; however, they may be given during the study after temporary or permanent discontinuation of IP without constituting a protocol deviation.

8.7.1 Concomitant medications

Medications considered necessary for the patient's health, other than those described below, may be given at the discretion of the Investigator.

All patients are to receive ASA concomitantly with the IP (see Section 8.2.2). Additionally, patients should receive medical treatment and be counseled on lifestyle modifications for cerebrovascular risk factors (eg, diabetes, hypertension, dyslipidaemia, atherosclerosis, and smoking) according to local and global guidelines (eg, AHA/ASA 2014).

Restricted medication/class of drug	Usage
Low-molecular weight heparins	Short-term treatment (≤7 days) with low-dose low-molecular weight heparin may be used in immobilised patients if required and at the Investigator's discretion
Non-steroidal anti-inflammatory drugs (NSAIDs)	Short-term treatment (≤7 days) is allowed at the Investigator's discretion Treatment with selective cycloxygenase-2 inhibitors is permitted, although use is cautioned
Digoxin	Ticagrelor modestly increases digoxin levels, which should therefore be monitored closely following initiation of IP
Strong CYP3A4 inducers (eg, rifampicin, phenytoin, carbamazepine, phenobarbital)	Co-administration with ticagrelor could decrease plasma levels of ticagrelor If required, treatment can be given at the Investigator's discretion

CYP3A substrates with narrow therapeutic index (eg, quinidine, simvastatin at doses >40 mg daily or lovastatin at doses >40 mg daily)	Co-administration with ticagrelor could increase plasma levels of simvastatin or lovastatin, which may put the patient at increased risk of statin-related adverse effects Treatment with lower doses or with other statins is not prohibited
P-glycoprotein/CYP3A inhibitors (eg, cyclosporine)	Co-administration with ticagrelor could increase plasma levels of ticagrelor If required, treatment can be given at the Investigator's discretion
Prohibited medication/class of drug	**Usage**
Antiplatelet agents other than ASA (eg, GPIIb/IIIa inhibitors, clopidogrel, ticlopidine, prasugrel, dipyridamole, ozagrel, and cilostazol; ticagrelor other than as IP)	Patients who develop an indication (acute coronary syndrome or percutaneous coronary intervention) for dual antiplatelet therapy must discontinue IP and be treated with standard of care
Anticoagulants (eg, warfarin, oral thrombin and factor Xa inhibitors, bivalirudin, hirudin, argatroban, fondaparinux, long-term or high-dose use of low-molecular weight heparin)	Anticoagulants in combination with antiplatelet therapy increase the risk for bleedings
Strong CYP3A inhibitors (eg, ketoconazole, clarithromycin, nefazadone, ritonavir, atazanavir)	Co-administration with ticagrelor could increase plasma levels of ticagrelor
Traditional/herbal medicines known to have antiplatelet or anticoagulant properties (eg, *Salvia miltiorrhiza*, breviscapine)	These agents in combination with antiplatelet therapy may increase the risk of bleeding
Rescue/supportive medication/class of drug	**Usage**
Thrombolytic therapy (eg, alteplase)	If intravenous or intraarterial thrombolytic therapy is required, IP must be discontinued for at least 24 hours after thrombolytic therapy

8.7.2 Surgery and other invasive procedures

IP (ticagrelor/placebo) should be discontinued at least 5 days prior to any elective/subacute major surgery. This is particularly important for surgery with potential for major bleeding. To minimise the risk of thrombotic complications while off IP, it is also recommended that IP not be discontinued for significantly longer than 5 days prior to surgery. For reference, ESC guidelines recommend discontinuation of ticagrelor 3 to 5 days prior to coronary artery bypass grafting (ESC 2014). Potential discontinuation of ASA prior to major surgery should occur according to local practice. After surgery, IP and ASA should be restarted at the Investigator's discretion, taking the risk of bleeding versus the risk of new thrombotic events into consideration.

For carotid endarterectomy and other invasive procedures such as coronary angiography, IP and/or ASA may be continued or interrupted temporarily at the discretion of the Investigator, based on the risk of bleeding versus the risk of new thrombotic events. The Society for Vascular Surgery guidelines recommend that perioperative antithrombotic therapy for carotid endarterectomy should include ASA (Grade 1, Level of Evidence A; Ricotta et al 2011). After the surgical or interventional procedure, IP and/or ASA should be restarted (if interrupted) as soon as possible.

