AstraZeneca

Revised Clinical Study Protocol

Drug Substance	Ticagrelor
Study Code	D5134C00001
Edition Number	2
Date	16 March 2015

A Randomised, Double-Blind, Multinational Study to Prevent Major Vascular Events with Ticagrelor Compared to Aspirin (ASA) in Patients with Acute Ischaemic Stroke or TIA

[SOCRATES –Acute Stroke Or Transient IsChaemic Attack TReated with Aspirin or Ticagrelor and Patient OutcomES]

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Date

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1	20 Feb 2015		
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1	8 May 2014		
2	11 Dec 2014		

Revised Clinical Study Protocol Synopsis
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PROTOCOL SYNOPSIS

A Randomised, Double-Blind, Multinational Study to Prevent Major Vascular Events with Ticagrelor Compared to Aspirin (ASA) in Patients with Acute Ischaemic Stroke or TIA

[SOCRATES –Acute Stroke Or Transient IsChaemic Attack TReated with Aspirin or Ticagrelor and Patient OutcomES]

International Co-ordinating Investigators

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France

Study centre(s) and number of subjects planned

This study will be conducted in approximately 1000 investigational centres in approximately 40 countries worldwide. The study is event driven and the true event rate will determine the number of patients to be randomised in order to collect the needed 844 primary events. Thus the final number of randomised patients will depend on the collection of the primary events and the actual sample size will be determined based on blind data review. It is expected that 13600 patients will be randomised to study treatment. However, a lower than predicted event rate could make it necessary to increase sample size beyond 13600 patients. If event rate is instead higher than predicted, less than 13600 patients would be sufficient.

Study period		Phase of development
Estimated date of first subject enrolled	Q4 2013	IIIb
Estimated date of last subject completed	Q2 2016	

Objectives

Primary objective

The primary objective of the study is to compare the effect of 90-day treatment with ticagrelor (180 mg [two 90 mg tablets] loading dose on Day 1 followed by 90 mg twice daily maintenance dose for the remainder of the study) vs acetylsalicylic acid (ASA)-aspirin™[1]

[1] **ASPIRIN™ (acetylsalicylic acid) is a trademark of Bayer AG, Germany**

(300 mg [three 100 mg tablets] loading dose on Day 1 followed by 100 mg once daily maintenance dose for the remainder of the study) for the prevention of major vascular events (composite of stroke, myocardial infarction [MI], and death) in patients with acute ischaemic stroke or transient ischaemic attack (TIA).

Secondary objectives

The first secondary objective of the study is to compare the effects of treatment with ticagrelor vs ASA on:

- Prevention of subsequent ischaemic stroke

Other objectives

Other objectives are to compare the effects of treatment with ticagrelor vs ASA on:

- Net clinical outcome (stroke + MI + death + life threatening bleeding)
- Prevention of composite of ischaemic stroke, MI and cardiovascular [CV] death
- Prevention of all-cause death, CV death and MI, individually
- Severity of stroke and overall disability of patients using modified Rankin Scale
- Prevention of all stroke (including haemorrhagic stroke), fatal stroke and disabling stroke, individually
- Rate of worsening, ie, progression of the index stroke event assessed by deterioration of clinical symptoms and/or an increase in the score on the National Institute of Health Stroke Scale (NIHSS)
- Health care resource and utilities assessed by Euro Quality of Life-5 Dimensions to support health technology assessment and health economic modelling

Safety objectives

The overall safety objective of this study is to assess the safety and tolerability of therapy with ticagrelor compared with ASA in patients with acute ischaemic stroke or transient ischaemic attack. Bleeding events will be analysed using the adjudicated PLATO bleeding definitions. Bleeding events will also be analysed using the Thrombolysis in Myocardial Infarction (TIMI) Study Group and Bleeding Academic Research Consortium (BARC) class 3, 4, and 5 definitions. Specific focus will be on:

- Time to first major bleeding event using the PLATO study definition
- Time to discontinuation of study medication due to any bleeding event
- Evaluation of non-serious adverse events and serious adverse events

Study design

This is a randomised, double-blind, double-dummy, parallel-group, international, multicentre study to assess the prevention of major vascular events (stroke, MI and death) in patients treated with ticagrelor 90 mg twice daily compared to ASA 100 mg once daily in patients with acute ischaemic stroke or transient ischaemic attack. At the end of 90 days of study treatment, patients will be treated with standard of care therapy of the Investigator's choice and followed for 30 days for assessment of adverse events and efficacy endpoints.

Target subject population

Men or women ≥40 years of age with either acute ischaemic stroke **or** high-risk transient ischaemic attack as defined here, and randomisation occurring within 24 hours after onset of symptoms.

Acute ischaemic stroke, defined as:

- Neurological deficit attributed to the focal brain ischaemia, **and** either of the following:
  - Persistent signs or symptoms of the ischaemic event at the time of randomisation

  OR

  - Acute, ischaemic brain lesion documented by computed tomography scan or magnetic resonance imaging (diffusion-weighted imaging) within 24 hours of onset of symptoms
- National Institute of Health Stroke Score ≤5

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 ≥4 **and** TIA symptoms not limited to isolated numbness, isolated visual changes, or isolated dizziness/vertigo
  - Symptomatic intracranial arterial occlusive disease documented by transcranial doppler, ultrasound or vascular imaging, defined as at least 50% narrowing in diameter of a vessel that could account for the clinical presentation
  - Documented internal carotid arterial occlusive disease, defined as at least 50% narrowing in diameter of a vessel that could account for the clinical presentation.

Study medication, dosage and mode of administration

Ticagrelor monotherapy: ticagrelor, 180 mg (two tablets of 90 mg) loading dose on Day 1 followed by 90 mg twice daily or corresponding placebo given orally.

Comparator, dosage and mode of administration

ASA monotherapy: ASA, 300 mg (three tablets of 100 mg) on Day 1, followed by 100 mg once daily or corresponding placebo given orally.

Duration of treatment

Patients will be treated for 90 days.

Outcome variable(s):

- Efficacy

The primary efficacy variable is time from randomisation to first occurrence of any event from the composite of all strokes (ischaemic or haemorrhagic), MI and all cause death

- Safety
  - Time to first major bleeding event using the PLATO definition
  - Time to discontinuation of study medication due to any bleeding event
  - Evaluation of non-serious adverse events and serious adverse events

Statistical methods

All efficacy analyses will be based on the intent-to-treat principle using the full analysis set, using events adjudicated by the Clinical Event Adjudication Committee.

Analysis of the primary composite efficacy variable and the first secondary efficacy variable, ischaemic stroke, will comprise the confirmatory analysis for the ticagrelor versus ASA. The first secondary variable, time to first ischaemic stroke, will be tested in the confirmatory sense only if the primary comparison is significant. The time from randomisation to the first occurrence of any event in a given endpoint will be compared using the Cox proportional hazards model with a factor for treatment group. The p-value, hazard ratio (HR) and 95% confidence interval will be reported. One interim analysis will be performed following the accrual and confirmation by adjudication of 50% of planned primary events (422). Primary events are all major vascular events (composite of stroke, MI and death). The study may be stopped either for futility or efficacy. The futility stopping boundary is HR >0.954 and the efficacy stopping boundary is a 2-sided p-value <0.001 for the primary endpoint. The final analysis will be conducted at a significance level of 4.98% with the family-wise error rate controlled at 5.00%.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this Clinical Study Protocol.

Abbreviation or special term	Explanation
$ABCD^2$ score	The $ABCD^2$ score is a risk assessment tool designed to improve the prediction of short-term stroke risk after a transient ischaemic attack.
ACS	Acute coronary syndrome
ADP	Adenosine diphosphate
AE	Adverse event
AHA	American Heart Association
ALT	Alanine aminotransferase
AMI	Acute myocardial infarction
ARR	Absolute risk reduction
ASA	Acetylsalicylic acid
ASCOD	Atherosclerosis, Small-vessel disease, Cardiac pathology, Other causes, Dissection
AST	Aspartate aminotransferase
BARC	Bleeding Academic Research Consortium
BP	Blood pressure
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CAST	Chinese Acute Stroke Trial
CEC	Clinical Event Adjudication Committee
CHARISMA	Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance
CHD	Coronary heart disease
CSA	Clinical study agreement
CSP	Clinical study protocol
CSR	Clinical study report
CT	Computed tomography
CV	Cardiovascular
CYP3A	Cytochrome P450 3A
DAE	Discontinuation of Investigational Product due to Adverse Event

Abbreviation or special term	Explanation
DMC	Data monitoring committee
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
eCRF	Electronic case report form
EoT	End of Treatment
EQ-5D	European Quality of Life-5 Dimensions Questionnaire
EQ-VAS	EQ-Visual Analogue Scale
FAS	Full Analysis Set
FASTER	Fast Assessment of Stroke and Transient ischaemic attack to prevent Early Recurrence
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GRand	AstraZeneca Global randomisation system
HECON	Health Economic
HR	Hazard Ratio
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ID	Identification
IPA	Inhibition of Platelet Aggregation
IRB	Institutional Review Board
IST	International Stroke Trial
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LTFU	Lost to follow-up
MedDRA	Medical Dictionary for Regulatory Activities
MATCH	Management of Atherothrombosis with Clopidogrel in High-risk patients with recent transient ischaemic attack or ischaemic stroke
mg	Milligram
MI	Myocardial Infarction
mRS	Modified Rankin Scale

Abbreviation or special term	Explanation
MRI	Magnetic Resonance Imaging
NIHSS	National Institute of Health Stroke Scale
NSAIDs	Non Steroidal Anti-Inflammatory Drugs
NSTE-ACS	Non-ST elevation acute coronary syndrome
OAE	Other Significant Adverse Event
PCI	Percutaneous coronary intervention
PLATO	PLATelet inhibition and patient Outcomes
POINT	Platelet-Oriented Inhibition in New TIA and minor ischaemic stroke
PRO	Patient Reported Outcomes
PTDV	Premature Treatment Discontinuation Visit
SPS3	The Secondary Prevention of Small Subcortical Strokes trial
RRI	Relative risk increase
RRR	Relative risk reduction
rt-PA	Recombinant tissue plasminogen activator
SAE	Serious adverse event
SCV	Study Closure Visit
SDV	Source Data Verification
STE-ACS	ST-elevation acute coronary syndrome
SUSAR	Suspected Unexpected Serious Adverse Reactions
TC	Telephone contact
TIA	Transient Ischaemic Attack
URL	Upper Reference Limit
vs	Versus
WBDC	Web Based Data Capture

1. INTRODUCTION

1.1 Background

Cerebrovascular disease is the second leading cause of death worldwide and the third leading cause of death in the United States (US). Transient ischaemic attack (TIA) is a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischaemia, without acute infarction; an ischaemic stroke is a cerebral infarction. The duration of symptoms no longer features prominently in the new American Heart Association (AHA) definitions (Easton 2009). Rather, the results of brain imaging studies assume primary importance; evidence of infarction constitutes a stroke regardless of the timing of symptom resolution. Overall, 87% of strokes are ischaemic and 13% haemorrhagic. Furthermore, ~19% are considered cardioembolic, ~26% lacunar, ~15% from carotid disease, and ~36% are of unknown origin. In Asia, haemorrhagic strokes are more common, with recent data indicating that ~18% of all strokes in Japan and ~15% in Korea are haemorrhagic.

Patients who experience ischaemic stroke or TIA are particularly at high risk for developing new ischaemic stroke, even when treated with aspirin, the current standard of care. More effective antiplatelet therapy could significantly reduce the overall burden of TIA/stroke if initiated soon after symptom onset.

Antiplatelet agents reduce the risk of ischaemic stroke in various settings: atrial fibrillation, small-vessel stroke, and large-vessel atherothrombosis. Aspirin reduces the risk of death or subsequent stroke after stroke or TIA. In long-term management of ischaemic stroke patients, clopidogrel monotherapy is also recommended and approved as an alternative to aspirin, as is the combination of aspirin plus dipyridamole (Furie 2011, Lansberg 2012, ESO 2008). Although clopidogrel plus aspirin after stroke/TIA reduces the incidence of new stroke, it increases the risk of major haemorrhage and is not recommended for long-term management based upon outcomes in the MATCH trial (Diener 2004) and CHARISMA (Bhatt 2006) stroke cohorts, and the more recent SPS3 trial (SPS3 Investigators 2012). Thrombosis risk is extremely high soon after a TIA, but risk of haemorrhage is expected to be lower than after a completed stroke; thus a more potent antiplatelet therapy may be more effective and relatively safe in this setting. The benefits and risks of adding clopidogrel to aspirin in patients with acute stroke/TIA were evaluated in a pilot trial (FASTER) of 392 Canadian patients (Kennedy 2007) and a larger trial (CHANCE) of 5170 Chinese patients (Wang 2013). The 90-day risk of stroke in both trials decreased 36% and 32% respectively compared to aspirin alone, and therapy with clopidogrel plus aspirin was well tolerated. To confirm these findings in Western patients, another study (POINT 2011) is enrolling patients with acute ischaemic stroke or TIA to test the benefit and risks of more intense platelet inhibition using clopidogrel plus aspirin versus aspirin alone.

Other than aspirin, the only approved therapy after acute cerebral ischaemia, intravenous recombinant tissue plasminogen activator (rt-PA), targets the incident stroke, not prevention of subsequent events. Recombinant rt-PA is contraindicated after TIA and is considered inappropriate after minor ischaemic stroke. The benefits of oral antiplatelet agents, including

aspirin or clopidogrel as monotherapy for the chronic management of ischaemic stroke patients, exceed the increased risk of major haemorrhage in all settings of cerebral ischaemia. Intense transient platelet activation occurs after acute cerebral ischaemia (ischaemic stroke or TIA), coinciding with the period of greater risk for recurrence and progressive thrombosis. Clopidogrel plus aspirin after acute cerebral ischaemia blunts platelet activation better than aspirin alone, reduces micro-embolic signals, and tends to reduce clinical ischaemic events during the days after a stroke or TIA. Aspirin, a mainstay for long-term prevention of vascular events after stroke, reduces stroke, myocardial infarction (MI), and vascular death by 22%. Aspirin also improves outcomes after acute stroke, but the effect is modest and balanced by a small increased risk of intracerebral haemorrhage. The CAST (Chinese Acute Stroke Trial) and IST (International stroke trial) trials (CAST 1997, IST 1997), each enrolling about 20,000 patients, found that 2 to 4 weeks of treatment with aspirin after ischaemic stroke provided a 30% relative risk reduction (RRR) for recurrent ischaemic stroke, but absolute risk reduction (ARR) was only 0.7%, with 25% relative risk increase (RRI) for intracranial haemorrhage (absolute risk increase [ARI] 0.2%). On this basis, aspirin has become the standard of care for treating acute stroke, with dose in the range of 50 to 325 mg/day. Although both clopidogrel monotherapy and dipyridamole + aspirin are acceptable alternatives to aspirin for long-term therapy after stroke and TIA, neither has undergone testing in the acute setting.

Ticagrelor is a reversibly binding, potent, oral adenosine diphosphate (ADP) $P2Y_{12}$ receptor blocker. Ticagrelor 90 mg twice daily dosing has greater platelet inhibition than clopidogrel, and unlike clopidogrel, ticagrelor does not require metabolic activation. As a result, ticagrelor provides greater and more consistent interpatient antiplatelet effect. Recently, data from a study of platelet inhibition and patient outcomes (PLATO), a Phase III pivotal efficacy and safety study with a duration of up to 12 months comparing ticagrelor 90 mg twice daily to clopidogrel 75 mg once daily, following initial loading doses, in 18,624 patients with acute coronary syndromes (ACS) on aspirin background therapy, have demonstrated superiority of ticagrelor over clopidogrel in the prevention of fatal and non-fatal cardiovascular (CV) events. In PLATO, ticagrelor was superior to clopidogrel in reducing the rate of the composite efficacy endpoint of Cardiovascular (CV) death, myocardial infarction (MI), and stroke after ACS events (RRR 16%, ARR 1.9%; hazard ratio [HR] 0.84 [95% confidence interval {CI} 0.77, 0.92]; p=0.0003). Furthermore, ticagrelor, compared to clopidogrel, decreased separately the rates of CV death (RRR 21%; ARR 1.1%; Hazard Ratio (HR) 0.79 [95% CI 0.69, 0.91]; p=0.0013) and of MI (RRR 16%; ARR 1.1%; HR 0.84 [95% CI 0.75, 0.95]; p=0.0045), with no effect on stroke. PLATO-defined major bleeding for ticagrelor did not differ significantly from that of clopidogrel (HR 1.04 [95% CI 0.95, 1.13]; p=0.4336). Intracranial bleeding was reported in 26 patients (0.3%) in the ticagrelor group and 14 patients (0.2%) in the clopidogrel group (HR 1.87: 95% CI 0.98-3.58; p = 0.06) (Wallentin 2009).