If a patient suffers an acute stroke during the study with a potential indication for thrombectomy and/or thrombolysis, the treating physician should determine the appropriate treatment, taking into consideration the potential benefit of aggressive treatment and the increased risk of bleeding during simultaneous treatment with several antithrombotic agents. If thrombolysis is administered, IP should be discontinued for at least 24 h afterwards.

9. STATISTICAL ANALYSES BY ASTRAZENECA

9.1 Statistical considerations

A comprehensive Statistical Analysis Plan will be prepared prior to first patient randomised and any subsequent amendments will be documented, with final amendments completed prior to unblinding of the data. Analyses will be performed by AstraZeneca.

9.2 Sample size estimate

At least 647 primary endpoint events are needed to provide 90% power assuming a hazard ratio (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 is assumed at 30 days following randomisation. Hence, randomising approximately 11 000 patients to ticagrelor or placebo in a 1:1 ratio is expected to yield the 647 events needed. The study is event-driven and the final number of randomised patients will be determined based on blind data review.

9.3 Definitions of analysis sets

All variables, including safety variables, will be analysed using the full analysis set (FAS). All patients who have been randomised to IP will be included in the FAS irrespective of their protocol adherence and continued participation in the study. Patients will be analysed according to their randomised IP irrespective of whether the event occurred before or following discontinuation of IP.

9.4 Variables for analyses

9.4.1 Primary variable

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

9.4.2 Secondary variables

The secondary variables, presented in the hierarchical order in which they will be tested, are:

1. Time from randomisation to first subsequent ischaemic stroke

2. mRS score >1 at Visit 3

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

9.4.3 Safety variables

The safety variables are:

- 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

For the time-to-event variables, patients who have not experienced the event will be censored at Visit 3, Day 34, or the date of last event assessment, whichever occurs earlier; or, for the time from randomisation to discontinuation due to bleeding variable only, the day of the last dose of IP, if earlier.

9.4.4 Exploratory variables

The exploratory variables are:

- Time from randomisation to first subsequent stroke or death in patients with ipsilateral atherosclerotic stenosis
- mRS score >2 at Visit 3 in patients with subsequent stroke
- EQ-5D-5L profile

For the time-to-event variable, patients who have not experienced the event will be censored at Visit 3, Day 34, or the date of last event assessment, whichever occurs earlier. The mRS score for patients who have died prior to Visit 3 will by definition be 6.

9.5 Methods for statistical analyses

All analyses will be based on the intent-to-treat principle, using the FAS. In time-to-event analyses, the treatment groups will be compared using a Cox proportional hazards model with a factor for treatment group, using the Efron method for ties. P-values and 95% confidence intervals for the HR will be based on the Wald statistic. In summary tables of these analyses, in addition to HR with confidence intervals and p-values, presentations will include the number and percentage of patients with events and Kaplan-Meier estimates of the event rate per treatment group. Kaplan-Meier estimates of the cumulative proportion of patients with events will be calculated and plotted, with the number of patients at risk indicated below the plot at specific time points. If the total number of events is less than 15, only the number and percentage of patients with events will be presented, but no Kaplan-Meier estimates, HRs, confidence intervals, or p-values.

No multiplicity adjustment will be made to confidence intervals as they will be interpreted descriptively and used as a measure of precision. The primary variable and the secondary variables will be included in a confirmatory testing procedure.

Continuous variables will be summarised by treatment group using descriptive statistics, including the number of patients, mean, standard deviation, median, and range as appropriate. For categorical variables, counts and percentage per treatment group will be presented.

9.5.1 Analysis of the primary variable

The null hypothesis of no treatment effect, H0: HR (ticagrelor divided by placebo) = 1, versus the alternative hypothesis, H1: HR ≠ 1, will be tested at the 4.996% 2-sided significance level.

As an explorative analysis, primary events up to the end of the follow-up period will be analysed by repeating the primary analysis with event-free patients censored at Visit 4 (or Day 64) instead of Visit 3 (or Day 34).

9.5.2 Analysis of the secondary variables

The secondary variables will be included in the confirmatory testing procedure. Only if the treatment effect on the primary variable is significant at the 4.996% level will the secondary variables be tested in a confirmatory sense in the hierarchical order specified in Section 9.4.2.