In the overall PLATO population, 125 stroke events in the ticagrelor group and 106 in the clopidogrel group were observed (HR 1.17; 95% CI 0.91, 1.52). The numerical imbalance appears to be concentrated in the ST-elevation acute coronary syndrome (STE-ACS) subgroup (N=7,544; 56 ticagrelor, 35 clopidogrel: HR 1.63; 95% CI 1.07, 2.48), with lower rates and near equality by treatment in the non-ST elevation acute coronary syndrome (NSTE-ACS)

subgroup (N=11,080; 69 ticagrelor, 71 clopidogrel). Patients with STE-ACS undergo more invasive manipulation, with potentially more cardioembolic strokes.

Furthermore, in PLATO, 6.2% of randomised patients had a prior stroke or TIA, 564 assigned to ticagrelor and 588 to clopidogrel. They were older, more often hypertensive, diabetic, dyslipidemic, and had prior MI more often compared to the overall PLATO cohort. The prior stroke/TIA subgroup's primary efficacy endpoint yielded HR of 0.87 (95% CI 0.66, 1.13) in favour of ticagrelor compared to clopidogrel. After excluding TIA patients from this cohort, HR=0.84 (95% CI 0.61, 1.16) was observed. Major bleeding did not differ between the treatments in this subgroup. These findings are consistent with efficacy and safety results observed in the overall population. Intracranial bleeding was observed in 4 patients in the ticagrelor arm of this subgroup and 4 patients in the clopidogrel arm of this subgroup.

Further information regarding the background, pharmacological class, properties, and mechanism of action of ticagrelor can be found in the Investigator's Brochure (IB).

1.2 Research hypothesis

This study is designed to test the hypothesis that ticagrelor monotherapy is superior to ASA monotherapy in reducing the incidence of major vascular events, as measured by the composite of stroke, MI and death in patients with acute ischaemic stroke or TIA.

1.3 Rationale for conducting this study

Platelet activation and aggregation are important processes in most ischaemic strokes, regardless of underlying etiology. Platelet thrombi contribute to small vessel strokes, large vessel thombosis and embolism, and cardiac embolism (Mohr 1998). Inhibiting platelets reduces the risk of ischaemic stroke from all these major etiologies (ATC 2002, Chen et al 2000) and also reduces the risk of ischaemic cardiac complications in patients at high risk (ATC 2002). The benefits of platelet inhibition may be greatest in the acute period. Platelets are activated dramatically and transiently in patients with acute cerebral ischaemia, both from TIA and from ischaemic stroke (Htun 2006, Yip 2004), coincident with a period of greater risk for recurrence and progressive thrombosis (Kang 2003, Kang 2004). Antiplatelet therapy with clopidogrel added to ASA in patients with acute cerebral ischaemia blunts platelet activation compared to ASA alone (Serebruany 2005), reduces micro-embolic signals (Markus 2005, Wong 2010), and tends to reduce clinical ischaemic events during the days after a stroke or TIA.

The data from the FASTER pilot trial (Kennedy 2007) and CHANCE trial (Wang 2013) support the safety and efficacy of more intense platelet inhibition with clopidogrel combined with aspirin in reducing stroke risk in the short-term after acute minor ischaemic stroke or TIA. In both trials, patients were randomised within 24 hours after symptom onset to clopidogrel plus aspirin versus aspirin alone for 90 days. Both studies restricted the patient population to minor ischaemic stroke severity and TIA. This patient population is expected to have less intracerebral bleeding risk as opposed to moderate to severe stroke. In the CHANCE trial, the primary outcome, ischaemic or haemorrhagic stroke, occurred in 8.2% in the

clopidogrel plus aspirin arm and 11.7% in the aspirin arm - a highly significant 32% hazard reduction. Importantly, no increase in major haemorrhage, including intracerebral bleeds, was observed.

1.4 Benefit/risk and ethical assessment

Patients who experience ischaemic stroke or TIA are at high risk for developing subsequent events even when treated with aspirin, the current standard of care. Thrombosis risk is highest soon after the initial event, but treatment options are limited.

Ticagrelor requires no metabolic activation, providing a rapid onset and more consistent interpatient antiplatelet effect. In PLATO, in patients with ACS, on a background of aspirin, ticagrelor was superior to clopidogrel in reducing the rate of the composite efficacy endpoint of CV death, MI, and stroke (RRR 16%, ARR 1.9%; HR 0.84 [95% CI 0.77, 0.92]; p=0.0003) for up to 12 months of treatment.

Bleeding is the most important risk for all antiplatelet agents and especially dual antiplatelet therapy. Despite greater inhibition of platelet aggregation (IPA) with ticagrelor, results from the PLATO study showed that major bleeding with ticagrelor did not differ from that with clopidogrel on a background of aspirin. Although the total major bleeding did not differ between ticagrelor and clopidogrel in the PLATO study, non-procedural total major bleeding rates were significantly greater with ticagrelor compared to clopidogrel (3.1% vs 2.3%, HR 1.31 [95% CI 1.08, 1.60]; p = 0.006). In the CHANCE trial, clopidogrel plus aspirin was safe and effective compared to aspirin alone but the event rate on combination treatment was still very high with an 8.2% stroke risk at 90 days. These data confirm the need to further reduce the risk of recurrent stroke. Ticagrelor may be expected to reduce thrombotic events more effectively than currently approved therapies. Haemorrhagic risk is mitigated by excluding patients with large strokes and those with intracerebral haemorrhage. Adverse events (AE) observed in patients treated with ticagrelor, other than bleeding, include dyspnoea, and ventricular pauses that were largely asymptomatic. None of these events is considered to pose a significant risk as they can be adequately managed in the clinical setting.

Current treatment guidelines from the American Heart Association/American Stroke Association recommend that patients with acute ischaemic stroke and TIA be treated with aspirin immediately. According to American Heart Association/American Stroke Association guidelines (Furie 2011), “Aspirin prevents stroke among patients with a recent stroke or TIA (CCSG 1978, UK-TIA Study Group 1991, ATC 2002, Dutch TIA Trial 1991). In a meta-regression analysis of placebo-controlled trials of aspirin therapy for secondary stroke prevention, the relative risk reduction for any type of stroke (haemorrhagic or ischaemic) was estimated at 15% (95% CI, 6% to 23%) (Johnson 1999). The magnitude of the benefit is similar for doses ranging from 50 mg to 1500 mg (CCSG 1978, ATC 2002, UK-TIA Study Group 1991, Dutch TIA Trial 1991, Johnson 1999, SALT group 1991) although the data for doses <75 mg are limited (ATC 2002). In contrast, toxicity does vary by dose; the principal toxicity of aspirin is gastrointestinal haemorrhage, and higher doses of aspirin are associated with greater risk (UK-TIA Study Group 1991, Dutch TIA Trial 1991). For patients who use low-dose aspirin (≤325 mg) for prolonged intervals, the annual risk of serious gastrointestinal

haemorrhage is about 0.4%, which is 2.5 times the risk for nonusers (UK-TIA Study Group 1991, Dutch TIA Trial 1991, Weisman 2002, CAPRIE 1996). Aspirin therapy is associated with an increased risk of haemorrhagic stroke that is smaller than the reduced risk for ischaemic stroke, resulting in a net benefit (He 1998).

Meta-analyses have shown that the risk of haemorrhage is somewhat greater with higher doses of aspirin. Therefore, the dose of aspirin in this study will be 100 mg daily.

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective of the study is to compare the effect of 90-day treatment with ticagrelor (180 mg [two 90 mg tablets] loading dose on Day 1 followed by 90 mg twice daily maintenance dose for the remainder of the study) vs acetylsalicylic acid (ASA)-aspirin™[2] (300 mg [three 100 mg tablets] loading dose on Day 1 followed by 100 mg once daily maintenance dose for the remainder of the study) for the prevention of major vascular events (composite of stroke, MI and death) in patients with acute ischaemic stroke or TIA.

The primary efficacy variable is time from randomisation to first occurrence of any event from the composite of all strokes (including haemorrhagic stroke), MI and all cause death. This will be referred to as stroke, MI and death in the protocol.

2.2 Secondary objectives

The first secondary objective of the study is to compare the effects of treatment with ticagrelor vs ASA on:

- Prevention of subsequent ischaemic stroke

Other objectives

Other objectives are to compare the effects of treatment with ticagrelor vs ASA on:

- Net clinical outcome (stroke + MI + death + life threatening bleeding)
- Prevention of composite of ischaemic stroke, MI and CV death
- Prevention of all-cause death, CV death and MI, individually
- Severity of stroke and overall disability of patients using modified Rankin Scale (mRS) (See Appendix C)
- Prevention of all stroke (including haemorrhagic stroke), fatal stroke and disabling stroke, individually

[2] **ASPIRIN™ (acetylsalicylic acid) is a trademark of Bayer AG, Germany**

- Rate of worsening, ie, progression of the index stroke event by deterioration in clinical symptoms and/or an increase in the score on the National Institute of Health Stroke Scale (NIHSS) (See Appendix C)

- Health care resource and utilities assessed by Euro Quality of Life-5 Dimensions to support health technology assessment and health economic modelling

2.3 Safety objective

The overall safety objective of this study is to assess the safety and tolerability of therapy with ticagrelor compared with ASA in patients with acute ischaemic stroke or transient ischaemic attack. Bleeding events will be analysed using the adjudicated PLATO bleeding definitions. Bleeding events will also be analysed using the Thrombolysis in Myocardial Infarction (TIMI) Study Group and Bleeding Academic Research Consortium (BARC) class 3, 4, and 5 definitions. Specific focus will be on:

- Time to first major bleeding event using the PLATO study definition

- Time to discontinuation of study medication due to any bleeding event

- Evaluation of non-serious adverse events and serious adverse events

3. STUDY PLAN AND PROCEDURES

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca standard procedures.

3.1 Overall study design and flow chart

This is a randomised, double-blind, double-dummy, international, parallel-group, multicentre study to assess the prevention of major vascular events (stroke, MI and death) with ticagrelor compared to ASA in patients with acute ischaemic stroke or TIA. A total of approximately 13600 male and female patients will be randomised at approximately 1000 study sites. The study is event driven and the number of randomised patients is estimated to ensure collection of 844 primary events. Thus the final number of randomised patients will depend on the collection of the primary events and the actual sample size will be determined based on blind data review. If true event rate should turn out lower than predicted it could be necessary to increase sample size beyond 13600 in order to collect the needed primary events. If event rate is instead higher than predicted, less than 13600 patients would be sufficient.

Eligible patients with acute ischaemic stroke or high-risk TIA before randomisation and fulfilling all of the inclusion criteria (See Section 4.1) and none of the exclusion criteria (See Section 4.2) will be randomised. Patients will be randomised in a 1:1 ratio to receive either ASA or ticagrelor. Patients will be randomised within 24 hours of the start of symptom onset of an ischaemic stroke or TIA event, with the intention to enrol as soon as possible after

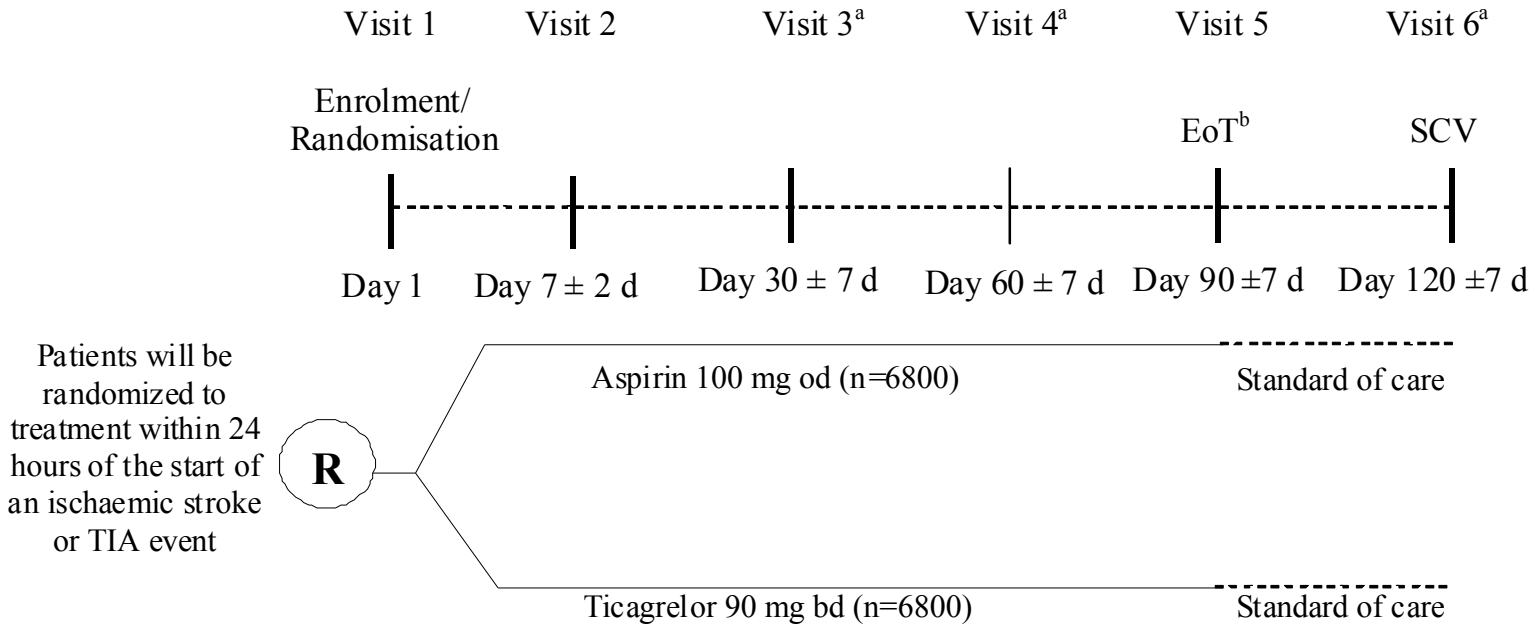
symptom onset. In patients with unknown exact time for symptom onset, the onset time will be measured from the time when the patient was last known to be symptom free.

The study consists of six visits. Four on-site visits: Visit 1, 2, 5 (End of Treatment [EoT] Visit) and 6 (Study Closure Visit [SCV]). In addition patients will be contacted by telephone at Day 30 (TC) for visit 3 and Day 60 (TC) for visit 4 and asked for study medication compliance and for the presence of any AEs and/or endpoints. At the end of 90 days study treatment, patients will be treated with standard of care therapy of Investigator's choice and followed for 30 days for assessment of adverse events and efficacy endpoints. All randomised patients should return for their Visit 6, Study Closure Visit, 30 ± 7 days, after their End of Treatment (EoT) Visit 5. If not possible, telephone contact should be made to ascertain endpoint and adverse event information. For detailed study plan see Table 1.

The study is designed, directed, and reported (presented at international medical congresses and published in peer reviewed journals) by an Executive Committee. An independent Data and Monitoring Committee (DMC) will be engaged to routinely monitor safety and efficacy data to recommend to the Executive Committee and the Sponsor whether or not the study should be stopped early for efficacy or safety based on the evaluation of the overall data. An independent Clinical Event Adjudication Committee (CEC) will adjudicate endpoint events and bleeding events for consistency. The Executive Committee will oversee the overall conduct of the study and in conjunction with AstraZeneca make final decisions on premature study stop based on the recommendations of the DMC. Members of an International Steering Committee, consisting of national lead investigators and supervised by the Executive Committee, will be responsible for providing clinical guidance on study implementation and conduct of the study in their respective countries (See Section 5.10).

All patients contacts that may result in reporting of AE, SAE or endpoint events between planned study visits should be documented as Unscheduled visits in the eCRF. Also if a patient develops any neurological worsening after randomization an unscheduled visit in eCRF should be used to record NIHSS and reporting of potential endpoint event. Patients who prematurely and/or permanently discontinue treatment with study medication but agree to continue in the study, should return for a Premature Treatment Discontinuation Visit (PTDV), which will be done as soon as possible but no later than 15 days after prematurely discontinuing treatment with study medication. After PTDV the patient will, whenever possible, continue attending subsequent study visits according to schedule until study closure on Day 120 after randomisation. All patients should attend the Study Closure Visit 6 in person (if necessary it may be a telephone contact). Patients who refuse to attend scheduled visits will be contacted for assessment of health status or vital status as per agreement, ie, by telephone or by collecting information from publicly available sources. For further details regarding discontinuing patients from study medications see Section 5.8, and for patients who must withdraw from the study, see Section 5.9. One interim analysis will be performed by the DMC following the accrual of 50% of planned primary events (422) adjudicated by the CEC and include both futility and efficacy analyses.

Figure 1 Study flow chart



bd Twice daily; d Day; EoT End of Treatment; od Once daily; R Randomisation; SCV Study closure visit; TIA Transient ischaemic attack

[a] Visits 3 and 4 are telephone contacts. Visit 6 may be a telephone contact, if necessary.

[b] After EoT Visit on Day 90 patients will be treated with Standard of Care therapy of Investigator's choice.

Table 1 Study Plan

Assessment	Visit 1 Enrolment/ randomisation[b]	Visit 2 Day 7 ± 2 d	Visit 3 TC Day 30 ± 7 d	Visit 4 TC Day 60 ± 7 d	PTDV ≤15 days after last dose[c]	Visit 5 EoT Day 90 ± 7 d	Visit 6 SCV[a] Day 120 ± 7 d
Signed Informed Consent	√						
Eligibility criteria	√						
Relevant medical and surgical history[d]	√						
Demographics	√						
Vital signs	√				√	√	
Modified Rankin Score	√				√	√	
NIHSS[e]	√				√	√	
ASCOD Classification of Stroke[f]	√				√	√	
Health Economic Assessment[g]	√	√			√	√	
CT/MRI[h]	√						
ABCD^2 Score for TIA patients	√						
Dispense Study Medication	√						
Return Study Medication					√	√	
Compliance/drug accountability					√	√	
Compliance reminder[i]	√ (72h)		√	√			
Current Medications	√	√	√	√	√	√	√
AEs, SAEs and Endpoints[j]	√	√	√[k]	√[k]	√	√	√[k]

[a] If necessary, Visit 6 may be a telephone contact.
[b] Randomisation should be done immediately after enrolment.
[c] The Premature Treatment Discontinuation visit (PTDV) is only done for patients who prematurely and permanently stop study medication.

[d] Relevant existing data from admission to hospital will be reviewed and recorded into the eCRF.

[e] NIHSS: Will be captured only in patients with stroke at randomisation, and at the time of subsequent suspected stroke event(s) in all patients. NIHSS will also be captured in all randomised patients at PTDV and visit 5.

[f] ASCOD classification can be done at any time during hospitalisation for both Stroke and TIA patients based on available data generated in clinical practice.

[g] See section 6.9.1 for details

[h] As standard of care, documented acute, ischaemic brain lesion by computed tomography (CT) scan or magnetic resonance imaging (MRI) captured within 24 hours of onset of symptoms of index event(s).

[i] At 72h after randomisation the patient will be reminded of the importance of compliance, either by TC or during hospitalisation. At TC at 30 and 60 days compliance will be asked for and any reported drug stops be recorded in the eCRF.

[j] SAEs will be recorded from the time of informed consent. AEs of interest and endpoints will be collected from the time of randomisation.

[k] In case any AE/SAE or endpoint is reported at TC the patient might need to visit site for evaluation at an unscheduled visit.

[l] Investigators should record Modified Rankin Score (MRS) at baseline based upon the patient's status before the onset of the index event (up to 72 hours).

AE Adverse events; ASCOD Atherosclerosis, Small-vessel disease, Cardiac pathology, Other causes, Dissection; CT computed tomography; eCRF electronic case report form; EoT End of treatment visit; MRI magnetic resonance imaging; NIHSS National Institute of Health Stroke Score; PTDV Premature treatment discontinuation visit; SAE Serious adverse events; SCV Study closure visit; TC telephone contact

3.2 Rationale for study design, doses and control groups

3.2.1 Overall rationale and study population

After ischaemic stroke or TIA, patients are at increased risk of subsequent ischaemic stroke, MI and death. Treatment options are limited; the most widely-used treatment for reducing the risk of subsequent events is aspirin. Due to unmet medical need and in view of limited options for acute stroke/TIA patients, the study is designed to improve upon the current standard of care. The target population will consist of patients with acute ischaemic stroke or TIA who present within 24 hours of onset of their symptoms, the time period during which patients are at the greatest risk of thrombosis. Recent studies have suggested that the stroke risk after minor ischaemic stroke is elevated in general. In FASTER and CHANCE trials, the risk of early stroke recurrence was greater in this group than in those initially diagnosed with TIA (Kennedy 2007, Wang 2013). Furthermore, in the Oxford cohort, 90-day stroke risk was similar for minor ischaemic stroke (18%) as for TIA (17%) (Coull 2004).

The risk of intracranial haemorrhage increases with larger infarctions (Kawano 2012). This has been demonstrated in studies of antiplatelet therapy (Adams 2008) and thrombolytics (Al-Khaled 2012). NIHSS is one marker for extent of infarction and is itself a predictor of haemorrhage risk in these populations.

Although there is no clear cut-off to define a population with small risk of intracranial haemorrhage and greater risk of infarction, NIHSS ≤ 5 is a reasonable cut-point, with a substantial short-term risk of new ischaemic events and limited risk of intracranial haemorrhage.

3.2.2 Study design

This is a randomised, double-blind, double-dummy, parallel-group study. Randomisation and double blinding will minimise potential bias. Parallel group design was chosen because a crossover study cannot assess major vascular outcome events. The study will be multicentre in numerous geographic regions to provide a wide applicability of results.

3.2.3 Primary and secondary endpoints

The primary endpoint (composite of stroke, MI and death) was chosen to reflect the enhanced efficacy of more intense and complete platelet inhibition. The first secondary endpoint will be ischaemic stroke. Other secondary endpoints include 1) net clinical outcome, 2) composite of ischaemic stroke, MI and CV death, 3) all strokes, disabling strokes and fatal strokes individually, 4) all cause death, CV death, and MI individually.

3.2.4 Dosing and study duration

A ticagrelor 180 mg loading dose followed by a 90 mg twice daily maintenance dose was selected as the dose to be tested in this study based on the available data. This dose showed high and consistent levels of IPA in Phase II studies with an acceptable safety profile. The pivotal Phase III study (PLATO) showed a positive benefit to risk ratio when a twice-daily

dose of 90 mg of ticagrelor was administered concomitantly with ASA (for more information see Sections 1.1 and 1.4).

ASA (300 mg loading dose on Day 1, followed by 100 mg once daily maintenance dose) was chosen as the active comparator, as this is the only drug approved and recommended for use in patients in the first days after acute ischaemic stroke and TIA (Lansberg 2012). In clinical management during the acute phase, patients are given a loading dose of aspirin (most commonly 150 to325 mg daily) for the first two days to provide greater platelet inhibition. Furthermore, meta-analyses have shown that the risk of haemorrhage is somewhat greater with higher doses of aspirin. Therefore, the daily maintenance dose of ASA in this trial will be 100 mg daily, after a 300 mg loading dose on Day 1. Treatment duration of 90 days has been selected with the goal of demonstrating short-term efficacy and safety in patients who are enrolled during the acute phase, when the risk of recurrent ischaemic events is highest. At the end of study treatment on Day 90, patients will be treated with standard of care therapy of the Investigator's choice. All patients will be followed for 30 days after study treatment discontinuation to document the consequences of withdrawal of ticagrelor and transitioning to standard of care.

4. SUBJECT SELECTION CRITERIA

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

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.

4.1 Inclusion criteria

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

1. Provision of informed consent prior to any study specific procedures

2. Men or women ≥40 years of age

3. Either acute ischaemic stroke or high-risk TIA as defined here and randomisation occurring within 24 hours after onset of symptoms:

Acute ischaemic stroke, defined as:

- Neurological deficit attributed to the focal brain ischaemia, **and** either of the following:
  - Persistent signs or symptoms of the ischaemic event at the time of randomisation,

  OR

- Acute, ischaemic brain lesion documented by computed tomography scan or magnetic resonance imaging (diffusion-weighted imaging) within 24 hours of onset of symptoms

- National Institute of Health Stroke Score ≤5

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 ≥4 **and** TIA symptoms not limited to isolated numbness, isolated visual changes, or isolated dizziness/vertigo

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

  - Documented internal carotid arterial occlusive disease, defined as at least 50% narrowing in diameter of a vessel that could account for the clinical presentation

4. Head Computed Tomography (CT) or MRI ruling out haemorrhage or other pathology, such as vascular malformation, tumour, or abscess that could explain symptoms or contraindicate therapy

4.1.1 $ABCD^2$ Score

The $ABCD^2$ score is a risk assessment tool designed to improve the prediction of short-term stroke risk after a transient ischaemic attack. The score is optimised to predict the risk of stroke within 2 days after a transient ischaemic attack, but also predicts stroke risk within 90 days. The $ABCD^2$ score is calculated by summing up points for five independent factors as shown in Table 2.

Table 2 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

4.2 Exclusion criteria

1. Planned use of antithrombotic therapy in addition to study medication including antiplatelets (eg, open label ASA, GPIIb/IIIa inhibitors, clopidogrel, ticlopidine, prasugrel, dipyridamole, ozagrel, cilostazol) and anticoagulants (eg, warfarin, oral thrombin and factor Xa inhibitors, bivalirudin, hirudin, argatroban, unfractionated and low molecular weight heparins). In addition, patients receiving or requiring dual antiplatelet therapy with ASA and $P2Y_{12}$ inhibitors will be excluded.

2. Known hypersensitivity to ticagrelor or ASA

3. Any history of atrial fibrillation, ventricular aneurysm or suspicion of cardioembolic pathology for TIA or stroke

4. Planned carotid, cerebrovascular, or coronary revascularisation that requires halting study medication within 7 days of randomisation

5. Receipt of any intravenous or intra-arterial thrombolysis or mechanical thrombectomy within 24 hours prior to randomisation

6. Anticipated concomitant oral or intravenous therapy with strong cytochrome P_{450} 3A (CYP3A) inhibitors **or** CYP3A substrates with narrow therapeutic indices that cannot be stopped for the course of the study

   – Strong inhibitors: ketoconazole, itraconazole, voriconazole, telithromycin, clarithromycin (but not erythromycin or azithromycin), nefazadone, ritonavir, saquinavir, nelfinavir, indinavir, atazanavir

– CYP3A substrates with narrow therapeutic index: cyclosporine, quinidine, simvastatin at doses >40 mg daily or lovastatin at doses >40 mg daily

7. Anticipated requirement for long-term (>7 days) non-steroidal anti-inflammatory drugs (NSAIDs)

8. Patients with known bleeding diathesis or coagulation disorder (eg, thrombotic thrombocytopenic purpura)

9. History of previous symptomatic non-traumatic intracerebral bleed at any time (asymptomatic microbleeds do not qualify), gastrointestinal (GI) bleed within the past 6 months, or major surgery within 30 days

10. Known severe liver disease (eg, ascites or signs of coagulopathy)

11. Renal failure requiring dialysis

12. Pregnancy or lactation

13. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site)

14. Inability of the patient to understand and/or comply with study procedures and/or follow-up, in the opinion of the Investigator

15. Previous enrolment or randomisation in the present study

16. Participation in another clinical study with an investigational product during the last 30 days

Procedures for withdrawal of incorrectly enrolled patients see Section 5.3.

5. STUDY CONDUCT

5.1 Restrictions during the study

Patients should not donate blood or bone marrow at any time during the study period.

There are no study-specific dietary or activity restrictions other than those typical for this patient population.

Restrictions regarding concomitant medications are described in Section 5.6.

5.2 Patient enrolment and randomisation

The Principal Investigator or delegate will:

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

2. Determine patient eligibility. See Sections 4.1 and Section 4.2.

3. Assign (using the Interactive Voice Response System/Interactive Web Response System [IVRS/IWRS], see Section 5.2.1) potential patients a unique enrolment number, beginning with 'E#'

4. Assign enrolled patient a unique randomisation code (patient number) obtained from IVRS/IWRS.

If a patient withdraws from participation in the study, then his/her enrolment/randomisation code cannot be reused.

5.2.1 Procedures for randomisation

Randomisation codes will be assigned strictly sequentially within each centre as subjects become eligible for randomisation. Randomisation codes will be generated in blocks to ensure approximate balance (1:1) between the two treatment arms. Once a block is exhausted, the next available block will be allocated by IVRS/IWRS system to a centre upon their next randomisation. Approximately 13600 patients will be randomised in this study.

At Visit 1 for patients who fulfil all the eligibility requirements, the investigator will access the IVRS/IWRS. The IVRS/IWRS will allocate a randomisation code and provide the investigator with unique treatment pack identification (ID) numbers for that patient for the Visit 1 supply of medication. Following randomisation, the first dose of study medication will be administered to the patient as soon as possible.

The randomisation codes will be computer generated by AstraZeneca R&D using the AZ Global Randomisation system (GRand) and loaded into the IVRS/IWRS database.

5.3 Procedures for handling patients incorrectly enrolled or randomised

Patients who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule.

The following steps should be taken in the event that a patient who does not meet inclusion/exclusion criteria is found to have been inadvertently enrolled in an AstraZeneca study.

(a) The investigator or monitor should inform the AstraZeneca study team physician immediately. Ensuring patient safety must always be the number one priority.

(b) Study treatment must be discontinued in all cases where continued treatment is deemed to pose a safety risk to the patient. After a discussion between the study team physician and investigator, a decision may be reached that the patient should discontinue study medication. The rationale for discontinuing study therapy must be clearly documented. The patient should remain in the study for follow up in accordance with defined study procedures including follow-up on endpoints through the end of the study consistent with the intention-to-treat principle.

(c) In those cases where continuation of study therapy is judged not to present a concern related to safety and disease management, the rationale for continuing study therapy must be clearly documented. The patient should continue follow up in accordance with defined study procedures.

5.4 Blinding and procedures for unblinding the study

5.4.1 Methods for ensuring blinding

The two medications to be administered in the study have different appearances. Due to this and the different dosing schedules, all patients will take either ticagrelor/matching placebo or ASA/matching placebo in a double-dummy fashion to maintain the blinding. Each pack 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. The study drug dosing regimens are:

1. ticagrelor 90 mg and ASA placebo in the morning, ticagrelor 90 mg in the evening

   or

2. ticagrelor placebo and ASA 100 mg in the morning, ticagrelor placebo in the evening

No member of the extended study delivery team at AstraZeneca, personnel at investigational centres or any CRO handling data will have access to the randomisation scheme during the conduct of the study, with the exception of the Supply Chain Study Management department, and the Patient Safety department at AstraZeneca.

A DMC will review efficacy and safety data on a periodic basis, including the incidence of AEs and safety assessments to ensure the ongoing safety of study patients. An independent statistician will be contracted to provide the DMC with essential safety and efficacy data during the study. The DMC responsibilities, authorities, and procedures will be documented in a DMC charter. The personnel involved in the clinical study at AstraZeneca will remain blinded to these analyses and will have no knowledge of the results presented to the DMC.

5.4.2 Methods for unblinding the study

Individual treatment codes, indicating the treatment for each randomised patient, will be available to the investigator(s) or pharmacists, from the Interactive Voice Response System/ Interactive Web Response System (IVRS/IWRS). Routines for this will be described in the IVRS/IWRS user manual that will be provided to each centre.

The treatment code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment. The AstraZeneca physician or delegate should be consulted whenever possible prior to the investigator breaking the blind. The investigator documents and reports the action 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 study medication should be continued if considered appropriate.

AstraZeneca retains the right to break the code for serious adverse events (SAEs) that are unexpected and are suspected to be causally related to a study drug 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.

5.5 Treatments

5.5.1 Identity of investigational product(s)

Table 3 Identity of study medication

Study Medication	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
Acetylsalicylic acid 100 mg	Plain, round, white, enteric coated tablet, 100mg	Bayer
Acetylsalicylic acid placebo	Plain, round, white, enteric coated tablet, placebo to match 100 mg	AstraZeneca

5.5.2 Doses and treatment regimens

At Visit 1 (randomisation) eligible patients will be randomly assigned to 1 of 2 treatments:

- Treatment 1: ticagrelor 180 mg (two 90 mg tablets) with placebo for ASA loading dose on Day 1, followed by 90 mg twice daily given orally together with placebo for ASA once daily.

- Treatment 2: ASA 300 mg (three 100 mg tablets) with placebo for ticagrelor loading dose on Day 1, followed by 100 mg daily given orally together with placebo for ticagrelor twice daily.