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

The time from randomisation to first subsequent ischaemic stroke will be analysed in the same manner as the primary variable. The proportion of patients with mRS score >1 at Visit 3 will be analysed using a logistic regression model with treatment group, history of stroke, and baseline NIHSS score as explanatory variables.

9.5.3 Analysis of the safety variables

The time-to-event safety variables will be analysed in the same manner as the primary variable, but will not be included in the confirmatory testing procedure. SAEs and DAEs, summarised by system organ class and preferred term using the Medical Dictionary for Regulatory Activities, will be presented by treatment group using descriptive statistics.

9.5.4 Analysis of the exploratory variables

The time from randomisation to first subsequent stroke or death in patients with ipsilateral atherosclerotic stenosis will be analysed in the same manner as the primary variable. The proportion of patients with subsequent stroke and mRS score >2 at Visit 3 will be analysed using a logistic regression model with treatment group, history of stroke, and baseline NIHSS score as the explanatory variables. EQ-5D-5L data will be presented by treatment group using descriptive statistics.

9.5.5 Subgroup analysis

Subgroup analyses will be performed to evaluate variation of treatment effect on the primary variable and on GUSTO Severe bleeding events. The subgroup variables (eg, "age") and their categories (eg, "<65 years") will be defined in the Statistical Analysis Plan. Tests for interaction between treatment and each subgroup variable will be 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 have occurred in each subgroup category. The subgroup categories will be examined in Cox proportional hazards models with a factor for treatment group. Kaplan-Meier estimates, HRs, and 95% confidence intervals will be reported if at least 15 events have occurred within the subgroup category.

9.5.6 Interim analysis

One interim analysis will be performed by the DMC following the accrual of 70% of the planned primary events (453). The efficacy stopping boundary at the interim is a 2-sided p-value <0.001 for the primary endpoint (corresponding to a critical value of 0.734). The interim p-value is 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 is made at the interim, all subsequent testing of secondary variables will be done at a significance level of 0.1%.

The study may be stopped for futility if the observed HR for the primary endpoint is >0.933 (taking all available study information into account), corresponding to a predictive power of 5%.

10. STUDY AND DATA MANAGEMENT BY ASTRAZENECA

10.1 Training of study site personnel

Before the first patient is entered into the study, an AstraZeneca representative will review and discuss the requirements of the CSP and related documents with the investigational staff and also train them in any study-specific procedures and WBDC system utilised.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved. The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

10.2 Monitoring of the study

During the study, an AstraZeneca representative will have regular contacts with the study site, including visits to:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the CRFs, and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the CRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (eg, clinic charts)
- Perform source data review, ie, review source documents for important areas where there is no associated eCRF data field, and monitoring of the research centre's critical processes

The AstraZeneca representative will be available between visits if the Investigator(s) or other staff at the centre needs information and advice about the study conduct.

10.2.1 Risk-based quality management

Quality by design will be implemented, including a focus on identifying key risks to patient safety, data quality, and good clinical practice (GCP)/regulatory compliance. A risk-based approach to monitoring will be applied. A mix of monitoring strategies will be implemented: on-site monitoring, remote monitoring (site-level monitoring activities performed at a location other than the research centre), and centralised monitoring systems. Monitoring strategies will be tailored to risks, permit timely oversight (through central/remote monitoring and use of technology), and will be focused on Critical Processes and Critical Data. Central monitoring will be used to check that data is consistent and complete, identify unusual distribution of data, identify higher risk sites to target additional monitoring, and to ensure routine review of data is completed in real time.

10.2.2 Source data

The location of source data is defined in the CSA. The Principal Investigator must provide direct access to source data/documents for trial-related monitoring, audits, institutional review board/independent ethics committee (IRB/IEC) review, and regulatory inspection.

10.2.3 Study agreements

The Principal Investigator at each centre should comply with all the terms, conditions, and obligations of the CSA, or equivalent, for this study. In the event of any inconsistency between this CSP and the CSA, the terms of CSP shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the CSA shall prevail.

Agreements between AstraZeneca and the Principal Investigator should be in place before any study-related procedures can take place, or patients are enrolled.