Randomisation and treatment pack assignment will be managed via the IVRS/IWRS, and the first dose of study medication should be taken at Visit 1. Subsequent maintenance doses should be taken morning and evening, at approximately 12-hour intervals, for the remainder of the treatment period. If the patient is randomised and takes the loading dose before 2PM on Day 1, the first maintenance dose of ticagrelor/ticagrelor placebo should be given before the patient goes to sleep on Day 1, at least 6 hours after the loading dose; if the loading dose is taken after 2PM on Day 1, the subject should take the first maintenance dose of ticagrelor/ticagrelor placebo in the morning on Day 2 as early as possible.

All patients should continue study treatment for 90 days. At the end of 90 days of study treatment, patients will be treated with standard of care therapy of the Investigator's choice and followed for 30 days.

5.5.3 Additional study drug (NA)

5.5.4 Labelling

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

5.5.5 Storage

All study drugs should be kept in a secure place under appropriate storage conditions. The study medication label on the study supplies specifies the appropriate storage conditions.

5.6 Concomitant and post-study treatment(s)

Recording of concomitant medications will be made at each visit. Medication use 1 month before the study and until the end of the study will be recorded. All ASA containing medication will be captured on a separate module in the eCRF with route of administration and total daily dose. All other concomitant medication will be captured (without total daily dose and route of administration) on a separate module in the eCRF.

5.6.1 Oral antiplatelet and parenteral thrombolytic therapies

Concomitant dual antiplatelet therapy at start of study: Patients requiring dual antiplatelet therapy (eg, ASA plus clopidogrel, ASA plus prasugrel, ASA plus ticagrelor, or ASA plus dipyridamole) will be excluded at randomisation, as the purpose of this study is to primarily test the benefits of mono-antiplatelet therapy. However, after randomisation, patients who

develop an indication (ACS or Percutaneous coronary intervention (PCI)) for dual antiplatelet therapy must discontinue study therapy and be treated with standard of care.

Anticoagulation therapy: Neither high dose thrombosis treatment nor low dose thrombosis prevention treatment with low molecular weight heparins (LMWH) or unfractionated heparins is allowed as concomitant treatment in the SOCRATES study. All other anticoagulation therapy is also prohibited as concomitant medication. If a medical indication for anticoagulation therapy occurs during the study, the study medication should be temporarily discontinued and restarted when there is no longer an indication for such treatment.

Concomitant intravenous or intra-arterial thrombolytics: Receipt of any intravenous or intra-arterial thrombolytic therapy within 24 hours prior to randomisation is prohibited. After randomisation, if patient requires intravenous or intra-arterial thrombolytic therapy, the study medication must be discontinued for at least 24 hours.

5.6.2 Non-steroidal anti-inflammatory drugs (NSAIDs)

Clinical experience with NSAIDs in combination with ticagrelor is limited at this time. Short-term treatment with NSAIDs up to 7 days is allowed during the study at the investigator's discretion. However, chronic daily dosing with non-selective NSAIDs (eg, patients with rheumatoid arthritis) may increase the potential for gastrointestinal bleeding so either alternative therapy or concomitant acid suppression therapy is recommended. Treatment with selective cycloxygenase-2 inhibitors is permitted, although use is cautioned.

5.6.3 Digoxin and other p-glycoprotein interactions

Ticagrelor modestly increases digoxin levels. Therefore digoxin levels should be monitored closely following initiation of study medication and with any change in study medication. Other p-glycoprotein substrates may be expected to have similar changes in pharmacokinetics. For additional details please see the Investigator's Brochure.

5.6.4 CYP450 interactions

5.6.4.1 CYP3A inhibitors

Strong inhibitors of this enzyme (eg, ketoconazole, itraconazole, voriconazole, telithromycin, clarithromycin [but not erythromycin or azithromycin], nefazadone, ritonavir, saquinavir, nelfinavir, indinavir, atazanavir, or over 1 litre daily of grapefruit juice) should not be co-administered with ticagrelor as plasma levels of ticagrelor would be substantially increased.

5.6.4.2 CYP3A substrates or inducers

Concomitant therapy with simvastatin or lovastatin at doses higher than 40 mg daily is not permitted since administration with ticagrelor will result in higher serum concentrations and may put patients receiving more than 40 mg per day of simvastatin or lovastatin at increased risk of statin-related adverse effects. There are no restrictions to other statin therapies (ie, doses of simvastatin or lovastatin ≤40 mg daily or any dose of any other statin is permitted). Investigators are advised to check lipid levels and adjust statin dosages per local practice and

appropriate guidelines. Standard monitoring of patients for possible statin-associated myopathy should be conducted.

Co-administration of ticagrelor with strong inducers of CYP3A also should be avoided (eg, rifampin/rifampicin, rifabutin, phenytoin, carbamazepine, phenobarbital).

Discontinuation of study medication is up to the judgment of the investigator. If continued antiplatelet medication is judged necessary, there may be a need for extra caution regarding bleeding tendency. The investigator should document the use and duration of all treatments (including CYP3A substrates and inducers) in the eCRF.

5.6.5 Surgery

Ticagrelor should be discontinued at least 5 days prior to any surgery. In particular, cardiac surgery and non-cardiac surgery with potential for major bleeding should be performed at least 5 days after stopping study medication. There is a trade-off between stopping study medication too early and risking thrombotic events versus continuing treatment too close to surgery and risking haemorrhage. Thus, it is also recommended that study medication not be discontinued for significantly longer than 5 days so as to minimize the risk of thrombotic complications while off study medication.

Other medication, which is considered necessary for the patient's safety and well being, may be given at the discretion of the investigator and recorded in the appropriate sections of the eCRF.

After surgery, study medications should be restarted when the risk of bleeding is deemed low in the judgment of the investigator, and the investigator should record all peri-procedural bleeding events.

5.6.6 Other surgery and invasive procedures

For other surgery or other invasive procedures such as coronary angiography or PCI, study medication may be continued or interrupted temporarily at the discretion of the investigator. As with all other surgeries, investigators should collect and record all peri-procedural bleeding events.

After the surgery or procedure, study medications should be restarted (if interrupted) as soon as possible.

Other medication, which is considered necessary for the patient's safety and well being, may be given at the discretion of the investigator and recorded in the appropriate sections of the eCRF.

5.7 Treatment compliance

The administration of all medication (including study medication) should be recorded in the appropriate sections of the eCRF.

At Visit 1, patients will receive enough study medication to cover up to End of Treatment Visit 5. Patients will be asked to return all unused study medications and empty packages to the clinic at EoT (or PTDV). A pill count should be done at a patient level and recorded in the eCRF by the study site personnel.

5.7.1 Accountability

The study medication provided for this study will be used only as directed in the study protocol.

The study personnel will account for all study medication dispensed 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.

Patients will be asked to return all unused study medication to the investigational centre at EoT (or PTDV). The investigator or delegate will enter the amount of returned tablets in the eCRF. At each visit, any patient found to be non-compliant will be counselled on the importance of taking their study medication as prescribed.

Any study medication deliberately or accidentally destroyed must be recorded. Any discrepancy between dispensed and returned study medication should be explained.

The investigator will retain the returned medication until the trial monitor or delegate collects it, along with any medication not dispensed. The monitor is responsible for confirming the investigator or delegate has recorded the quantities of returned and unused tablets at a patient level before medication is returned to the sponsor and/or destroyed. Following drug accountability, the trial monitor or delegate will advise on the appropriate method for destruction of unused study medication (including the empty bottles etc). Destruction of study medication must only be conducted by an authorized site.

Certificates of delivery and return must be signed.

5.8 Discontinuation of investigational product

Patients may be discontinued from study treatment and assessments at any time. Specific discontinuation criteria are presented below.

5.8.1 Temporary discontinuation from study medication

If study drug must be temporarily discontinued, restart it as soon as possible.

- Severe thrombocytopenia (platelet count <50,000/uL). Patients may restart study medication once the severe thrombocytopenia resolves
- Surgery or procedures associated with major haemorrhage, see Section 5.6.5
- Major bleeding, see Section 6.4.6.4

- Need of treatment with prohibited concomitant medications, see Section 5.6
- For other surgery or other invasive procedures, study medication may be continued or interrupted temporarily at the discretion of the investigator, see Section 5.6.6.

5.8.2 Permanent discontinuation from study medication

- 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:

1. Incorrectly enrolled patient in whom the inclusion/exclusion criteria violation would put the patient at undue risk
2. Adverse response thought to be related to the study medication for which the investigator thinks continued treatment may put the patient at undue risk
3. Adverse event for which the investigator thinks continued treatment may put the patient at undue risk
4. Severe non-compliance to study protocol
5. Pregnancy
6. Atrial fibrillation for which the patient receives anticoagulation therapy

Discontinuation of study medication does not mean discontinuation of follow-up or termination of study participation. Study assessments or telephone follow-up should be continued in all cases if possible, see Sections 5.8.3 and 5.9.

5.8.3 Procedures for discontinuation of a patient from study medication

Patients permanently discontinuing study medication should be given conventional therapy, if applicable, and should always be asked to continue the regular visits as described below.

A patient that decides to discontinue study medication will always be asked about the reason(s) for their desire to discontinue study medication and the presence of (if any) adverse events. These data will be ascertained and documented by the Investigator and recorded in the eCRF. Adverse events will be followed up (see Sections 6.4.3 and 6.4.4); and the patient should return all study drugs.

It is essential to collect as much data as possible for all patients throughout the study and especially all potential endpoint events. Complete withdrawal from the study (withdrawal of consent) has a direct negative impact on the potential validity of all study data and should be avoided wherever possible.

If the patient permanently discontinues study medication prior to the closure of the study, there could be several different options for their continuation in the study as described below.

If a patient is withdrawn from study, see Section 5.9.

5.8.3.1 Patient agrees to undergo Premature Treatment Discontinuation Visit and then continues in-person study visits

This is the preferred option, and patients who discontinue study medication will always be asked if they agree to this approach. If agreed, as above, the patient will undergo their PTDV at the time study medication is stopped. The patient will, after the PTDV, continue attending subsequent study visits (eg, Visit 2, Visit 3 TC, Visit 4 TC, Visit 5 EoT and Visit 6 SCV) according to schedule (See Table 1). Data collection should continue according to the study protocol.

5.8.3.2 Patient refuses to continue in-person study visits but agrees to undergo modified follow-up

If the patient refuses to continue in-person study visits, but agrees to undergo modified follow-up, the in-person PTDV visit should be done at the time study medication is stopped. The subsequent visits until the end of study, 120 days after randomisation, will be conducted as modified follow-ups (eg, regular telephone contacts, a contact at study closure, or other means). Such a patient has not withdrawn his/her consent or withdrawn from the study.

5.8.3.3 Patient refuses any form of follow-up

If the patient refuses any form of follow-up, he/she officially withdraws from the study and withdraws consent. This decision must be documented (see Section 5.9). At the end of each patient's planned participation in the double-blind portion of the study (90 days after randomisation), vital status will be collected from publicly available sources, in accordance with local regulations. This approach should be avoided if possible and is further described in Section 5.9.

5.8.4 End of Treatment

At Visit 5 EoT (and PTDV) visit physicians caring for the patient will decide which antiplatelet medication the patient should receive as part of his/her ongoing clinical care.

5.8.5 Study Closure Visit

All randomised patients should return for their Visit 6, Study Closure Visit, 30 ± 7 days after their End of Treatment (EoT) Visit 5. If not possible, telephone contact should be made to ascertain endpoint and adverse event information.

5.9 Withdrawal from study

Patients are at any time free to withdraw from the study (ie, discontinue study medication permanently and withdraw from visit assessments), without prejudice to further treatment (withdrawal of consent). Withdrawal of consent from the study must be ascertained and

documented by the Investigator and recorded in the eCRF as well as in the Informed Consent Form (ICF). The ICF should be re-signed and dated by both the patient and the investigator, if possible. Such patients will always be asked about the reason(s) and the presence of any adverse events. The reason for permanent discontinuation of treatment with the study medication and the date of the last intake of the study medication must be documented in the eCRF.

Patients permanently discontinuing from study medication should be given conventional therapy, if applicable, and should always be asked to continue to attend protocol visits as described in section 5.8.3. If the patient denies any additional protocol follow-up and officially withdraws consent from the study, one of the alternatives a) to c) should be followed:

a) The patient should at the time of discontinuation of treatment and withdrawal of consent from continued assessment, if possible, undergo the PTDV. The patient should return all study medication.

b) If the patient does not agree to this option (which must be documented), a modified PTDV (eg. a telephone contact) should be arranged. The approach taken should be registered in the eCRF and ICF. The patient should return all study medication.

c) If the patient does not agree to a) or b) this must be documented and recorded in the eCRF and ICF. The patient should return all study medication.

At the end of each patient's planned participation in the double-blind portion of the study (90 days after randomisation) and at 120 days after randomisation, vital status will be collected for all patients who withdraw consent by collecting information from publicly available sources, in accordance with what local regulations allow when informed consent has been withdrawn.

To ensure validity of study data, it is very important to collect as much data as possible throughout the study and especially vital status (dead or alive). Therefore, AstraZeneca or delegate will request that investigators attempt to collect information on patients' vital status from publicly available sources at EoT (Visit 5) (90 days after randomisation) and at Visit 6 (120 days after randomisation) if informed consent has been withdrawn completely. Withdrawn patients will not be replaced.

5.10 Study committees

Executive Committee

The Executive Committee will be responsible for the overall design, interpretation, supervision, and reporting (presented at international congresses and published in peer reviewed journals) of the study, including the development of the protocol and any protocol amendments. The Executive Committee will make recommendations to AstraZeneca with regard to early stopping or modifications of the study based on the information received from the DMC. The Executive Committee membership will be comprised of designated

international academic leaders and non-voting members of the Sponsor, and will operate under a separate charter.

International 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 Executive Committee. Members of the committee will be responsible for providing clinical guidance on study implementation and conduct in their respective country.

Clinical Event Adjudication Committee (CEC)

An independent CEC will be appointed and will adjudicate all primary efficacy and safety endpoints. The committee members will not be aware of treatment codes for any patient or clinical efficacy and safety event. The CEC charter details the precise responsibilities and procedures applicable for the CEC.

Data Monitoring Committee (DMC)

An independent DMC will be appointed and will report to the Executive Committee.

The DMC will be responsible for safeguarding the interests of the patients in the outcome study by assessing the safety of the intervention during the study, and for reviewing the overall conduct of the clinical study. 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.

The DMC charter will be prepared to detail precise roles and responsibilities and procedures to ensure maintenance of the blinding and integrity of the study in the review of accumulating data and interactions with the Executive Committee.

6. COLLECTION OF STUDY VARIABLES

The investigator will ensure that data are recorded in a timely fashion on the eCRF as specified in the study protocol and in accordance with the instructions provided.

6.1 Recording of data

The RAVE Web based Data Capture (WBDC) system will be used for data collection and query handling.

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).

Data will be entered in the eCRF using the RAVE Web Based Data Capture (WBDC) system at the study site. Study personnel will be trained and responsible for entering data specified in the protocol into the WBDC system and according to the eCRF Instructions. When data have been entered, reviewed, edited, and Source Data Verification (SDV) performed as appropriate

by an AstraZeneca representative, the data will be frozen to prevent further editing. The Principal Investigator will be notified to sign the eCRF electronically as per the eCRF instructions. A copy of the eCRF data will be archived at the study site.

For reporting of Patient Reported Outcome and Health Economic Data, see section 6.5.

6.2 Data collection at enrolment and follow-up

6.2.1 Enrolment procedures

Each patient will undergo enrolment procedures during Visit 1. The following data will be collected in the eCRF:

- Demographics (including sex, date of birth, race, ethnic group)
- Relevant medical and surgical history will be reviewed and collected at enrolment for baseline characteristics in the eCRF
- Current concomitant medications
- Vital Signs (heart rate and blood pressure. Weight and height for calculation of body mass index)
- Modified Rankin Score (see Appendix C and Table 1)
- NIH Stroke Score (see Appendix C and Table 1)
- ASCOD Classification of Stroke (Amarenco 2013) (see Appendix C and Table 1)
- $ABCD^2$ Score for TIA patients
- CT scan/MRI results
- EQ-5D questionnaire (baseline for patients' health related quality of life, will be collected at all clinic visits in countries where a validated form is available in the local language)
- Employment status data for health economic assessment for the patient and, if applicable, the primary caregiver based on information from the patient.
-

6.2.2 Follow-up procedures

Each patient will undergo follow-up procedures during Study Closure Visit. The following data will be collected in the eCRF:

- Concomitant medications

- Non-serious AEs of interest /SAEs
- Endpoints

6.2.3 Protocol procedures

Patients will have routine visits and procedures as outlined in Section 3.1. Any new suspected endpoint events, non-serious AEs of interest, DAEs, SAEs, and current medications will be recorded in the eCRF. It will be the responsibility of the Investigator to obtain all necessary source documents including medical records from institutions where a hospitalisation may have occurred.