10.2.4 Archiving of study documents

The Investigator follows the principles outlined in the CSA for archiving study documents.

10.3 Study timetable and end of study

The study is event-driven and expected to start in Q1 2018 and to end by Q4 2019. The end of the study is defined as ‘the last visit of the last patient undergoing the study’. The expected recruitment period is 21 months. AstraZeneca will notify Investigators when recruitment is complete.

Individual sites can be closed if the study procedures are not being performed according to GCP (including late data entry), or if recruitment is slow. All eCRFs should be completed and cleaned and all patients should be followed up for endpoints and vital status before a site is closed. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with ticagrelor.

10.4 Data management by AstraZeneca

Data management will be performed by AstraZeneca Data Management Centre staff at Cognizant according to the Data Management Plan. AEs and medical/surgical history will be classified according to the terminology of the latest version of the Medical Dictionary for Regulatory Activities. Medications will be classified according to the World Health Organisation Drug Dictionary. Classification coding will be performed by the Medical Coding Team at the AstraZeneca Data Management Centre.

The data collected through third party sources will be obtained and reconciled against study data. Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The Data Management Plan will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process.

When all data have been coded, validated, signed and locked, clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked.

SAE reconciliation

SAE reports are reconciled between the eCRF and the Patient Safety database.

11. ETHICAL AND REGULATORY REQUIREMENTS

11.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonisation/GCP, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

11.2 Patient data protection

The Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

11.3 Ethics and regulatory review

An IRB/IEC should approve the final CSP, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the patients. The Principal Investigator will ensure the distribution of these documents to the applicable IRB/IEC, and to the study site staff. The opinion of the IRB/IEC should be given

in writing. The Principal Investigator should submit the written approval to AstraZeneca before enrolment of any patient into the study. The IRB/IEC should approve all advertising used to recruit patients for the study.

AstraZeneca should approve any modifications to the Informed Consent Form that are needed to meet local requirements. If required by local regulations, the CSP should be re-approved by the IRB/IEC annually.

Before enrolment of any patient into the study, the final CSP, including the final version of the Informed Consent Form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations. AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities. AstraZeneca will provide Regulatory Authorities, IRB/IECs, and Principal Investigators with safety updates/reports according to local requirements.

11.4 Informed consent

The Principal Investigator(s) at each centre will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each patient is notified that they are free to discontinue from the study at any time
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed Informed Consent Form is given to the patient
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the informed consent form that is approved by an IRB/IEC

11.5 Changes to the protocol and Informed Consent Form

Study procedures will not be changed without the mutual agreement of the EC and AstraZeneca.

If there are any substantial changes to the CSP, then these changes will be documented in a CSP amendment and where required in a new version of the CSP (Revised CSP). The

amendment is to be approved by the relevant IRB/IEC and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised CSPs. AstraZeneca will distribute any subsequent amendments and new versions of the CSP to each Principal Investigator(s). For distribution to IRB/IEC, see Section 11.3.

If a CSP amendment requires a change to a centre's Informed Consent Form, AstraZeneca and the centre's IRB/IEC are to approve the revised Informed Consent Form before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each IRB/IEC.

11.6 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an IRB/IEC may perform audits or inspections at the centre, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the CSP, GCP, guidelines of the International Conference on Harmonisation, and any applicable regulatory requirements. The Investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the centre.

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Appendix A NIHSS questionnaire

Interval: [ ] Baseline [ ] 2 hours post treatment [ ] 24 hours post onset of symptoms ±20 minutes
[ ] 7-10 days [ ] 3 months [ ] Other _____(___ ___)

Time: ___ ___:___ ___ [ ]am [ ]pm

Person Administering Scale _____

Administer stroke scale items in the order listed. Record performance in each category after each subscale exam. Do not go back and change scores. Follow directions provided for each exam technique. Scores should reflect what the patient does, not what the clinician thinks the patient can do. The clinician should record answers while administering the exam and work quickly. Except where indicated, the patient should not be coached (i.e., repeated requests to patient to make a special effort).