If the patient experiences a suspected clinical efficacy endpoint event or a bleeding event, the following actions should be taken whenever possible and in accordance with current guidelines and local practice standards:

Symptoms of cardiac ischaemia (ie, potentially representing unstable angina or MI):

- Cardiac biomarkers of necrosis (troponin and/or CK-MB) should be collected serially and measured by local labs according to local standards for at least 24 hours.
- A standard 12-lead ECG should be obtained during or as soon as possible after the episode of ischaemia and serially according to local standards until resolution of symptoms.

Coronary Revascularisation (ie, PCI or Coronary Artery Bypass Graft [CABG]):

- Cardiac biomarkers of necrosis (troponin and/or CK-MB) should be measured locally immediately before the procedure and serially (every 8 hours x 3 or until hospital discharge) after the procedure.
- A standard 12-lead ECG should be obtained before the procedure, immediately post-procedure, and, if possible, in the morning following the procedure.
- For patients undergoing major surgery, all banked blood products administered (ie, the number of packed red blood cell or whole blood transfusions [units transfused and volume in mL], fresh frozen plasma [volume in mL], platelets [units transfused and volume in mL] and cryoprecipitate [volume in mL]) and those undergoing CABG, the chest tube output in the first 24 hours should be noted.

Focal neurological symptoms (ie, potentially representing stroke or transient ischaemic attack):

- Complete neurological exam
- Brain imaging (CT scan or MRI)

Bleeding (either unexpected or of unanticipated quantity):

- Record last stable haemoglobin before start of bleeding (or haematocrit if haemoglobin unavailable). Haemoglobin (or haematocrit if haemoglobin unavailable) should be measured locally serially until resolution of the bleeding.
- Record the date, time and number of all banked blood products administered.

Patient health related quality of life

- EQ-5D questionnaire as described in Section 6.9

Health care resource utilisation

Information on hospitalisations, rehabilitation and long-term care as described in Section 6.9.

6.3 Efficacy

Clinical efficacy endpoints will be collected in the eCRF. These events 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. Safety endpoint events will be identified similarly.

For each suspected endpoint, the investigator will complete information specific to that type of endpoint on the eCRF and compile relevant additional source information. Once all relevant information has been collected, the endpoint will be sent to the Clinical Events Adjudication Committee (CEC) for adjudication. The investigator should use the following definitions when assessing possible endpoint events. The definitions for death, MI, and stroke are based on the standardised draft definitions for endpoints (Hicks 2012). Additional details about the definitions and evaluations of endpoint events will be explained in the CEC charter.

It is essential that investigators collect all relevant and required endpoint data as soon as possible and provide it to the CEC. Investigators must report all suspected endpoints in the eCRF, even those that may not meet strict definitions, to ensure all potential endpoints are reviewed and adjudicated by the CEC.

Any neurological worsening after randomization must be reported as a possible endpoint and be evaluated by the adjudication committee, even if the event is mild. SOCRATES does not differentiate between worsening of an index stroke due to ischemia and a new stroke, and the distinction between worsening from ischemia rather than other causes should be left to the adjudicators.

6.3.1 Death

All deaths reported post-randomisation will be recorded and adjudicated. Deaths will be sub-classified by the adjudication committee as cardiovascular or non-cardiovascular.

- Cardiovascular death includes sudden cardiac death, death due to acute MI, death due to heart failure, death due to stroke, death due to other cardiovascular causes (eg. dysarrhythmia unrelated to sudden cardiac death, pulmonary embolism, cardiovascular intervention [other than one related to an AMI - Acute myocardial infarction], aortic aneurysm rupture, or peripheral artery disease), and deaths for which there was no clearly documented non-cardiovascular cause (presumed CV death). Death due to intracranial haemorrhage (including fatal haemorrhagic stroke) will be considered CV death.

- Additionally, CV deaths will be sub-classified by coronary heart disease (CHD) death and non-CHD death. CHD death includes sudden cardiac death, death due to acute MI, and the subset of death due to other cardiovascular causes that are secondary to a coronary revascularization procedure.

- Non-cardiovascular death includes death due to haemorrhage (including gastrointestinal bleeding), pulmonary causes (respiratory failure, pneumonia) malignancy, trauma, suicide, infection/sepsis or any other clearly defined cause (eg. liver failure or renal failure).

- Deaths with unknown/uncertain cause will be categorised as cardiovascular death and included in the primary composite endpoint. Any death with unknown/uncertain cause within 30 days of a stroke, MI or procedure/surgery will be considered a death due to the stroke, MI or procedure/surgery, respectively.

6.3.2 Myocardial Infarction: Third universal definition (Thygesen 2012)

Criteria for acute myocardial infarction

The term acute MI should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia. Under these conditions any one of the following criteria meets the diagnosis for MI:

- Detection of a rise and/or fall of cardiac biomarker values (preferably cardiac troponin [cTn]) with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following:

  – Symptoms of ischaemia.

  – New or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB)

  – Development of pathological Q waves in the ECG

  – Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

  – Identification of an intracoronary thrombus by angiography or autopsy

- Cardiac death with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased

- PCI-related MI is arbitrarily defined by elevation of cTn values (>5 x 99th percentile URL) in patients with normal baseline values (≤99th percentile URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischaemia or (ii) new ischaemic ECG changes or (iii) angiographic findings consistent with a procedural complication, or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required

- Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischaemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL

- CABG- related MI is arbitrarily defined by elevation of cardiac biomarker values (>10 x 99th percentile URL) in patients with normal baseline cTn values (≤99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

Criteria for prior myocardial infarction

Any one of the following criteria meets the diagnosis for prior MI:

- Pathological Q waves with or without symptoms in the absence of non-ischaemic causes

- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischaemic cause

- Pathological findings of a prior MI

- Universal Classification of MI

The following classification will be used by the CEC for classification of MI and will not be captured in the eCRFs.

Type 1: Spontaneous MI

- Spontaneous myocardial infarction related to atherosclerotic plaque rupture, ulceration, Assuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis. The patient may have underlying severe CAD but on occasion non-obstructive or no CAD

Type 2: Myocardial infarction secondary to an ischaemic imbalance

- In instances of myocardial injury with necrosis where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand, eg. coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy-/brady-arrhythmias, anaemia, respiratory failure, hypotension, and hypertension with or without left ventricular hypertrophy

Type 3: Myocardial infarction resulting in death when biomarker values are unavailable

- Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischaemic ECG changes or new LBBB, but death occurring before blood samples could be obtained, before cardiac biomarker could rise, or in rare cases cardiac biomarkers were not collected

Type 4a: Myocardial infarction related to percutaneous coronary intervention (PCI)

- Myocardial infarction associated with PCI is arbitrarily defined by elevation of cTn values >5 x 99th percentile URL in patients with normal baseline values (<99th percentile URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischaemia, or (ii) new ischaemic ECG changes or new LBBB, or (iii) angiographic loss of patency of a major coronary artery or a side branch or persistent slow- or no-flow or embolization, or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required

Type 4b: Myocardial infarction related to stent thrombosis

- Myocardial infarction associated with stent thrombosis is detected by coronary angiography or autopsy in the setting of myocardial ischaemia and with a rise and/ or fall of cardiac biomarkers values with at least one value above the 99th percentile URL

Type 5: Myocardial infarction related to coronary artery bypass grafting (CABG)

- Myocardial infarction associated with CABG is arbitrarily defined by elevation of cardiac biomarker values >10 x 99th percentile URL in patients with normal baseline cTn values (<99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

6.3.3 Stroke

A stroke is defined as an acute episode of neurological dysfunction caused by focal or global brain, spinal cord, or retinal vascular injury.

Stroke will be further sub-classified as:

Ischaemic stroke: An acute focal infarction of the brain or retina (and does not include anterior ischaemic optic neuropathy [AION]).

Criteria:

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

2. Rapid worsening of an existing focal neurological deficit that is judged by the Investigator to be attributable to a new infarction. Criteria for symptoms attributable to new infarction *may* include symptoms that persist and are judged by the investigator to be attributable to new infarction, imaging evidence of infarction, or no evidence of a non-ischaemic etiology.

TIA: A neurological deficit of sudden onset, resolving completely, attributed to focal brain or retinal ischaemia without evidence of associated acute focal infarction of the brain.

Criteria:

Rapid onset of a focal neurological deficit that is without evidence of acute focal infarction of the brain, and is not attributable to a non-ischaemic etiology (brain infection, trauma, tumour, seizure, severe metabolic disease, or degenerative neurological disease)

Unknown/No imaging performed: If the type of stroke could not be determined by imaging or other means (from lumbar puncture, neurosurgery, or autopsy) but is judged to fulfil the stroke definition above, the stroke will be classified as ischaemic for purposes of the study.

Haemorrhagic stroke: Haemorrhagic stroke is defined as an acute episode of focal or global cerebral or spinal dysfunction caused by a nontraumatic intraparenchymal, intraventricular, or subarachnoid haemorrhage.

Symptomatic haemorrhagic transformation of an ischaemic stroke: Any extravascular blood within an area of known acute/subacute infarction that is judged to be nontraumatic, and responsible for neurologic symptoms. To be considered symptomatic, the haemorrhagic transformation must be judged to be partially responsible for the patient's clinical neurologic presentation (ie, the area of infarction is not adequate to explain the neurologic deficit, or a secondary neurologic deterioration occurred corresponding to the timing of haemorrhagic transformation).

Criteria (must meet both of the following):

1. Imaging evidence (by CT scan or MRI) of extravascular blood within the area of infarction.

2. Symptoms judged to be related to the haemorrhagic transformation. Scenarios which may be judged as symptomatic:

(a) Symptoms are out of proportion to what would be expected for the size and location of the infarct at presentation;

(b) Clinical deterioration, defined by an increase of 4 points or more in the score on the NIHSS or leading to death, occurring after the initial **ischaemic** event, and identified as the result of the haemorrhagic transformation; or

(c) Mass effect secondary to the haemorrhagic transformation causing symptoms.

Asymptomatic haemorrhagic transformation of an ischaemic stroke: Any extravascular blood within an area of known acute/subacute infarct, judged to be nontraumatic, without any related neurologic symptoms.

Criteria (must meet both of the following)

1. Imaging evidence (by CT scan or MRI) of extravascular blood within the area of infarct.

2. No symptoms related to the haemorrhagic transformation, or clinical deterioration with less than a 4 point increase in score on the NIHSS judged to be related to the haemorrhagic transformation.

6.4 Safety

The Principal Investigator is responsible for ensuring that all staff involved in the study is familiar with the content of this section. See Section 6.4.5 for details on reporting of serious adverse events that are also endpoints in the study.

6.4.1 Definition of adverse events

An adverse event 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.

Any deterioration of the disease targeted in the study and associated symptoms should not be regarded as an adverse event as far as the deterioration can be anticipated (see Section 6.4.3, Disease progression)

6.4.2 Definitions of serious adverse event

A serious adverse event 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 guidance on the definition of a SAE, see Appendix B to the CSP.

6.4.3 Recording of adverse events

Time period for collection of adverse events

Only non-serious AEs of interest (ie, bleeding events, dyspnoea, renal impairment/increased creatinine, bradyarrhythmia, increased LFTs, gout/uric acid increases, pneumonia, gynecomastia, abnormal uterine bleeding and all malignancies excluding non-melanoma skin cancers) and discontinuations due to adverse events (DAEs) will be collected from time of randomisation throughout the treatment period and including the follow-up period, until the Study Closure Visit.

All SAEs will be recorded from the time of informed consent, with the exception of events defined as disease progression and those described below.

SAEs will be recorded at all visits in patients who prematurely discontinue treatment with study medication. Non-serious AEs of interest and DAEs will be recorded until the Study Closure Visit but no less than 30 days after last dose of study medication.

Follow-up of unresolved adverse events

Any SAEs and non-serious 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 eCRF. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/DAE(s) and SAE(s) at the end of the study, if judged necessary.

Variables

- The following variables will be collected and recorded for each non-serious AE of interest and DAE:
- AE (verbatim)
- The date when the AE started and stopped
- Maximum intensity
- Whether the AE is serious or not
- Investigator causality rating against the study medication (yes or no)
- Action taken with regard to study medication
- Outcome

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

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed (if performed)
- Autopsy results
- Causality assessment in relation to Study procedure(s)
- Causality assessment in relation to Other medication
- Description of AE

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is described below. 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 an SAE.

The following definitions for intensity rating are:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

Causality collection

The Investigator will assess causal relationship between study medication 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 study medication?'

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

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'.

A guide to the interpretation of the causality question is found in Appendix B to the CSP.

Adverse Events based on signs and symptoms

All non-serious AEs of interest and AEs leading to discontinuation (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/you were last asked?'*, or revealed by observation will be collected and recorded in the eCRF. 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.

Adverse Events based on examinations and tests

Results from local laboratory testing performed for the routine care of the patient should only be recorded in the patient chart. If there is a suspicion of Hy´s Law liver affection (see appendix D) data on liver enzymes should be entered in the e-CRF. In association with a suspected endpoint event, different assessments may have to be undertaken which could include local laboratory assessments, and will be collected in the patient chart and eCRF as appropriate.

The results from protocol-mandated vital signs will be summarised in the Clinical Study Report. Deterioration as compared to baseline in investigator-initiated assessment of

laboratory values and protocol-mandated vital signs should, therefore, only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the study medication.

If a non-serious AE of interest, DAE or SAE is detected through deterioration in a laboratory value/vital sign and is associated with clinical signs and symptoms, the sign or symptom will be reported and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg. renal failure versus increasing creatinine). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as non-serious AEs and SAEs.

NB. Cases where a patient shows an aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥3xULN **or** total bilirubin ≥ 2xULN may need to be reported as SAEs, please refer to Appendix D to the Clinical Study Protocol 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions.

Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the investigational product is being studied**.** It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of following cerebrovascular events should be considered as disease progression and not an AE. Events, which are unequivocally due to disease progression, should not be reported as an AE/SAE during the study.

- Worsening of stroke signs and symptoms or development of new symptoms consistent with deficits in the original territory of the acute ischaemic infarct. If the event qualifies for new stroke it should be reported as an endpoint.

- New strokes will be reported as endpoints and should not be reported as AE/SAEs (See Section 6.4.5).

6.4.4 Reporting of serious adverse events

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

If any SAE occurs during the course of the study, then investigators 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 the necessary information is provided to the AstraZeneca Patient Safety data entry site **within one calendar day** of initial receipt for fatal and life threatening events **and within five 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 immediately, or **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 how to proceed.

6.4.4.1 Reporting Procedure of Serious Adverse Events using Web-based Data Capture (WBDC) System

The investigators and other site personnel will access WBDC system and report SAE information by entering it into the relevant eCRF module. Upon entry of the SAE information, an automated email alert will be sent to the designated AstraZeneca representative. If the system is unavailable, the investigator(s) should take other appropriate measures to provide the SAE report to the AstraZeneca representative immediately, recognising that the same reporting time frames still apply. The investigators are responsible for completing the eCRF as soon as the system becomes available again.

If initial or the subsequent reports are made by means other than WBDC, necessary information on any SAEs should finally be entered into eCRF via WBDC system by the investigators.

6.4.5 Reporting of serious adverse events that are also endpoints in the study

The following endpoints in the study, although qualifying as SAEs, will only be reported as endpoints:

- Stroke
- MI
- Death

These endpoints will not be reported to health authorities as SAEs to avoid unnecessary unblinding of efficacy endpoints that are also SAEs. In addition, unstable angina and TIAs will also be sent for adjudication to ensure that they are not MI or stroke. If the event of unstable angina or TIA is not confirmed to be an MI or stroke, and it meets SAE criteria, then the event will be reported as an SAE. All other events when meeting SAE criteria will be reported as SAEs, with the exception of procedure related bleeding if expected for the procedure and those events due to underlying disease progression. If it is determined by the

CEC that any of the above events do not meet endpoint criteria, the events if meeting serious criteria will be captured as SAEs and reported to the health authorities as appropriate.

6.4.6 Bleeding assessments

For all bleeding events that are unexpected or of unanticipated quantity, the investigator will complete information on the eCRF specific to that bleeding event. In addition, for all reported bleeding events (excluding those which are self-limited and do not prompt medical evaluation or intervention) relevant information will be compiled and sent to the CEC for adjudication. Additionally, bleeding events will be reported as SAEs if serious criteria are met unless they qualify as endpoints in the study (haemorrhagic stroke and fatal bleeding).

The CEC will adjudicate and evaluate bleeding events (excluding minimal) according to the PLATO bleeding definitions. Programmed algorithms based on data elements collected on the eCRFs will provide TIMI and Bleeding Academic Research Consortium (BARC) classifications ((Mehran 2011).).