Instructions	Scale Definition	Score
1a. Level of Consciousness: The investigator must choose a response if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.	0= **Alert**: keenly responsive 1= **Not alert**: but arousable by minor stimulation to obey, answer, or respond 2= **Not alert**: requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements 3= Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid and areflexic	____
1b. LOC Questions: The patient is asked the month and his/her age. The answer must be correct - there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier, or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiner not "help" the patient with verbal or non-verbal cues.	0= **Answers both** questions correctly 1= **Answers one** question correctly 2= **Answers neither** question correctly	____
1c. LOC Commands: The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to him or her (pantomime), and the result scored (i.e., follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.	0= **Performs both** tasks correctly 1= **Performs one** task correctly 2= **Performs neither** task correctly	____
2. Best Gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye	0= **Normal**	

movements will be scored, but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1. If a patient has an isolated peripheral nerve paresis (CN III, IV or VI), score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness, or other disorder of visual acuity or fields should be tested with reflexive movements, and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.	1= **Partial gaze palsy**: gaze is abnormal in one or both eyes, but forced deviation for total gaze paresis is not present 2= **Forced deviation**: or total gaze paresis not overcome by the oculocephalic maneuver	____
3. Visual: Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat, as appropriate. Patients may be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia, is found. If patient is blind from any cause, score 3. Double simultaneous stimulation is performed at this point. If there is extinction, patient receives a 1, and the results are used to respond to item 11.	0= **No visual loss** 1= **Partial hemianopia** 2= **Complete hemianopia** 3= **Bilateral hemianopia** (blind including cortical blindness)	____
4. Facial Palsy: Ask – or use pantomime to encourage – the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barriers obscure the face, these should be removed to the extent possible.	0= **Normal**: symmetrical movements 1= **Minor paralysis**: flattened nasolabial fold, asymmetry on smiling 2= **Partial paralysis**: total or near total paralysis of lower face 3= **Complete paralysis**: one or both sides	____
5. Motor Arm: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine). Drift is scored if the arm falls before 10 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	0= **No drift**: limb holds 90 (or 45) degrees for a full 10 seconds 1= **Drift**: limb holds 90 (or 45) degrees, but drifts down before full 10 seconds, does not hit bed or other support 2= **Some effort against gravity**: limb cannot get to or maintain 90 (or 45) degrees, drifts down to bed, but has some effort against gravity 3= **No effort** against gravity: limb falls 4= **No movement** 5a. **Left Arm** 5b**. Right Arm**	____
6. Motor Leg: The limb is placed in the appropriate position: hold the leg at 30 degrees (always tested supine). Drift is scored if the leg falls before 5	0= **No drift**: leg holds 30-degree position for full 5 seconds	

seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic leg. Only in the case of amputation or joint fusion at the hip, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	1= **Drift**: leg falls by the end of the 5- second period but does not hit bed 2= **Some effort** against gravity: leg falls to bed by 5 seconds, but has some effort against gravity 3= **No effort** against gravity: leg falls to bed immediately 4= **No movement** 6a. **Left Leg** 6b. **Right Leg**	____
7**. Limb Ataxia**: This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, ensure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice. In case of blindness, test by having the patient touch nose from extended arm position.	0= **Absent** 1= **Present in one limb** 2= **Present in two limbs** UN= **Amputation** or joint fusion Explain: _____	____
8. Sensory: Sensation or grimace to pinprick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas (arms [not hands], legs, trunk, face) as needed to accurately check for hemisensory loss. A score of 2, "severe or total sensory loss," should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will, therefore, probably score 1 or 0. The patient with brainstem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic, score 2. Patients in a coma (item 1a=3) are automatically given a 2 on this item.	0= **Normal**: no sensory loss 1= **Mild to moderate sensory loss**: patient feels pinprick is less sharp or is dull on the affected side, or there is a loss of superficial pain with pinprick, but patient is aware of being touched 2= **Severe to total sensory loss**: patient is not aware of being touched in the face, arm and leg	____
9. Best Language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. For this scale item, the patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet and to read from the attached list of sentences. Comprehension is judged from responses here, as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in a coma (item 1a=3) will automatically score 3 on this item. The examiner	0= **No aphasia**: normal 1= **Mild to moderate aphasia**: some obvious loss of fluency or facility of comprehension,without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension however makes conversation about provided material difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content from patient's response	____

must choose a score for the patient with stupor or limited cooperation, but a score of 3 should be used only if the patient is mute and follows no one-step commands.	2= **Severe aphasia**: all communications is through fragmentary expression, great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited, listener carries burden of communication. Examiner cannot identify materials provided from patient response 3= **Mute, global aphasia**: no usable speech or auditory comprehension	
10. Dysarthria: If patient is thought to be normal, an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the patient is intubated or has other physical barriers to producing speech, the examiner should record the score as untestable (UN), and clearly write an explanation for this choice. Do not tell the patient why he or she is being tested.	0= **Normal** 1= **Mild to moderate dysarthria**: patient slurs at least some words and, at worst, can be understood with some difficulty 2= **Severe dysarthria**: patient speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric UN= **Intubated:** or other physician barrier	___
11. Extinction and Inattention (formerly Neglect): Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosagnosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable.	0= **No abnormality** 1= **Visual, tactile, auditory, spatial, or personal inattention**: extinction to bilateral simultaneous stimulation in one of the sensory modalities 2= **Profound hemi-inattention or extinction to more than one modality**: does not recognize own hand or orients to only one side of space	___


COOKIE
JAR

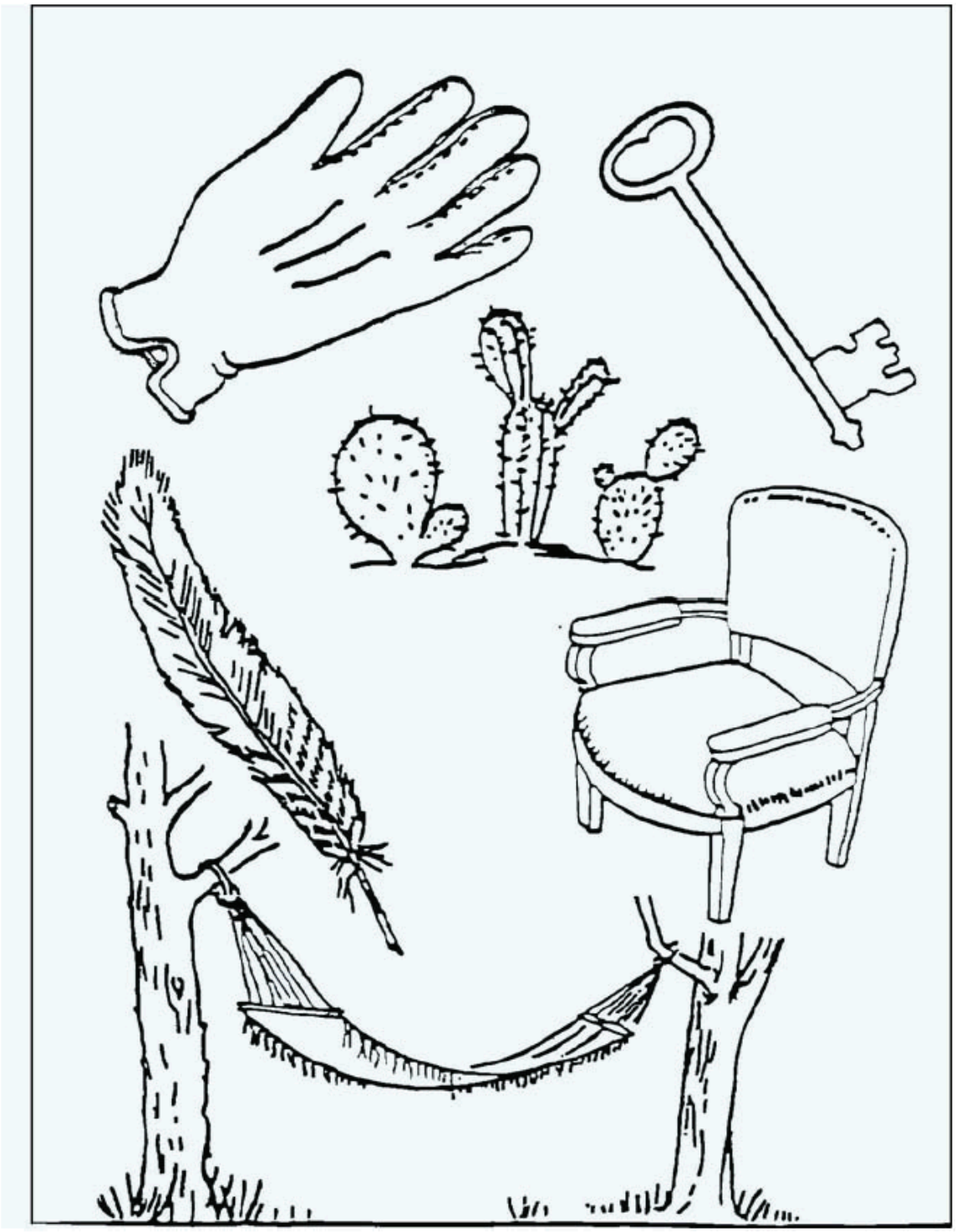
You know how.