6.4.6.1 PLATO definitions of bleeding events

Bleeding events will be classified as shown below:

For patients experiencing a bleeding event that fulfils criteria in more than one category, the bleed will be assigned to the most severe category. The PLATO bleeding definition classification is a modification of the CURE definitions (Yusuf 2001).

Major bleed – fatal/life-threatening

Any one of the following:

- Fatal
- Intracranial
- Intrapericardial bleed with cardiac tamponade
- Hypovolaemic shock or severe hypotension due to bleeding and requiring pressors or surgery
- Clinically overt or apparent bleeding associated with a decrease in Hb of more than 50 g/L[a] (3.1 mmol/L[b]; 0.775 mmol/L[c])[d]

[a] Reference range 130 to 180 g/L (males); 120 to 160 g/L (females)
[b] Reference range Hb tetramer 8.1 to 11.2 mmol/L (males); 7.4 to 9.9 mmol/L (females)
[c] Reference range Hb monomer 2.02 to 2.80 mmol/L (males); 1.85 to 2.47 mmol/L (females)
[d] To account for transfusions, Hb measurements will be adjusted for any PRBCs or whole blood given between 2 blood measurements. A transfusion of one unit of blood will be assumed to result in an increase of 10 g/L[a];

- Transfusion of 4 or more units (whole blood or packed red blood cells [PRBCs]) for bleeding.

Major bleed – other

Any one of the following:

- Significantly disabling (eg. intraocular with permanent vision loss)
- Clinically overt or apparent bleeding associated with a decrease in Hb of 30 g/L[a] (1.9 mmol/L[b]; 0.465 mmol/L[c])[d] to 50 g/L[a] (3.1 mmol/L[b]; 0.775 mmol/L[c])[d]
- Transfusion of 2-3 units (whole blood or PRBCs) for bleeding.

Minor bleed

- Requires medical intervention to stop or treat bleeding (eg. epistaxis requiring visit to medical facility for packing).

Minimal bleed

All others (eg. bruising, bleeding gums, oozing from injection sites, etc) not requiring intervention or treatment.

All blood product transfusions during the study will be recorded in the eCRF using both units and volumes of fluid. Bleeding event data will contain all elements needed to classify by TIMI and BARC criteria.

6.4.6.2 BARC definitions of bleeding events

In this study bleeding events will also be classified according to the BARC definitions as shown below. For patients experiencing a bleeding event that fulfils criteria in more than one category, the bleed will be assigned to the most severe category.

Type 0: No bleeding

Type 1: Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalisation, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional

Type 2: Any overt, actionable sign of haemorrhage (eg. more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not

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0.62 mmol/L[b]; 0.155 mmol/L[c] in Hb. Therefore, to calculate the true change in Hb if there has been an intervening transfusion between 2 blood measurements, the following calculations should be performed:
Δ Hb = [baseline Hb – post transfusion Hb] + [number of transfused units x conversion factor in Hb[e]].
[e] Conversion factor = 10 g/L[a]; 0.62 mmol/L[b]; 0.155 mmol/L[c]

fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalisation or increased level of care, or (3) prompting evaluation

Type 3

Type 3a:

- Overt bleeding plus haemoglobin drop of 3 to <5 g/dL[a] (provided haemoglobin drop is related to bleed)
- Any transfusion with overt bleeding

Type 3b:

- Overt bleeding plus haemoglobin drop ≥5 g/dL[a] (provided haemoglobin drop is related to bleed)
- Cardiac tamponade
- Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/haemorrhoid)
- Bleeding requiring intravenous vasoactive agents

Type 3c:

- Intracranial haemorrhage (does not include microbleeds or haemorrhagic transformation, does include intraspinal)
- Subcategories confirmed by autopsy or imaging or lumbar puncture
- Intraocular bleed compromising vision

Type 4: CABG-related bleeding[b]

- Perioperative intracranial bleeding within 48 h
- Reoperation after closure of sternotomy for the purpose of controlling bleeding

[a] Corrected for transfusion (1 U packed red blood cells or 1 U whole blood=1 g/dL hemoglobin).
[b] CABG indicates coronary artery bypass graft. Platelet transfusions should be recorded and reported but are not included in these definitions until further information is obtained about the relationship to outcomes. If a CABG-related bleed is not adjudicated as at least a type 3 severity event, it will be classified as not a bleeding event. If a bleeding event occurs with a clear temporal relationship to CABG (ie, within a 48-h time frame) but does not meet type 4 severity criteria, it will be classified as not a bleeding event.

– Transfusion of ≥5U whole blood or packed red blood cells within a 48-h period[c]

– Chest tube output ≥2L within a 24-h period

Type 5: Fatal bleeding

Type 5a:

– Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious

Type 5b:

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

6.4.6.3 Bleeding associated with procedures

Bleeding associated with procedures should **only** be reported as both a bleeding event and an AE/SAE if it exceeds what can be expected for the procedure.

6.4.6.4 Procedures for study medication in case of bleeding

Study medication must be stopped immediately in case of a bleed deemed to be clinically significant in the judgment of the investigator (eg. a significant fall in haemoglobin, need for transfusion, haemodynamically significant, or in a critical location such as intracranial, intraspinal, intraocular, or pericardial), but may be reinstated when the risk of bleeding is deemed low in the judgment of the Investigator. The study medication administration need not be stopped in case of a minor bleeding. All bleedings should be treated and followed up according to local clinical practice. Major bleeding events should be managed according to need with general support and blood. It should be noted that platelet transfusion may or may not reverse bleeding in a patient receiving ticagrelor as the new platelets may be inhibited by ticagrelor as long as it is circulating in the blood. For this reason, investigators should not unblind in order to decide whether or not to treat or withhold platelet transfusions.

Treatment of bleedings should be symptomatic and handled according to the clinical routines at the investigational site.

6.4.7 Laboratory safety assessment

At enrolment existing laboratory data will be reviewed and collected in the patient chart for comparative purposes and baseline characteristics should an AE occur.

Follow-up testing for abnormal laboratory results should be performed according to local practice.

[c] Cell saver products are not counted.

At the follow-up visits, laboratory safety assessments will not be routinely done, but may be performed locally at the investigator's discretion. In association with a suspected endpoint event, different assessments may have to be undertaken which could include local laboratory assessments.

See Section 6.4.3 for AEs based on examinations and tests.

6.4.7.1 Management of abnormal liver chemistry tests

The investigator should report any patient meeting potential Hy's Law criteria; Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥3x Upper Limit of Normal (ULN) and Total Bilirubin (TBL) ≥2x ULN at any point during the study, irrespective of Alkaline Phosphatase (ALP). The AST or ALT and total bilirubin values do not have to be elevated at the same visit or within any specified timeframe. Potential cases should be reported for patients on or off study treatment from Visit 1 through the Study Closure to the appropriate AstraZeneca representative.

NB. In case a patient shows an AST **or** ALT ≥3xULN **or** total bilirubin ≥ 2xULN please see Appendix D. 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions.

6.4.8 ECG

At enrolment existing ECG data from the index event will be reviewed, collected, and stored with the patient chart for comparative purposes should an AE occur in the future.

6.4.9 Vital signs

Heart rate and blood pressure

Heart rate, systolic and diastolic BP (blood pressure) will be assessed using non-invasive equipment after the patient has been at rest for 5 minutes. Results will be recorded in the eCRF.

6.5 Patient reported outcomes (PRO)

Patients' health related quality of life will be measured using the EQ-5D quality of life questionnaire, see Section 6.9.1.

6.6 Pharmacokinetics (NA)

6.7 Pharmacodynamics (NA)

6.8 Pharmacogenetics (NA)

6.9 Health economics

Patients' health related quality of life will be measured using the EQ-5D quality of life questionnaire.

6.9.1 Health economic assessment

The EQ-5D has been extensively used within the cardiovascular field to assess patient health related quality of life in trials of new treatments and has showed both high validity and reliability (Brooks 1996).

The EQ-5D consists of two parts: the EQ-5D descriptive system and the EQ-Visual Analogue Scale (EQ-VAS). The EQ-5D descriptive system is a self-administered instrument consisting of five questions, each representing one dimension (Brooks 1996). The 5 dimensions are mobility, self-care, usual activities, pain and discomfort, and anxiety and depression. For each dimension responders are asked to state their status on a three level ordinal scale; whether they experience no problems (Level 1), some problems (Level 2) or severe problems (Level 3). Health states defined by the 5 dimensions can be converted into a weighted health state index (health state utility) by applying scores from the EQ-5D value sets elicited from general population samples (Dolan 1997, Dyer 2010). The EQ-VAS records the respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labelled 'Best imaginable health state' and 'Worst imaginable health state'.

The EQ-5D paper form will be filled in by the patients, or a proxy (site personnel or family member) under the supervision of the study staff. The study staff will transfer the responses into the eCRF. All patients will be asked to complete the EQ-5D questionnaire at all on-site visits from Visits 1 until and including EoT Visit 5. The EQ-5D will only be administered in countries where an official language version is available. Descriptive analysis and reporting of the data will be carried out in the Clinical Study Report (CSR) including converting the EQ-5D to utilities using the UK tariff for all patients. Additional analysis using the single index value to support cost-effectiveness analysis will be reported separate from the main study in a separate health economic (HECON) sub-study report.

Information on health care resource utilisation associated with hospitalisation admissions, rehabilitation, long-term care and health related quality of life will be collected up to Visit 5 EoT to enable health technology assessment, health economic analysis and health economic modelling. Resource utilisation and health related quality of life will be recorded in the eCRF beginning at randomisation. The following types of resources will be recorded for all hospitalisations, rehabilitation in hospital and long-term care:

- Admission date
- Discharge date
- Discharge destination
- Ward type information including duration of stay
  - General
  - CCU (Coronary Care unit)

- ICU (Intensive Care Unit)

- Final discharge diagnosis
- Major secondary discharge diagnosis (if present)
- Main procedures
- In addition, data will be collected on (at all on-site visits):
- Outpatient rehabilitation therapy
- Unscheduled visits to a physician
- Status at 3 months
- Employment status (at baseline and visit 5 and if applicable at PTDV)
- Employment status of primary caregiver based on information from patient (at baseline and visit 5 and if applicable at PTDV)

The variables collected to support health economic evaluation are the EQ-5D questionnaire at randomisation (baseline), Day 7 or hospital discharge and 90 days as well as information on all hospitalisations, all rehabilitations and on long-term care, during the course of the study will also be ascertained. Descriptive reporting of the resource utilization data and health related quality of life data based on the EQ-5D will be carried out in the CSR. The data will be combined with economic data and life expectancy data collected independently of the study to construct comparative health economic analyses between treatment groups. The economic analysis and cost-effectiveness analyses that include data external to the study will not be included in the CSR.

7. BIOLOGICAL SAMPLING PROCEDURES (NA)

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 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 (ICH)/Good Clinical Practice (GCP), applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

8.2 Subject 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.

8.3 Ethics and regulatory review

An Ethics Committee (EC) / Institutional Review Board (IRB) should approve the final study protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the patient. The investigator/Head of the study site will ensure the distribution of these documents to the applicable Ethics Committee/IRB, and to the study site staff.

The opinion of the Ethics Committee should be received in writing. The investigator should submit a notification of direction/determination as well as a copy of the IRB written approval to AstraZeneca before enrolment of any patient into the study.

The Ethics Committee/IRB 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 protocol should be re-approved by the Ethics Committee annually.

Before enrolment of any patient into the study, the final study protocol, 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, Ethics Committees/IRB and Principal Investigators with safety updates/reports according to local requirements, including SUSARs (Suspected Unexpected Serious Adverse Reactions), where relevant.

Each Principal Investigator is responsible for providing the Ethics Committees/IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the study medication. AstraZeneca will provide this information to the Principal Investigator so that he/she can meet these reporting requirements.

8.4 Informed consent

The Principal Investigator(s) at each centre (or delegate) will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study including the importance of continued follow-up for endpoints and safety events until the end of the study even if study medication has been discontinued

- 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 ICF(s) is/are stored in the Investigator's Study File

- Ensure a copy of the signed ICF 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 ICF that is approved by an Ethics Committee/IRB

8.5 Changes to the protocol and informed consent form

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

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol (Revised Clinical Study Protocol).

The amendment is to be approved by the relevant Ethics Committee and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). For distribution to Ethics Committee see Section 8.3.

If a protocol amendment requires a change to a centre's Informed Consent Form, AstraZeneca and the centre's Ethics Committee 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 Ethics Committee.

8.6 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an Ethics Committee 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 protocol, GCP, guidelines of the ICH, and any applicable regulatory requirements. The investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the centre.

9. STUDY MANAGEMENT BY ASTRAZENECA

9.1 Pre-study activities

Before the first patient is entered into the study, it is necessary for a representative of AstraZeneca to visit the investigational study site to:

- Determine the adequacy of the facilities
- Determine availability of appropriate patients for the study
- Discuss with the investigator(s)/ Head of the study site (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of AstraZeneca or its representatives. This will be documented in a Clinical Study Agreement between AstraZeneca and the investigator/ Head of the study site.

9.2 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 the WBDC system utilised.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff and documented, 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).

9.3 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 investigators

- 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 eCRFs and that study drug accountability checks are being performed
- Perform source data verification (SDV) (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)

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.

9.3.1 Source data

Refer to the Clinical Study Agreement (CSA) for location of source data.

Access to source documents and source data is essential to inspection and review of clinical studies by the Food and Drug Administration (FDA).

9.4 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.

9.4.1 Archiving of study documents

The Investigator follows the principles outlined in the CSA.

9.5 Study timetable and end of study

The study is expected to start in Q4 2013 and to end by Q2 2016.

Planned treatment duration in the study: 90 days

Study period: Q4 2013 to Q2 2016.

AstraZeneca will notify investigators when recruitment is complete.

The end of the entire study is defined as 'the last visit of the last patient undergoing the study'.

The study may be terminated at individual centres if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with ticagrelor.

10. DATA MANAGEMENT BY ASTRAZENECA OR DELEGATE

Data will be entered in the WBDC system at the study site. Trained study staff will be responsible for entering data on the observations, tests and assessments specified in the protocol into the WBDC system and according to the eCRF instructions. The eCRF instructions will also guide the study site in performing data entry. Data entered in the WBDC system will be immediately saved to a central database and changes tracked to provide an audit trail. The data will then be Source Data Verified, reviewed/ queried and updated as needed. The investigator is responsible for signing the eCRF and this can be delegated to a trained investigator. The eCRF is signed electronically as per the eCRF instructions. The data will be validated as defined in the Data Management Plan. Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trail. 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 will be frozen and then locked to prevent further editing. When all data have been coded, validated, signed, and locked, a clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked. A copy of the eCRF will be archived at the study site when the study has been locked.

PRO (EQ-5D) paper form will be filled in by the patients, or a proxy (site personnel or family member) under the supervision of the study staff. The study staff will transfer the responses into the eCRF.

Dictionary coding

Medical coding is done using the most current version of MedDRA and AstraZeneca Drug Dictionary.

Management of external data

The data collected through third party sources will be obtained and reconciled against study data. The Data Management Center determines the format of the data to be received from external vendors and coordinates the flow of data to an external environment or clinical database (if applicable). Data Management will ensure that the data collection tool (IVRS/IWRS, etc) will be tested/validated as needed. External data reconciliation will be done with the clinical database as applicable.

Serious Adverse Event (SAE) Reconciliation

SAE Reconciliation Reports are produced and reconciled with Patient Safety database.

11. EVALUATION AND CALCULATION OF VARIABLES BY ASTRAZENECA OR DELEGATE

11.1 Calculation or derivation of efficacy variable(s) (NA)

11.2 Calculation or derivation of safety variable(s)

11.2.1 Other significant adverse events (OAE)

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and DAEs. Based on the expert's judgement, significant adverse events of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered OAEs and reported as such in the Clinical Study Report. A similar review of laboratory/vital signs/ECG data will be performed for identification of OAEs.

Examples of these are marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment.

11.3 Calculation or derivation of patient reported outcome variables

See Section 6.9.

11.4 Calculation or derivation of health economic variables

See Section 6.9.

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION BY ASTRAZENECA OR DELEGATE

12.1 Description of analysis sets

12.1.1 Efficacy analysis set

All patients who have been randomised to study treatment will be included irrespective of their protocol adherence and continued participation in the study. Patients will be analysed according to their randomised study medication irrespective of whether the event occurred before or following discontinuation of study medication. Patients who withdraw consent to participate in the study will be included up to the date of their study termination except for vital status known through public records (for use in the analysis of all cause death). All efficacy variables will be analysed using the full analysis set (FAS).

12.1.2 Safety analysis set

All patients who received at least 1 dose of randomised ticagrelor or ASA, and for whom any post-dose data are available will be included in the safety population. Throughout the safety results sections, erroneously treated patients (eg, those randomised to ticagrelor but actually

given ASA) will be accounted for in the actual treatment group. Patients will be censored at 7 days after their last dose of study medication.

12.2 Methods of statistical analyses

12.2.1 Efficacy analyses

All efficacy analyses will be based on the intent-to-treat principle using the FAS, including only events adjudicated by the CEC. Investigators are instructed to report all suspected endpoints in the eCRF, even those that may not meet strict endpoint definitions, to ensure all potential events are reviewed and adjudicated by the CEC. The time from randomisation to the first occurrence of any event in the given endpoint will be compared using the Cox proportional hazards model with a factor for treatment group, using the Efron method for ties. The p-value (calculated using the score test), hazard ratio (HR) and 95% confidence interval will be reported. No multiplicity adjustment will be made to the confidence intervals as they will be interpreted descriptively and used as measures of precision. Kaplan-Meier estimates of the cumulative risk of each composite endpoint and its individual components will be calculated and plotted.

The analysis of the primary composite efficacy variable and the first secondary efficacy variable, ischaemic stroke for the test of ticagrelor against ASA will comprise the confirmatory analysis. The first secondary variable, time to first ischaemic stroke, will be tested in the confirmatory sense only if the primary comparison is significant (see Section 12.2.3).

Based on data from the FASTER (Kennedy 2007), CHANCE (Wang 2013) and SCAST (Sandset 2011) trials, the number of patients that withdraw from the study is expected to be low (1 to 2%). The impact of the withdrawals on the primary results will be assessed by sensitivity analyses using the following methods: based on the missing follow-up time in drop-outs, ie, the time from censoring to study closure (the expected number of events that might have been observed if the drop-outs had completed the study can be calculated using an event rate similar to that observed in the study). The primary analysis will be recalculated with these residual events allocated in different proportions to the treatment groups to assess the robustness of the results with regard to the censoring of drop-outs.

12.2.1.1 Primary efficacy variable

The primary analysis will compare the time from randomisation to the first occurrence of any event in the composite endpoint of stroke, MI and death. The null hypothesis will be that the risk/hazard of an event on ticagrelor is equal to the corresponding risk/hazard on ASA ie;

H_0: HR (ticagrelor divided by ASA) = 1

The alternative hypothesis will be that the HR is greater, or less than 1, ie:

H_1: HR $\neq$ 1

The hypothesis will be tested at 4.98% two-sided significance level.

The HR and 95% confidence interval will be reported. Kaplan Meier estimates of the cumulative incidence to the first occurrence of any event in the composite endpoint will be calculated and plotted.

The assumption of proportional hazards for the factor for treatment group will be assessed visually using log-cumulative hazard plots. The effect of any departures from proportional hazards will be discussed as part of the presentation of results of the analyses.

Subgroup analysis will be performed to evaluate variation of treatment effect, as well as a test of interaction with treatment for each subgroup variable. The p-values of the subgroup analyses and interaction tests will not be adjusted for multiple comparisons as the tests are exploratory and will be interpreted descriptively. Hazard ratios and 95% confidence intervals will be reported for each subgroup. Relevant subgroups will be examined for e.g. age, sex, race, weight/BMI, diabetes and other medical history characteristics.

12.2.1.2 Secondary efficacy variable included in a hierarchical test sequence

The analysis of the primary composite variable will be repeated for the secondary efficacy variable for the test of ticagrelor against ASA:

- Time from randomisation to first occurrence of any ischaemic stroke

The analysis of the primary and this secondary efficacy variable will comprise the confirmatory analysis. In order to address the issue of multiple testing, a hierarchical test sequence will be used.

If the treatment effect on the primary efficacy variable is significant at the 4.98% level, the secondary efficacy variable listed above will be tested in a confirmatory sense. Otherwise it will be tested in an exploratory manner.

12.2.1.3 Other secondary efficacy variables

1. Time from randomisation to first occurrence of any of the events which comprise the Net Clinical Outcome

2. Time from randomisation to first occurrence of any event of the composite of ischaemic stroke, MI and CV death

3. Time from randomisation to first occurrence of all-cause death

4. Time from randomisation to first occurrence of CV death

5. Time from randomisation to first occurrence of MI

6. Severity of stroke and overall disability of patients at the end of study using mRS, see Appendix C

7. Time from randomisation to first occurrence of all stroke (including haemorrhagic stroke)

8. Time from randomisation to first occurrence of fatal stroke

9. Time from randomisation to first occurrence of disabling stroke

10. Change from baseline in the score on the NIHSS, see Appendix C

11. Health care utilization and utilities assessed by EQ-5D questionnaire

For the time to event variables (1 to 5 and 7 to 9 above), ticagrelor and ASA treatment groups will be compared using the Cox proportional hazards model with a factor for treatment group. Kaplan-Meier estimates of the cumulative incidence of each event will be calculated and plotted and 95% CI for the hazard ratios presented.

The difference between treatment groups in the NIHSS, EQ-5D, hospitalizations and the modified Rankin Score will be analysed descriptively. See Section 6.9 for a description of collection and further analysis of health economic data.

12.2.2 Safety variables

Analysis of time from first dose of study medication to each of the following endpoints will be performed:

- The first PLATO major bleeding event

- Discontinuation of study medication due to any bleeding event

Treatment groups will be compared using the Cox proportional hazards model with a factor for treatment group. Kaplan-Meier estimates of the cumulative incidence of each event will be calculated and plotted and 95% CI for the hazard ratios presented. The safety assessment will also include analysis of total major bleeding events, fatal bleeding events, fatal or life threatening bleeding events, combined major and minor bleeding events across different categories as well as different categories of major and minor bleeding events separately. Exploration of potential risk factors for bleeding events, including subgroups and use of concomitant antithrombotic therapy, will be performed.

Bleeding events will be analysed according to adjudicated PLATO bleeding, the Thrombolysis in Myocardial Infarction (TIMI) Study Group and Bleeding Academic Research Consortium (BARC) class 3, 4, and 5 definitions (see the CEC charter).

MedDRA will be used for the coding and classification of AEs and SAEs in the database. AEs will be summarised by system organ class and preferred term using MedDRA. Summaries will be presented by treatment group using descriptive statistics. All AEs relating to bleeding will be summarised separately and the total number of bleeding events will be assessed.

12.2.3 Interim analyses

One interim analysis will be performed by the DMC following the accrual and confirmation by adjudication of 50% of planned primary events (422). The study may be stopped either for futility or for efficacy. The efficacy stopping boundary at the interim analysis is a 2-sided p-value <0.001 for the primary endpoint (composite of stroke, MI, and death). The interim p-value is small enough for the final analysis to be conducted at a significance level of 4.98%, with the family wise error rate controlled at 5.00%. These boundaries were estimated in East V5.2 using a Haybittle-Peto procedure (Haybittle 1971, Peto 1976). The futility stopping boundary is to stop if the observed HR for the primary endpoint is >0.954, corresponding to a predictive power of 10%. This provides > 88.7% overall power at the end of the study.

If a recommendation to stop the study for efficacy is made at the interim, all subsequent testing will be done at the same significance level as for the interim.

The DMC charter contains more information about the DMC procedures. A copy of the treatment codes will be made available to the statistician on the DMC. The Executive Committee and AstraZeneca will not be made aware of the treatment codes until after clean file and database lock are declared. Similarly, all summary output reviewed at each DMC meeting will be held in confidence by the DMC members until the end of the study when clean file and database lock are declared. Further details are given in the DMC charter.

12.2.4 Censoring

Patients who have not had the event(s) in question will be censored at the earliest of EoT Visit 5 (90 days) and the last study contact when all components of the endpoint in question were assessed. In the analysis of CV death and composites including CV death, censoring will occur at the date of death from non-cardiovascular causes. For endpoints not including death, all deaths are censoring events.

Complete endpoint information will be pursued with every effort for all patients regardless of their study medication status, unless they exercise their right to withdraw consent. Patients who have a non-fatal event will continue study follow-up. For patients who withdraw consent and for whom only vital status (known to be alive at study closure, or date of death) may be obtained from public records, the occurrence of all components of the primary endpoint cannot be assessed. Thus the primary endpoint and its components stroke, MI, and death will be censored at the time of consent withdrawal for those patients who withdraw consent and for whom only vital status is known from public records. However, the determination of all-cause death as a sole outcome event will utilise all publicly known mortality data, even that extending beyond date of consent withdrawal. The vital status information will be included in the analysis of all-cause death as a single secondary endpoint, in sensitivity analyses and tabulations.

Similarly, complete information on the primary endpoint may not be obtained for patients who are lost to follow-up (LTFU). Any such patient will be censored in the analysis of the primary composite endpoint at the last contact where all elements of the endpoint were assessed. A

patient will not be recorded as LTFU until the end of the study, after every allowable effort to get in contact has been made. Hence, it is anticipated that the number of patients LTFU will be limited.

Should it be that information about vital status after the End of Treatment Visit is collected for patients that are lost to follow-up, one sensitivity analysis will censor such observations at the date of the End of Treatment Visit and another will include all known events.

12.2.5 Post study follow-up period

Data collected at Study Closure Visit will be presented using descriptive statistics per treatment. The FAS will be used for the efficacy endpoints and the safety analysis set will be used for the adverse events.

12.3 Determination of sample size

Based on data from the FASTER trial (Kennedy 2007), CHANCE trial (Wang 2013) and SCAST trial (Sandset 2011) a primary endpoint (stroke, MI, death) rate of 10% in the ASA arm is assumed at 3 months following randomisation. A HR in favour of ticagrelor of 0.8, is also assumed. Blind data review has revealed a lower than anticipated primary endpoint rate of approximately 6.4% instead of the 9% originally anticipated. Randomising 13600 patients to the ASA and ticagrelor in a 1:1 ratio is expected to yield the 844 primary events providing 88.7% power at the final significance level of 4.98%, defined in Section 12.2.3. The study is event driven and the number of patients is estimated to ensure collection of 844 events. The final number of randomised patients will depend on the collection of the primary events and the actual sample size will be determined based on blind data review.

12.4 Data monitoring committee

See Section 5.10.

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca contacts

The Principal Investigator is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and is to be reported as such, see Section 6.4.4**

In the case of a medical emergency the investigator may contact the Study Team Physician or delegate.

Name	Role in the study	Address & telephone number
	Lead Study Physician	AstraZeneca R&D, Mölndal 431 83 Mölndal, Sweden
	Study Physician	AstraZeneca R&D, Mölndal 431 83 Mölndal, Sweden
	Clinical Development Manager	AstraZeneca R&D, Mölndal 431 83 Mölndal, Sweden

13.2 Overdose

An overdose of ticagrelor is defined as an intake of greater than 4 ticagrelor tablets/day during the maintenance phase.

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 it must be decided whether the patient should be hospitalized 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 IB.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then investigators 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 SAE, standard reporting timelines apply, see Section 6.4.4. For other overdoses, reporting should be done within 30 days.

13.3 Pregnancy

All outcomes of pregnancy should be reported to AstraZeneca.

13.3.1 Maternal exposure

If a patient becomes pregnant during the course of the study, the study medication should be discontinued immediately.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the study medication 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 a pregnancy on an AstraZeneca study medication occurs during the course of the study, then investigators or other site personnel should 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 within 1 or 5 days for SAEs, see Section 6.4.4, and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

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

13.3.2 Paternal exposure

There are no restrictions against fathering a child when treated with ticagrelor. If paternal exposure pregnancy occurs in the course of the study, then investigators or other site personnel should inform appropriate AstraZeneca representatives immediately, or no later than **24 hours** as described in the maternal exposure Section 13.3.1.

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AstraZeneca

Clinical Study Protocol Appendix B

Drug Substance	Ticagrelor
Study Code	D5134C00001
Edition Number	1
Date	21 August 2013

Appendix B
Additional Safety Information

FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

Life threatening

'Life-threatening' means that the subject 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 subject'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 subject 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 subject 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.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- 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

The following factors should be considered 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 subject 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?

- Dechallenge 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.

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

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

A "reasonable possibility" could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

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

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

- Is there a known mechanism?

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. 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 Appendix C	
Drug Substance	Ticagrelor
Study Code	D5134C00001
Edition Number	2
Date	5 June 2014

Appendix C

Modified Rankin Scale, NIH Stroke Scale, Euro Quality of Life-5 Dimensions and ASCOD

INTRODUCTION

The research activities and adhering scales described in this appendix are Modified Rankin Scale, NIH Stroke Scale, Euro Quality of Life-5 Dimensions, and ASCOD.

DEFINITIONS AND USE

Modified Rankin Scale (mRS): This scale will be used to measure severity of stroke and overall disability of patients. MRS requires a user certificate.

NIH Stroke Scale (NIHSS): Rate of worsening, i.e., progression of the index stroke event assessed by deterioration in clinical symptoms and/or an increase in the score on the NIHSS. NIHSS requires certification every other year.

NB: Note that the intervals shown in the NIH Stroke Scale:

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

are not applicable in the SOCRATES Study (D5134C00001).

Euro Quality of Life-5 Dimensions (EQ-5D): Patients' health related quality of life will be measured using the EQ-5D quality of life questionnaire to support health technology assessment and health economic modelling. The EQ-5D paper form will be filled in by the patients, or a proxy (site personnel or family member) under the supervision of the study staff. EQ-5D will only be administered in countries where an official language version is available. The English version for UK is included in Appendix C. Translations of EQ-5D into local languages have been performed according to a linguistic validation process.

ASCOD (Atherosclerosis, Small-vessel disease, Cardiac pathology, Other causes, Dissection): Classification of Stroke (5 categories to grade).

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MODIFIED RANKIN SCALE (MRS)

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

TOTAL (0–6): _____

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***Stroke* 1988;19(5):604-7**

NIH STROKE SCALE

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 (not stereotyped). 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 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.	0 = **Normal.** 1 = **Partial gaze palsy;** gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present. 2 = **Forced deviation,** or total gaze paresis not overcome by the oculocephalic maneuver.	_____

NIH STROKE SCALE

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

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** of one or both sides (absence of facial movement in the upper and lower face).	_____
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 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 (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. 3 = **No effort against gravity;** limb falls. 4 = **No movement.** UN = **Amputation** or joint fusion, explain: _____ **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 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.	0 = **No drift;** leg holds 30-degree position for full 5 seconds. 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.** UN = **Amputation** or joint fusion, explain: _____ **6a. Left Leg** **6b. Right Leg**	_____ _____

NIH STROKE SCALE

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

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 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.	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 materials difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content from patient's response. 2 = **Severe aphasia;** all communication 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's 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 physical barrier, explain:_____	_____

Rev 10/1/2003

NIH STROKE SCALE

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

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** or 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.	_____

_____

_____

Rev 10/1/2003


COOKIE
JAR

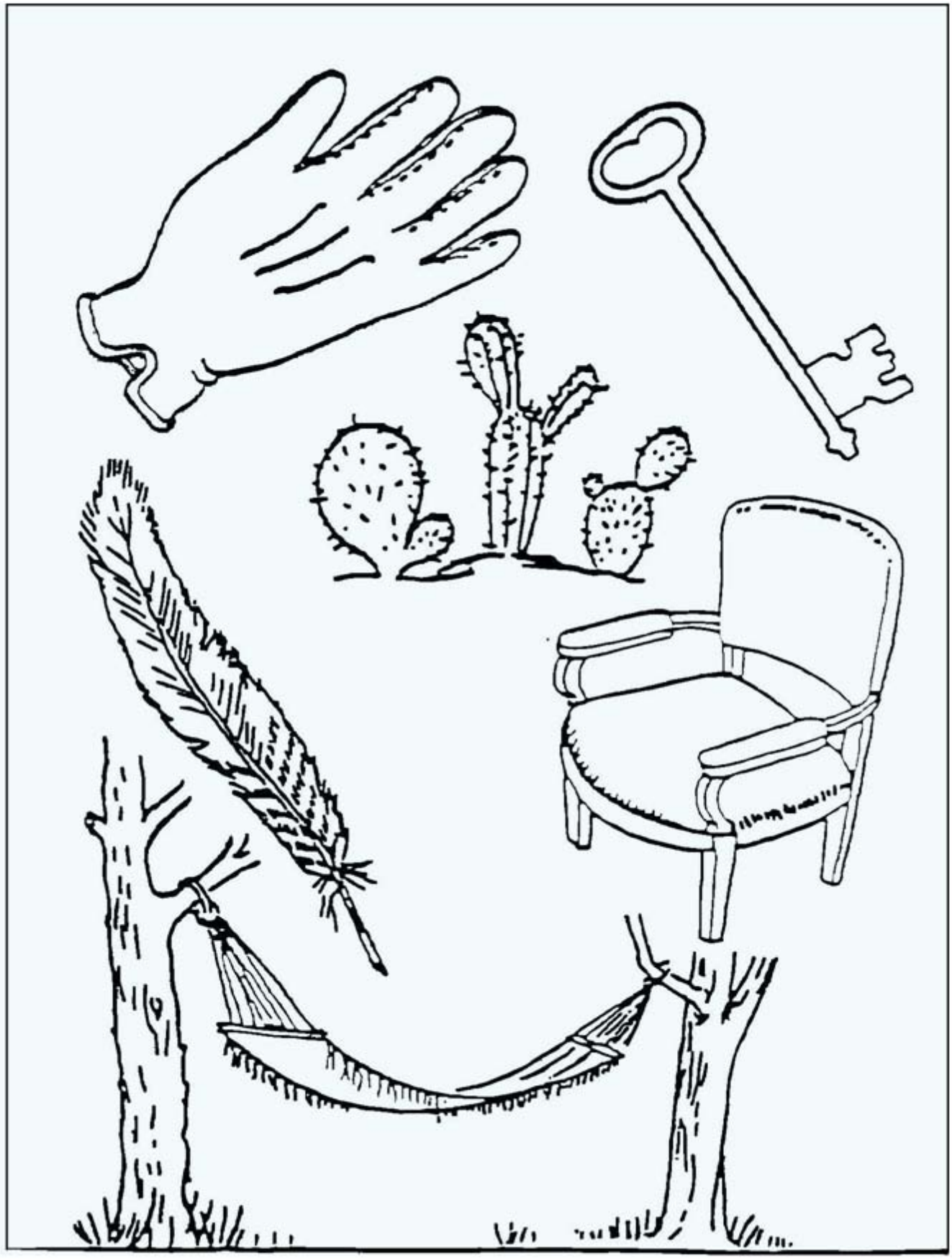
You know how.