Down to earth.

I got home from work.

Near the table in the dining room.

They heard him speak on the radio last night.



MAMA

TIP – TOP

FIFTY – FIFTY

THANKS

HUCKLEBERRY

BASEBALL PLAYER

Appendix B EQ-5D-5L (English version for the United Kingdom)

A copy of the English version of the EQ-5D-5L questionnaire for the United Kingdom follows on the next 3 pages.

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

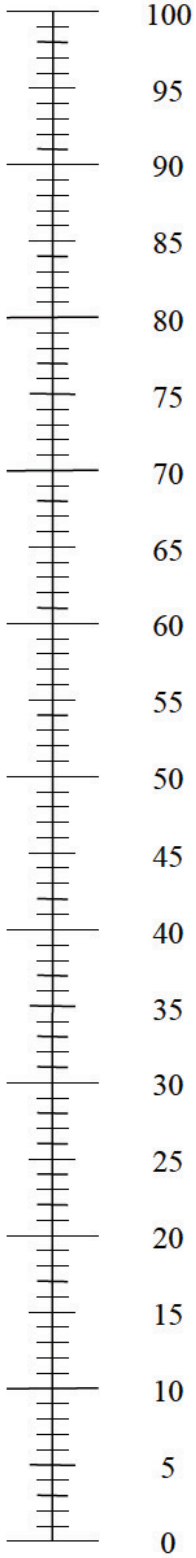
PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

The best health you can imagine



The worst health you can imagine

- We would like to know how good or bad your health is

TODAY.

- This scale is numbered from 0 to 100.
- 100 means the <u>best</u> health you can imagine.
  0 means the <u>worst</u> health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐

Appendix C Additional safety information

Further guidance on the definition of a serious adverse event (SAE)

Life threatening

'Life-threatening' means that the patient was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the patient's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the patient or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used. The following are examples of events that are medically important:

- Angioedema not severe enough to require intubation but requiring IV hydrocortisone treatment
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse

A guide to interpreting the causality question

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the patient actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?

- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.

- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?

- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

CLINICAL STUDY PROTOCOL SIGNATURE PAGE

A Randomised, Double-Blind, Placebo-Controlled, International, Multicentre, Phase III Study to Investigate the Efficacy and Safety of Ticagrelor and ASA Compared with ASA in the Prevention of Stroke and Death in Patients with Acute Ischaemic Stroke or Transient Ischaemic Attack

[THALES - Acute STroke or Transient IscHaemic Attack Treated with TicAgreLor and ASA for PrEvention of Stroke and Death]

D5134C00003	Version 3, 08 May 2019

This clinical study protocol has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this clinical study protocol. I will conduct the study according to the procedures specified herein, and according to the principles of Good Clinical Practice and local regulations.

Signature: [redacted] May 11, 2019

S. Claiborne Johnston, MD, PhD Date
International co-ordinating investigator
Dean, Dell Medical School
[redacted]

CLINICAL STUDY PROTOCOL SIGNATURE PAGE

A Randomised, Double-Blind, Placebo-Controlled, International, Multicentre, Phase III Study to Investigate the Efficacy and Safety of Ticagrelor and ASA Compared with ASA in the Prevention of Stroke and Death in Patients with Acute Ischaemic Stroke or Transient Ischaemic Attack

[THALES - Acute STroke or Transient IscHaemic Attack Treated with TicAgreLor and ASA for PrEvention of Stroke and Death]

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Signature: [redacted] May 10, 2019

Pierre Amarenco, MD Date
International co-ordinating investigator
Paris University.
[redacted]

SIGNATURE PAGE

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