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

Health Questionnaire

(English version for the UK)
(validated for use in Eire)

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some 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 with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑

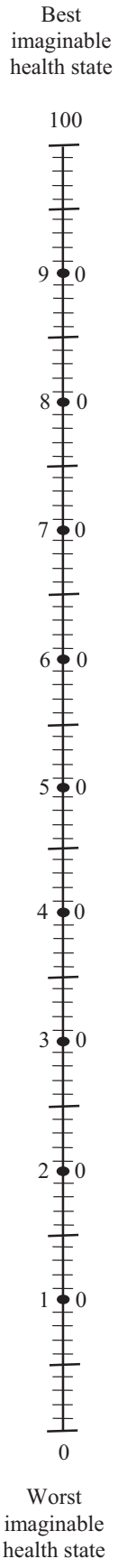
I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



ASCOD Phenotyping of Ischemic Stroke

In the SOCRATES study, the investigator will be expected to assess each patient against the ASCOD stroke classification scale (Amarenco 2013). In ASCOD, there are 5 categories for consideration:

A (Atherosclerosis)
S (Small-vessel disease)
C (Cardiac pathology)
O (Other causes)
D (Dissection)

The investigator will rate each phenotype, using Tables 1 and 2 below, and record the result in the electronic Case Report Form in the clinical database (RAVE). Each patient's final overall classification will be automatically determined by the system.

Table 1. Method of Classification

Grades of diseases	
1	If the disease is present and can potentially be a cause
2	If the disease is present, but the causal link is uncertain
3	If the disease is present, but the causal link is unlikely
0	If the disease is absent
9	If the workup is insufficient to grade the disease

Table 2. Grades of predefined ASCOD phenotypes

A: Causality grades for atherothrombosis		
A1 (potentially causal)	Atherothrombotic stroke defined as:	
	(1)	Ipsilateral atherosclerotic stenosis between 50 and 99% in an intra- or extracranial artery supplying the ischemic field; *or*
	(2)	Ipsilateral atherosclerotic stenosis <50% in an intra- or extracranial artery with an endoluminal thrombus supplying the ischemic field; *or*
	(3)	Mobile thrombus in the aortic arch; *or*
	(4)	Ipsilateral arterial occlusion in an intra- or extracranial artery with evidence of underlying atherosclerotic plaque supplying the ischemic field
A2 (causal link is uncertain)	(1)	Ipsilateral atherosclerotic stenosis 30-50% in an intra- or extracranial artery supplying the ischemic field; or
	(2)	Aortic plaque ≥4 mm without mobile lesion
A3 (causal link is unlikely, but the disease is	(1)	Plaque (stenosis <30%) in an intra- or extracranial artery, ipsilateral to the infarct area;
	(2)	Aortic plaque <4 mm without mobile thrombus;

present)	(3)	Stenosis (any degree) or occlusion in a cerebral artery not supplying the infarct area (e.g. contralateral side or opposite circulation);
	(4)	History of myocardial infarction, coronary revascularization or peripheral arterial disease;
	(5)	Ipsi- or bilateral atherosclerotic stenosis 50-99% with bihemispheric MR-DWI lesion
A0 (atherosclerosis not detected)	Ruling out atherosclerosis:	
	(1)	Extracranial arterial stenosis: one or several of the following diagnostic tests are performed and are negative: US-Duplex, CTA, MRA, XRA, or autopsy;
	(2)	Intracranial arterial stenosis: one or several of the following diagnostic tests are performed and are negative: US-TCD, MRA, CTA, XRA, or autopsy
	(3)	Aortic arch atheroma: TEE with specific assessment of the aortic arch (when the probe is pulled back at the end of the cardiac examination, turn the probe counter clockwise and take time to watch the aortic arch) or specific aortic arch assessment with CTA
A9 (incomplete workup)	US-Duplex, US-TCD, or CTA, or MRA, or XRA or autopsy not performed. [A minimum workup is extra- and intracranial assessment of cerebral arteries – maximum workup also includes transesophageal assessment of the aortic arch (or a default CTA of the aortic arch)]	
S: Causality grades for small-vessel disease		
S1 (potentially causal)	Combination of:	
	(1)	Lacunar infarction: small deep infarct <15 mm (in perforator branch territory) on MRI-DWI (or a default CT) in an area corresponding to the symptoms and at least one of the three following criteria:
	(2)	One or several small deep older infarct(s) of lacunar type in other territories, *and/or*
	(3)	Severe (confluent – Fazekas III) leukoaraiosis, or microbleeds, or severe dilatation of perivascular spaces (‘état criblé’);
	(4)	Repeated, recent (<1 month), TIAs attributable to the same territory as the index infarct
S2 (causal link is uncertain)	(1)	Only one, recent, lacunar infarction and no other abnormality on MRI (or CT) *or*
	(2)	Clinical syndrome suggestive of a deep branch artery stroke, without ischemic lesion in the appropriate area seen on MRI or CT (main clinical syndrome suggesting a deep branch artery – lacunar – stroke: pure hemiparesis, pure hemisensory loss, ataxic hemiparesis, dysarthria-clumsy hand syndrome, unilateral sensorimotor deficit, others: hemichorea, hemiballism, pure dysarthria, etc.)

S3 (causal link is unlikely, but the disease is present)	Severe (confluent – Fazekas III) leukoaraiosis visible on MRI and/or CT scan, and/or microbleeds visible on T2*-weighted MRI, and/or severe dilattation of perivascular spaces (visible on T2-weighted MRI), and/or one or several old, small deep infarcts of lacunar type
S0 (small-vessel disease not detected)	Ruling out small-vessel disease stroke: negative MRI (T2, FLAIR, GRE, DWI) and no appropriate clinical syndrome suggestive of a deep branch artery stroke
S9 (incomplete workup)	MRI (or CT) not performed
C: Causality grades for cardiac pathology	
C1 (potentially causal)	Cardiogenic stroke defined as acute, or recent and older bihemispheric or supra- and infratentorial territorial or cortical ischemic lesions and signs of systemic embolism with detection of at least one of the following potential causes: (1) Mitral stenosis (surface <1.5 cm^2); (2) Mechanical valve; (3) Myocardial infarction within 4 weeks preceding the cerebral infarction; (4) Mural thrombus in the left cavities; (5) Aneurysm of the left ventricle; (6) History or presence of documented atrial fibrillation – whether paroxysmal (> 60 s), persistent or permanent – or flutter, with or without left atrial thrombus or spontaneous echo; (7) Atrial disease (tachycardia-bradycardia syndrome); (8) Dilated or hypertrophic cardiomyopathies; (9) Left ventricle ejection fraction <35%; (10) Endocarditis; (11) Intracardiac mass; (12) PFO *and* thrombus in situ; (13) PFO *and* concomitant pulmonary embolism or proximal DVT preceding the index cerebral infarction; (14) Aforementioned cardiac pathologies (C1) with single or without obvious cerebral ischemic lesion
C2 (causal link is uncertain)	Regardless of stroke pattern: (1) PFO + atrial septal aneurysm; (2) PFO and pulmonary embolism or proximal DTV concomitant but NOT preceding the index cerebral infarction; (3) Intracardiac spontaneous echo-contrast; (4) Apical akinesia of the left ventricle and decreased ejection fraction (but >35%); (5) History of myocardial infarction or palpitation and multiple brain infarction, repeated either bilateral or in two different arterial territories (e.g. both anterior and posterior circulation);

	(6)	No direct cardiac source identified, but multiple brain infarction, repeated either bilateral or in two different arterial territories (e.g. both anterior and posterior circulation) and/or evidence of systemic emboli: renal or splenic or mesenteric infarction (on CT, MRI, or autopsy) or embolism in peripheral artery supplying arm or leg
C3 (causal link is unlikely, but the disease is present)	One of the following abnormalities present in isolation: PFO, ASA, strands, mitral annulus calcification, calcification aortic valve, nonapical akinesia of the left ventricle, transient atrial fibrillation <60 s, atrial hyperexcitability	
C0 (cardiac pathology not detected or not suspected)	Ruling out a cardiac source of embolism: minimum is negative ECG and examination by a cardiologist; maximum is negative ECG/telemetry/24-Holter ECG/long-term ECG recording (implantable device, transtelephonic ECG, loop recorder) and negative TEE for atrium, valves and septal abnormalities, negative TTE for PFO and assessment of left ventricle, negative cardiac CT/MRI, negative abdominal CT/MRI (search for old or simultaneous subdiaphragmatic visceral infarction)	
C9 (incomplete workup)	Minimum is ECG and examination by a trained cardiologist in the absence of cardiac imaging	
O: Causality grades for other causes		
O1 (potentially causal)	(1)	Dolichoectasia with complicated aneurysm;
	(2)	Polycythemia vera or thrombocytemia >800,000/mm^3;
	(3)	Systemic lupus;
	(4)	Disseminated intravascular coagulation;
	(5)	Antiphospholipid antibody syndrome (including >100 GPL units or lupus anticoagulant);
	(6)	Fabry's disease;
	(7)	Coexisting meningitis;
	(8)	Sickle cell disease;
	(9)	Ruptured intracranial aneurysm with or without vasospasm of the artery supplying the infarcted area;
	(10)	Severe hyperhomocysteinemia;
	(11)	Horton's disease;
	(12)	Other cerebral inflammatory or infection angiitis;
	(13)	Moyamoya disease, etc….
O2 (causal link is uncertain)	(1)	Saccular aneurysm (with a suspicion of embolism from it)
	(2)	Coincidental migraine attack with neurological deficit lasting >60 min in patients with history of migraine aura
O3 (causal link is unlikely but the disease is present)	(1)	Arteriovenous malformation;
	(2)	Thrombocythosis <800,000/mm^3;
	(3)	Antiphospholipid antibody <100 GPL units;
	(4)	Homocysteinemia <40 μmol/l;

	(5)	Malignoma with associated hypercoagulation (high D-dimer levels), deep vein thrombosis or pulmonary embolism and/or recent chemotherapy
O0 (no other cause detected)	Ruling out other causes: negative: cerebrospinal fluid, complete hemostasis, cerebral arterial imaging, family history of inherited disease, inflammatory markers (erythrocyte sedimentation rate, C-reactive protein), hematologic tests (platelet, leucocytes, and eosinophilic counts, hematocrit), specific tests according to the suspected disease (e.g. genetic test, retinal angiography for Susac syndrome)	
O9 (incomplete workup)	Unable to reasonably exclude other causes based on best available diagnostic tests and stroke-specific history	
D: Causality grades for dissection		
D1 (potentially causal)	(1)	Arterial dissection by direct demonstration (evidence of mural hematoma: hypersignal on FAT-saturated MRI or at autopsy or on TOF-MRA or CT on axial sections showing both enlargement of the arterial wall by the hematoma with narrowing of the lumen or on echography showing an hypoechoic arterial wall with narrowing of the lumen and sudden enlargement of the carotid or vertebral (V2) artery diameter;
	(2)	Arterial dissection by indirect demonstration or by less sensitive or less specific diagnostic test (only long arterial stenosis beyond the carotid bifurcation or in V2, V3 or V4 without demonstration of arterial wall hematoma: on X-ray angiography, and/or echography and/or CTA and/or MRA) or unequivocal US with recanalization during follow-up
D2 (causal link is uncertain)	(1)	Arterial dissection by weak evidence (suggestive clinical history, e.g., painful Horner's syndrome or past history of arterial dissection);
	(2)	Imaging evidence of fibromuscular dysplasia of a cerebral artery supplying the ischemic field
D3 (causal link is unlikely, but the disease is present)	(1)	Kinking or dolichoectasia without complicated aneurysm or plicature;
	(2)	Fibromuscular dysplasia on arteries not supplying the ischemic field
D0 (no dissection detected or suspected)	Ruling out dissection: negative FAT-saturated MRI of suspected artery or good quality, normal X-ray angiography (too early FAT-saturated MRI performed within 3 days of symptom onset can be falsely negative and then should be repeated). If there is no clinical suspicion of dissection, the patient can be classified D0 provided good-quality extra- or intracranial cerebral artery and cardiac evaluations have been performed	
D9 (incomplete workup)	In patients aged less than 60 years and with no evidence of A1, A2, S1, C1, or O1 category: no FAT-saturated MRI performed on the extra- or intracranial artery supplying the ischemic field or no X-ray angiography performed (all performed within 15 days of symptom onset)	

LIST OF REFERENCES

Amarenco 2013

Amarenco P, Bogousslavsky J, Caplan LR, Donnan GA, Wolf, ME, Hennerici MG. The ASCOD Phenotyping of ischemic stroke (Updated ASCO phenotyping). Cerebrovasc Dis 2013;36:1-5. Published online July 30, 2013.

AstraZeneca

Clinical Study Protocol Appendix D	
Drug Substance	Ticagrelor
Study Code	D5134C00001
Edition Number	1
Date	21 August 2013

Appendix D

Actions Required in Cases of Combined Increase of Aminotransferase and Total Bilirubin - Hy's Law

TABLE OF CONTENTS PAGE

1. INTRODUCTION

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

2. DEFINITIONS

Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) **and** Total Bilirubin (TBL) ≥ 2xULN at any point during the study irrespective of an increase in Alkaline Phosphatase (ALP). The elevations do not have to occur at the same time or within a specified time frame.

Hy's Law (HL)

AST or ALT ≥ 3x ULN **and** TBL ≥ 2xULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug. The elevations do not have to occur at the same time or within a specified time frame.

3. IDENTIFICATION OF POTENTIAL HY'S LAW CASES

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3xULN
- AST ≥ 3xULN
- TBL ≥ 2xULN

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative
- Promptly enter the laboratory data into the laboratory CRF

4. FOLLOW-UP

4.1 Potential Hy's Law Criteria not met

If the patient does not meet PHL criteria the Investigator will:

- Inform the AstraZeneca representative that the patient has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

4.2 Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team

The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up and the continuous review of data.

Subsequent to this contact the Investigator will:

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician
- Complete the three Liver CRF Modules as information becomes available
- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

5. REVIEW AND ASSESSMENT OF POTENTIAL HY'S LAW CASES

The instructions in this Section should be followed for all cases where PHL criteria are met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP. The AstraZeneca Medical Science Director and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there **is** an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF

- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the AZ standard processes

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Report an SAE (report term 'Hy's Law') according to AstraZeneca standard processes:

  - The 'Medically Important' serious criterion should be used if no other serious criteria apply

  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above

- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review

6. REFERENCES

FDA Guidance for Industry (issued July 2009) ‘Drug-induced liver injury: Premarketing clinical evaluation’:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf