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**Revised Clinical Study Protocol**

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| Drug Substance | Ticagrelor |
| Study Code | D5136C00008 |
| Edition Number | 1.0 |
| Date | 27 August 2015 |

# A randomised, double-blind, double-dummy, parallel-group, multicenter, phase IIb study to evaluate the effect of ticagrelor 10 mg and 45 mg bid versus placebo in reducing the number of days with pain in young adults with sickle cell disease

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3 Sep 2015
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**The following Amendment(s) and Administrative Changes are included in this revised protocol:**

| Amendment No. | Date of Amendment | Local Amendment No. | Date of local Amendment |
|---|---|---|---|
| 1.0 | 27 August 2015 | | |
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| Administrative change No. | Date of Administrative Change | Local Administrative change No. | Date of local Administrative Change |
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# PROTOCOL SYNOPSIS

## A randomised, double-blind, double-dummy, parallel-group, multicenter, phase IIb study to evaluate the effect of ticagrelor 10 mg and 45 mg bid versus placebo in reducing the number of days with pain in young adults with sickle cell disease

### Study site(s) and number of patients planned

This study will be conducted at approximately 32 centres in approximately 8 countries. It is expected that approximately 90 patients of both sexes, from 18 to 30 years of age (inclusive) will be randomised to study treatment.

| Study period | | Phase of development |
|---|---|---|
| Estimated date of first patient enrolled | Q2 2015 | Phase IIb |
| Estimated date of last patient completed | Q3 2016 | |

### Study design

This is a randomised, double-blind, double-dummy, parallel-group, placebo-controlled, study evaluating 2 doses of ticagrelor in 90 patients aged 18 to 30 years, with sickle cell disease (SCD). Patients will start with a 4-week single-blind double-dummy placebo run-in period to determine the frequency of days with pain at baseline using an electronic diary (eDiary) every day. Approximately 180 patients will be enrolled for the run-in period in order to provide 90 patients meeting criteria for randomisation. Patients with ≥4 days of pain during last 4 weeks of the run-in period will be eligible for randomisation. Patients will then be randomised to double-blind double-dummy treatment period in a 1:1:1 ratio (30 to each treatment group) to receive ticagrelor 10 mg twice daily (bid), or 45 mg bid, or placebo bid for 12 weeks. Patient will be followed for safety assessment during and after 2 weeks of treatment completion.

During the 12 week treatment period, patients will complete a daily eDiary concerning daily pain intensity, pain location, use of analgesics and absence from school or work. At the end of the study patients will be asked to rate the change in their sickle cell pain compared to baseline. Platelet aggregation will be measured and reported as $P2Y_{12}$ reaction units (PRU) pre-dose and 2 hours post-dose at the randomisation and 1 week post randomisation. Pharmacokinetic (PK) parameters will be measured at 2 hours post-dose at randomisation; and pre-dose and at 2 hours post-dose, 1 week post randomisation. Biomarkers will be assessed pre-dose at randomisation, at 1 week and 4 week post randomisation. During the study, patients will be evaluated for adverse events (AEs) including bleeding and vaso-occlusive crisis (VOC).

## Objectives

| **Primary Objective:** | **Outcome Measure:** |
|---|---|
| To investigate the efficacy of 2 different doses of ticagrelor versus placebo in reducing the number of days with pain due to SCD | Number of days with pain due to SCD |

| **Secondary Objective:** | **Outcome Measure:** |
|---|---|
| To determine the efficacy of 2 different doses of ticagrelor versus placebo in reducing the intensity of pain due to SCD | Intensity of pain due to SCD |
| To access the efficacy of 2 different doses of ticagrelor versus placebo in reducing the use of analgesics due to SCD | Days of analgesic use |

| **Safety Objective:** | **Outcome Measure:** |
|---|---|
| To assess safety and tolerability of 2 different doses of ticagrelor versus placebo in patients with SCD | Number of major bleeding or clinically relevant non-major bleeding events<br>AE/ Serious Adverse Events (SAEs)<br>Vital signs, Laboratory Safety Samples |

| **Exploratory Objective:** | **Outcome Measure:** |
|---|---|
| To determine the efficacy of 2 different doses of ticagrelor versus placebo in reducing the frequency of VOC period in patients with SCD | Frequency of VOC |
| To assess the efficacy of 2 different doses of ticagrelor versus placebo in reducing the number of absent days from school/work in patients with SCD | Days absent from school/work |
| To assess the efficacy of 2 different doses of ticagrelor versus placebo in reducing the use of opioid analgesics in patients with SCD | Days of opioid analgesic use |
| To evaluate the pharmacokinetic (PK) properties of 2 doses of ticagrelor in young adult patients with SCD | Ticagrelor and active metabolite concentrations at Visits 2 and 3 |
| To assess the effect of 2 different doses of ticagrelor on inhibition of platelet aggregation and biomarkers of platelet activation | PRU at 0 and 2 hours post-dose on Visits 2 and 3. Change in Soluble Platelet Selectin (sP-selectin), Soluble CD40 Ligand (sCD40L) and Thromboxane B2 (TXB2) |

| Exploratory Objective: | Outcome Measure: |
|---|---|
| To assess the dose-plasma concentration - response relationship with regards to PRU | The relationship between ticagrelor dose, plasma concentration and PRU using a population PK and Pharmacokinetic/Pharmacodynamic (PK/PD) modelling approach |

**Target patient population**

Patients eligible for this study include young adults aged ≥ 18 to ≤ 30 years of age (age at Visit 1) who are diagnosed with SCD [homozygous sickle cell (HbSS) or sickle beta-zero-thalassemia (HbS/$\beta^0$)]. Patients with ≥4 days of pain over the last 4 weeks of run-in period will be eligible for randomisation. Approximately 180 patients will enter the run-in period in order to provide 90 patients meeting criteria for randomisation.

**Duration of treatment**

The study will start with a 4 week single-blind double-dummy placebo run-in period. Eligible patients will then be randomised in a 1:1:1 ratio (30 to each treatment group) to receive double-blind double-dummy ticagrelor 10 mg bid, 45 mg bid, or placebo bid for 12 weeks. Patients will be followed for 2 weeks safety assessment after 12 week study treatment period. The total expected study duration for an individual patient is approximately 18 weeks.

**Investigational product, dosage and mode of administration**

- Ticagrelor 10 mg will be administered orally bid as a tablet
- Ticagrelor 45 mg will be administered orally bid as a tablet
- Matching Placebo for Ticagrelor 10 mg will be administered orally bid as a tablet
- Matching Placebo for Ticagrelor 45 mg will be administered orally bid as a tablet

**Statistical methods**

No statistical comparisons are planned for the primary objective. PK, patient reported outcome (PRO) and safety measures will be summarized descriptively.

The number of days with pain due to SCD and the analysis of analgesic use due to SCD will be analysed using an ANCOVA model, with treatment, centre, baseline average value, as exploratory variables, and treatment as a fixed effect and centre as a random effect. Least squares differences in means between ticagrelor 45 mg and placebo and ticagrelor 10 mg and placebo with corresponding 90% confidence interval will be presented. The objectives will be analysed as a proportion of days, during the whole treatment period.

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# LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

| Abbreviation or special term | Explanation |
|---|---|
| ACS | Acute coronary syndrome |
| ADP | Adenosine Diphosphate |
| AE | Adverse event |
| ALP | Alkaline phosphatase |
| ALT | Alanine aminotransferase |
| ANCOVA | Analysis of covariance |
| AST | Aspartate transaminase |
| ATP | Adenosine triphosphate |
| AUC | Area Under the plasma concentration time Curve |
| AZ | AstraZeneca |
| β-hCG | beta-human chorionic gonadotropin |
| bid | bis in die (twice a day) |
| BP | Blood pressure |
| CPTP | Cyclopentyltriazolopyrimidines |
| CRO | Clinical Research Organisation |
| CSA | Clinical Study Agreement |
| CSR | Clinical Study Report |
| CV | Coefficient of Variation |
| CYP3A4 | Cytochrome P450 3A4 |
| EC | Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC) |
| ECG | Electrocardiogram |
| eCRF | Electronic case report form |
| eDiary | Electronic diary |
| EMA | European Medicines Agency |
| ENT-1 | Equilibrative nucleoside transporter-1 |
| ePRO | Electronic Patient Reported Outcomes |
| GCP | Good Clinical Practice |

| Abbreviation or special term | Explanation |
|---|---|
| GMP | Good Manufacturing Practice |
| GRand | Global Randomisation system |
| Hb | Haemoglobin |
| HBsAg | Hepatitis B surface antigen |
| HbSS | Homozygous sickle cell anemia |
| HbS/$\beta^0$ | Sickle beta-zero-thalassaemia |
| HCV | Hepatitis C virus |
| HIV | Human immunodeficiency virus |
| HU | Hydroxyurea |
| IATA | International Air Transport Association |
| IB | Investigators' Brochure |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonisation |
| International Co-ordinating Investigator | If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally. |
| ID | Identification |
| IP | Investigational product |
| ITT | Intention-to-treat |
| IVRS | Interactive Voice Response System |
| IWRS | Interactive Web Response System |
| LDH | Lactate dehydrogenase |
| LFT | Liver function test |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NRS | Numerical Rating Scale |
| NSAIDs | Non-steroidal anti-inflammatory drugs |
| PCP | Phencyclidine |
| PGIC | Patient Global Impression of Change |
| P-gp | P-glycoprotein |
| PI | Principal Investigator |
| PK | Pharmacokinetic |
| PKPD | Pharmacokinetic/Pharmacodynamic |

| Abbreviation or special term | Explanation |
|---|---|
| PREGOUT | Pregnancy Outcome |
| PREGREP | Pregnancy Report |
| PRO | Patient Reported Outcome |
| PRU | $P2Y_{12}$ reaction units |
| RBC | Red Blood Cell |
| SAE | Serious adverse event |
| SAP | Statistical Analysis Plan |
| SCD | Sickle Cell Disease |
| sCD40L | Soluble CD40 ligand |
| SD | Standard Deviation |
| $t_{max}$ | Time to maximum concentration |
| ULN | Upper limit of normal |
| VOC | Vaso-occlusive crisis |
| WBDC | Web Based Data Capture |

# 1. INTRODUCTION

## 1.1 Background and rationale for conducting this study

Ticagrelor is an orally active, reversibly binding cyclopentyl-triazolo-pyrimidine $P2Y_{12}$ receptor antagonist that produces dose-related inhibition of adenosine diphosphate (ADP) induced platelet aggregation (Htun and Steinhubl 2013). Ticagrelor is indicated to reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS).

### 1.1.1 Disease under treatment

Sickle cell disease (SCD) is an autosomal recessive inherited disorder in which the abnormal gene product is an altered haemoglobin β-chain. Polymerization of deoxygenated sickle haemoglobin leads to decreased deformability of red blood cells (RBCs). Due to a complex interplay of adhesive events, these altered erythrocytes can obstruct the vasculature, producing episodes of pain, organ ischemia and infarction and early mortality.

Sickling of RBCs is initiated by deoxygenation and subsequent polymerization of sickle haemoglobin resulting in mechanical vascular obstruction, and painful ischemia, commonly referred to as a vaso-occlusive crisis (VOC). Vaso-occlusion is initiated and sustained by interactions among sickle cells, endothelial cells, and constituents of plasma. Activated platelets promote the adherence of sickle cells to endothelial cells and thus participate in the vaso-occlusive process. Inhibition of platelet activation has been proposed as a potential therapeutic option in the treatment of children and adults with SCD.

In patients with SCD, platelets are activated during the non-crisis “steady state” and are further activated during painful episodes (Lee et al 2006). An exploratory study in adults with SCD suggested an association between a marker of platelet activation (soluble CD40 ligand) and frequency of pain episodes in the previous year (defined as a visit to a medical facility with administration of a parenteral analgesic) (Ataga et al 2012).

The rationale for the use of antiplatelet therapies in management of SCD derives from the hypothesis that platelets may play a role in amplifying and maintaining vaso-occlusion. The spectrum of clinical manifestations in SCD may result in part from recurrent episodes of disseminated microvascular ischemia-reperfusion injury (Polanowska-Grabowska et al 2010) that triggers vascular inflammation, with platelet-monocyte and platelet-neutrophil aggregates as important amplifiers of the process. In theory, antiplatelet therapy could decrease the incidence and severity of vaso-occlusion, and has the potential to affect other disease manifestations related to microvascular occlusion. This hypothesis positions platelets not only as players in acute VOC but also as important contributors to daily pain and to complications resulting from frequent microvascular occlusion such as pulmonary hypertension.

Previous clinical trials of antiplatelet medications aspirin (Osamo et al 1981, Greenberg et al 1983, Zago et al 1984), aspirin-dipyridamole (Chaplin et al 1980), ticlopidine (Cabannes et al 1984, Semple et al 1984) and eptifibatide (Lee et al 2007) in preventing the

thrombotic complications or effect on biomarkers of SCD in adults and children have been small and thus far inconclusive (recently reviewed and summarized by Charneski and Congdon 2010 and Wun et al 2013). A small double-blind, placebo controlled, Phase II trial with prasugrel administered for 30 days in adult patients with SCD demonstrated a trend toward fewer days with pain and decreased pain intensity in the prasugrel arm relative to placebo (Wun et al 2013). Platelet surface P-selectin and plasma soluble P-selectin, biomarkers of *in vivo* platelet activation, were significantly reduced in the patients randomised to prasugrel.

### 1.1.2 Study Drug

Ticagrelor, a member of the chemical class cyclopentyltriazolopyrimidines (CPTP), is a selective ADP receptor antagonist acting on the $P2Y_{12}$ ADP-receptor that can prevent ADP-mediated platelet activation and aggregation. Ticagrelor is orally active, and reversibly interacts with the platelet $P2Y_{12}$ ADP-receptor. Ticagrelor does not interact with the ADP binding site itself, but interacts with platelet $P2Y_{12}$ ADP-receptor to prevent signal transduction (Van et al 2009).

Ticagrelor has an additional mechanism of action, increasing local endogenous adenosine levels by inhibiting equilibrative nucleoside transporter-1 (ENT-1). Adenosine is formed locally at sites of hypoxia and tissue damage through degradation of released adenosine tri- and di-phosphate (ATP and ADP). As adenosine degradation is mostly restricted to the intracellular space, inhibition of ENT-1 by ticagrelor prolongs the half-life of adenosine and thereby increases its local extracellular concentration. Ticagrelor has no significant direct effect on adenosine receptors. In addition to the antithrombotic effects of ticagrelor, the adenosine mechanism could be hypothesized to benefit ischemic tissues during impending or ongoing VOC, via anti-inflammatory or vasodilatory effects (Nylander et al 2013).

Thus ticagrelor has 2 pharmacological properties with the potential to impact the manifestations of SCD.

### 1.1.3 Pharmacokinetic Properties and Product Metabolism in Humans

Ticagrelor demonstrates linear pharmacokinetics (PK) and exposure to ticagrelor and the active metabolite (AR-C124910XX) are approximately dose proportional up to 1260 mg.

Absorption of ticagrelor is rapid with a median time to maximum concentration ($t_{max}$) of approximately 1.5 hours. The formation of the major circulating metabolite AR-C124910XX (also active) from ticagrelor is rapid with a median $t_{max}$ of approximately 2.5 hours.

The mean absolute bioavailability of ticagrelor was estimated to be 36%. Ingestion of a high fat meal resulted in a 21% increase in ticagrelor area under the plasma concentration time curve (AUC) and 22% decrease in the active metabolite $C_{max}$ but had no effect on ticagrelor $C_{max}$ or the AUC of the active metabolite.

These small changes are considered of minimal clinical significance; therefore, ticagrelor can be given with or without food.

The steady state volume of distribution of ticagrelor is 87.5 L. Ticagrelor and the active metabolite are extensively bound to human plasma protein (>99.0%). Cytochrome P450 3A4 (CYP3A4) is the major enzyme responsible for ticagrelor metabolism and the formation of the active metabolite and their interactions with other CYP3A substrates range from activation through to inhibition. Ticagrelor and the active metabolite are weak P-glycoprotein inhibitors.

The major metabolite of ticagrelor is AR-C124910XX, which is also active as assessed by in vitro binding to the platelet $P2Y_{12}$ ADP-receptor. The systemic exposure to the active metabolite is approximately 30-40% of that obtained for ticagrelor.

The primary route of ticagrelor elimination is via hepatic metabolism. When radiolabeled ticagrelor is administered, the mean recovery of radioactivity is approximately 84% (57.8% in faeces, 26.5% in urine). Recoveries of ticagrelor and the active metabolite in urine were both less than 1% of the dose. The primary route of elimination for the active metabolite is most likely via biliary secretion. The mean $t_{1/2}$ was approximately 7 hours for ticagrelor and 8.6 hours for the active metabolite.

## 1.2 Rationale for study design, doses and control groups

### 1.2.1 Overall rationale and study population

This Phase II adult study is intended to supplement the pediatric program for ticagrelor in SCD. The current study will collect data on clinical manifestations such as pain and analgesic use to help in understanding the potential benefit of ticagrelor in early adulthood. A previous Phase II study in adult patients with SCD demonstrated a trend toward fewer days with pain when prasugrel was compared with placebo (Wun et al 2013).

The frequency of pain episodes increases late in the second decade of life and decreases in frequency after the fourth decade. In adults with SCD, a recent study has suggested that pain is far more prevalent and severe than previous studies have portrayed, as it is often managed by the patients at home (Smith et al 2008). With respect to efficacy, there are considerable data to indicate that the physiology of SCD pain in children may be different than in adults. SCD related pain in children is believed to be mostly ischemic in origin. In contrast, painful crises in adults are more complicated, and may have ischemic and neuropathic components (Ballas 2007). Neuropathic pain can result from frequently occurring acute pain, neuronal ischemic damage, and undertreated chronic pain. However, the transition from an ischemic state to an ischemic/neuropathic state is not well understood. Therefore, this study is designed to shed some light on the benefit of platelet inhibition in patients with SCD in early adulthood.

### 1.2.2 Study Design

The study will randomise patients with SCD aged ≥18 to 30 years inclusive to ticagrelor or placebo. The study will start with a 4-week single-blind double-dummy placebo run-in period to determine the frequency and intensity of days with pain at baseline using a daily electronic diary. Patients with ≥4 days of pain during last 4 weeks of the run-in period will be eligible for randomisation. Approximately 180 patients will enter the run-in period in order to provide 90 patients meeting criteria for randomisation. Patients will then be randomised in a

1:1:1 ratio (30 to each treatment group) to receive double-blind double-dummy treatment with ticagrelor 10 mg twice daily (bid), 45 mg bid, or placebo bid for 12 weeks.

In addition to study drug and protocol procedures, all standard clinical management will be utilized for patients participating in this study.

### 1.2.3 Primary and secondary outcome measures

The primary objective of this study is to study 2 different doses of ticagrelor versus placebo in reducing the number of days with pain due to SCD in young adults. The secondary objectives will include:

- Intensity of pain
- Use of analgesics

### 1.2.4 Dose and study duration

This is the first study with ticagrelor in young adult subjects with SCD. The doses chosen for this study are 10 mg and 45 mg twice a day. Based upon modeling and simulation, doses of 10 mg and 45 mg are predicted to provide mean reductions in $P2Y_{12}$ reaction units (PRU) 2 hours post-dose of 40-50% and 80-90% respectively. These doses provide a wide range of peak inhibition of the $P2Y_{12}$ receptor. The range of platelet inhibition covers a substantial portion of the pharmacodynamic (PD) effect of ticagrelor, while still minimizing the risk of exposure from doses used in the ACS program.

Dose selection in this study is informed by the substantial clinical pharmacology programme for ticagrelor in adults, which included 41 studies in approximately 1000 subject examining the exposure-response relationship, safety and drug interactions. The dose range of ticagrelor administered during these studies was up to 1260 mg and 900 mg was established as the maximum tolerated dose in healthy volunteers. The approved dose regimens in adults with ACS are a loading dose of 180 mg followed by 90 mg twice daily for up to 1 year.

The 12 week duration of this trial will provide information on the role $P2Y_{12}$ inhibition plays with respect to the frequency and intensity of pain in young adults with SCD.

## 1.3 Benefit/risk and ethical assessment

SCD is a chronic, lifelong condition with serious complications and manifestations in every organ system. The goals for management of this condition are prevention of infection, nutritional supplementation, management of pain, and prevention of complications; therefore, treatment is multifactorial. Bone marrow transplantation, although potentially curative, has the possibility of serious or fatal complications and therefore, is reserved for the most severe cases of SCD. Although VOC is a common cause of hospitalization and treatment with opioids, only 1 drug, hydroxyurea (hydroxycarbamide) is currently approved for reduction in the frequency of VOC. Although hydroxyurea reduces the incidence of many manifestations, it does not eliminate them, is poorly tolerated by some patients, and can cause myelosuppression. Furthermore, the safety of lifelong exposure beginning in childhood is

unknown. Thus, there is a clear unmet need for additional therapies that are better tolerated, safer, and more effective than available treatments.

Clinical experience with $P2Y_{12}$ inhibitors such as clopidogrel and prasugrel is relevant to the proposed ticagrelor SCD program. Clopidogrel has been marketed in the US since 1997, and there is substantial clinical experience. Completed studies in adults and children with SCD treated with prasugrel provide evidence that a $P2Y_{12}$ platelet aggregation inhibitor does not pose an unacceptable safety risk to adults with SCD enrolled in a well-controlled clinical study (Styles et al 2012, Wun et al 2013).

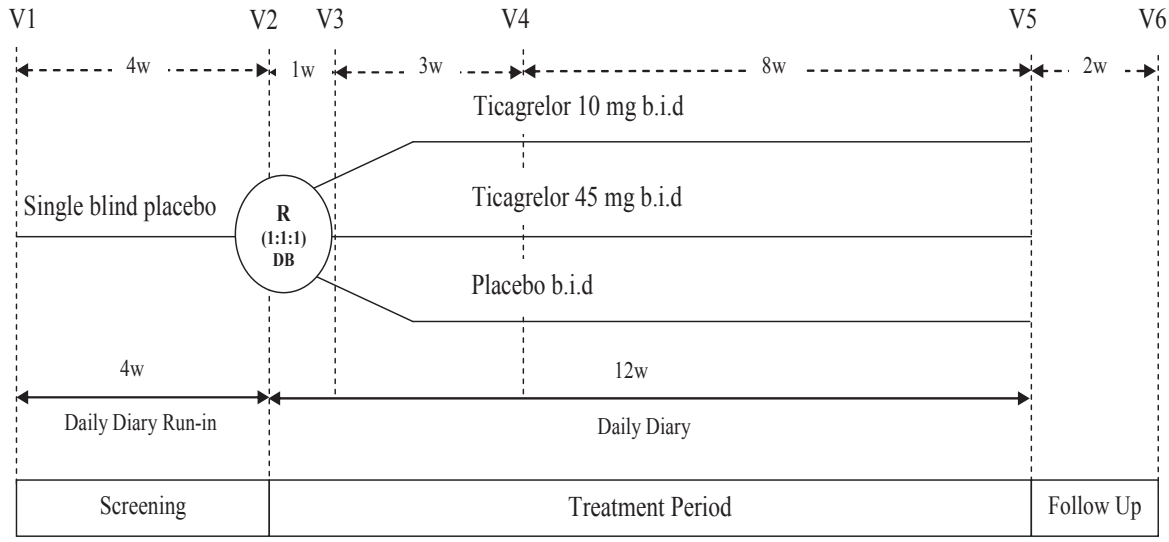
More than 11,000 adult healthy subjects or patients have been exposed to ticagrelor in the completed Phase I, II, and III studies and the overall conclusion based on these studies is that ticagrelor has generally been well tolerated. Occasionally patients taking ticagrelor report a sensation of breathlessness (dyspnea) without another obvious cause (refer to the Investigators' Brochure [IB]).

The proposed ticagrelor Phase II study design is focused on minimization of risk, including the exclusion of patients with ocular or central nervous system clinical findings which might predispose to significant bleeding, incorporating other exclusion criteria to minimize the bleeding risk, and doses that are lower than what was used in the ACS program for ticagrelor. The doses chosen for this study are 10 mg and 45 mg, both bid. The 10 mg dose is predicted to provide a peak effect of $P2Y_{12}$ inhibition of around 40-50%, as measured by PRUs. The 45 mg dose, half the clinical dose for ACS, should produce a peak effect of $P2Y_{12}$ inhibition of around 80-90%, as is often seen in patients receiving clopidogrel who are not poor metabolizers. The range of platelet inhibition covers a substantial portion of the PD effect of ticagrelor, while still minimizing the risk of exposure from doses used in the ACS program. The potential benefit of ticagrelor is reduction of the occurrence of daily pain, based on its mechanism of action as a potent $P2Y_{12}$ inhibitor and role of platelets involved in vaso-occlusion. Thus, in the context of the unmet need for treatment of pain in adults with SCD, the benefit-risk balance for the program is considered favorable.

## 1.4 Study Design

This study includes 3 periods Screening, Treatment and Follow-up. **Screening** period starts from enrolment (Visit 1) and patients will receive total 4-weeks (Day -28 to Day 0), single-blind double-dummy placebo treatment bid to determine the frequency and intensity of days with pain at baseline using a daily electronic diary (eDiary). Patients with ≥4 days of pain during the Screening period will be eligible for randomisation. **Treatment** period starts from randomisation (Visit 2) and then patients will receive total 12 weeks of double-blind double-dummy treatment bid until end of treatment (Visit 5). Patients may be asked to participate in a voluntary collection of biomarkers for exploratory analysis. **Follow-up** period starts after end of treatment and patients will be followed for safety assessment after 2 weeks (Visit 6, telephonic contact). During the study, patients will be evaluated for adverse events (AEs) including bleeding and VOC.

**Figure 1 Study Flow Chart**




R = Randomisation, DB = Double-blind, W = Week, V = Visit

# 2. STUDY OBJECTIVES

## 2.1 Primary objective

| **Primary Objective:** | **Outcome Measure:** |
|---|---|
| To investigate the efficacy of 2 different doses of ticagrelor versus placebo in reducing the number of days with pain due to SCD | Number of days with pain due to SCD |

## 2.2 Secondary objectives

| **Secondary Objective:** | **Outcome Measure :** |
|---|---|
| To determine the efficacy of 2 different doses of ticagrelor versus placebo in reducing the intensity of pain due to SCD | Intensity of pain due to SCD |
| To access the efficacy of 2 different doses of ticagrelor versus placebo in reducing the use of analgesics by patients with SCD | Days of analgesic use |

## 2.3 Safety objectives

| Safety Objective: | Outcome Measure : |
|---|---|
| To assess safety and tolerability of 2 different doses of ticagrelor versus placebo in patients with SCD | Number of major bleeding or clinically relevant non-major bleeding events<br>AE/ Serious Adverse Events (SAEs)<br>Vital signs, Laboratory Safety Samples |

## 2.4 Exploratory objectives

| Exploratory Objective: | Outcome Measure : |
|---|---|
| To determine the efficacy of 2 different doses of ticagrelor versus placebo in reducing the frequency of VOC period in patients with SCD | Frequency of VOC |
| To assess the efficacy of 2 different doses of ticagrelor versus placebo in reducing the number of absent days from school/work in patients with SCD | Days absent from school/work |
| To assess the efficacy of 2 different doses of ticagrelor versus placebo in reducing the use of opioid analgesics in patients with SCD | Days of opioid analgesic use |
| To evaluate the PK properties of 2 doses of ticagrelor in young adult patients with SCD | Ticagrelor and active metabolite concentrations at Visits 2 and 3 |
| To assess the effect of 2 different doses of ticagrelor on inhibition of platelet aggregation and biomarkers of platelet activation | PRU at 0 and 2 hours post-dose on Visits 2 and 3<br>Change in Soluble Platelet Selectin (sP-selectin), Soluble CD40 Ligand (sCD40L) and Thromboxane B2 (TXB2) |
| To assess the dose-plasma concentration - response relationship with regards to PRU | The relationship between ticagrelor dose, plasma concentration and PRU using a population PK and Pharmacokinetic/ Pharmacodynamic (PK/PD) modelling approach |

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

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

## 3.1 Inclusion criteria

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

1. Provision of signed and dated written informed consent prior to any study specific procedures not part of standard medical care.

2. Male and female young adults aged ≥18 to ≤30 years (at Visit 1), with confirmed medical history or diagnosis of homozygous sickle cell (HbSS) or sickle beta-zero-thalassaemia (HbS/$\beta^0$) by HPLC.

3. If treated with an anti-sickling agent such as hydroxyurea, dose must be stable for 3 months before enrolment.

At Visit 2 only - randomisation criteria:

4. Prior to dosing on Day 1, Visit 2, a negative serum pregnancy test performed at Screening (Visit 1) and a negative urine pregnancy test (dipstick) from Visit 2 must be available (for females).

5. Patient must have ≥4 days of pain during last 4 weeks of the single-blind run-in period to enter double-blind randomisation period.

## 3.2 Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled:

1. History of transient ischaemic attack or clinically overt cerebrovascular accident (ischaemic or haemorrhagic), severe head trauma, intracranial haemorrhage, intracranial neoplasm, arteriovenous malformation, or aneurysm.

2. Currently under treatment with chronic red blood cell transfusion therapy. If receiving erythropoietin, must have been prescribed for the preceding 6 months and be dose stabilised for at least 3 months prior to Day 1, Visit 2.

3. Currently experiencing a vaso-occlusive crisis at Visit 1.

4. Pre-dominate cause of pain is not sickle cell disease related.

5. History of or current proliferative retinopathy on ophthalmologic examination (most recent examination must be within 12 months prior to Visit 2).

6. Requiring treatment >3 days/week with non-steroidal anti-inflammatory drugs (NSAIDs).

7. Receiving chronic treatment with anticoagulants or antiplatelet drugs.

8. Ongoing bleeding or increased risk of bleeding complications.

9. Patient considered at risk of bradycardic events (e.g., known sick sinus syndrome or second or third degree atrioventricular block) unless already treated with a permanent pacemaker.

10. Is diagnosed with cancer (except non-melanoma skin and in situ cervical cancers) within the last 5 years.

11. Concomitant oral or intravenous therapy with strong CYP3A4 inhibitors*, CYP3A4 substrates with narrow therapeutic indices, or strong CYP3A4 inducers*, that cannot be stopped ≥5 half-lives, but not <10 days, before enrolment.

12. Surgical procedure planned to occur during the study.

13. Patients who are currently pregnant or breastfeeding or planning to become pregnant during the study.

14. Females of child bearing potential are not allowed to be included in this study unless they use a highly effective method of contraception, and must refrain from becoming pregnant from 1 month following the last dose. A highly effective method is defined as the one which results in a low failure rate (i.e., less than 1% per year) when used consistently and correctly. Examples of highly effective methods include implants, injectables, combined oral contraceptives, some intrauterine devices, sexual abstinence, or vasectomised partner.

15. Known hypersensitivity or contraindication to ticagrelor.

16. Concern for the ability of the patient to comply with study procedures and/or follow-up.

17. Any condition which, in the opinion of the Investigator, would make it unsafe or unsuitable for the patient to participate in this study.

18. Previous enrolment in the present study.

19. Participation in another clinical study with an investigational product (IP) or device during the last 30 days preceding enrolment.

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

* Strong CYP3A inhibitors and inducers according to draft Guidance for Industry "Drug Interaction Studies Study Design, Data Analysis, Implications for Dosing, and Labelling Recommendations" (Food and Drug Administration, 2012) and EMA interaction guideline in act as of 01 January 2013

At Visit 2 only – randomisation criteria:

21. Moderate or severe hepatic impairment, defined as Child-Pugh class B or C (see Appendix E) or renal failure requiring dialysis. Serum creatinine ≥1.2 mg/dL, liver direct bilirubin ≥2.0 mg/dL, alanine aminotransferase (ALT) or aspartate transaminase (AST) ≥3x upper limit of normal (ULN) range from test performed at Screening (Visit 1).

22. Known active or chronic infection characterised by any positive result from test performed at Screening (Visit 1) for serum hepatitis B surface antigen (HBsAg), antibodies against hepatitis C virus (HCV) and human immunodeficiency virus (HIV-1/2).

23. Hemoglobin <4.0 g/dL from test performed at Screening (Visit 1).

24. Platelets <100 x $10^9$/L from test performed at Screening (Visit 1).

Procedures for withdrawal of incorrectly enrolled patients see Section 3.4.

## 3.3 Patient enrolment and randomisation

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

The Investigator(s) will:

1. Obtain signed informed consent from the potential patient before any study specific procedures are performed. Patient is considered enrolled in the study after she/he has signed the informed consent form (ICF).

2. Assign (using the Interactive Voice Response System (IVRS) or Interactive Web Response System [IWRS]) potential patient a unique enrolment number, beginning with 'E + 4-digit site number + 3 digit patient number starting with 001. For example, the first patient at site 9999 would be assigned the patient number: E9999001. This number will be used for identification throughout the study and will not be used for any other participant.

3. Determine patient eligibility. See Section 3.

4. Assign eligible patient unique randomisation code (patient number), by accessing IVRS or IWRS, see Section 3.5. Patient is considered randomised in the study after this assignment.

**Patients entering the single-blind run-in period**

At the time of entry into the single-blind double-dummy placebo run-in period, the site will contact the IVRS/IWRS in order that run-in medication can be assigned and dispensed.

Patient who does not meet the eligibility criteria is considered as screen failure in the study. These patients will be terminated from the study and registered as Screen Failure by using IVRS/IWRS. See Section 3.10.1. Patients cannot be rescreened.

**Patients entering the double-blind treatment period**

Following completion of the single-blind run-in period, patients eligible for double-blind double-dummy treatment will be randomly assigned to 1 of the 3 treatment arms by the IVRS/IWRS in a 1:1:1 ratio (ticagrelor 10 mg + matching placebo for ticagrelor 45 mg: ticagrelor 45 mg + matching placebo for ticagrelor 10 mg: matching placebo for ticagrelor 10 mg + matching placebo for ticagrelor 45 mg) using a randomisation schedule.

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

## 3.4 Procedures for handling incorrectly enrolled or randomised patients

Patients who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study drug. There can be no exceptions to this rule. Patients who are enrolled, but subsequently found not to meet all the eligibility criteria must not be randomised or initiated on treatment, and must be withdrawn from the study.

Where a patient does not meet all the eligibility criteria but is randomised in error, or incorrectly started on treatment, the following steps to be taken:

(a) The Investigator or monitor should inform the study 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. A discussion should occur between the study physician and the Investigator, a decision may be reached that whether to continue or discontinue the patient from study treatment. The study physician must ensure all decisions are appropriately 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 (ITT) 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.

## 3.5 Methods for assigning treatment groups

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

codes will be generated in blocks to ensure approximate balance (1:1:1) between the 3 treatment arms (ticagrelor 10 mg bid, 45 mg bid, or placebo bid).

Randomisation will be done via IVRS/IWRS at Visit 2. The IVRS/IWRS will allocate randomisation codes sequentially within each country as patients become eligible for randomisation. Once a block of randomisation codes is exhausted, the next available block will be allocated by the IVRS/IWRS to the country.

For each patient randomised the IVRS/IWRS will provide the Investigator with a unique kit identification (ID) number matching the treatment arm assigned to the patient. Following randomisation, the first dose of study drug will be administered to the patient as soon as possible. At randomisation and subsequent dispensing visit the patient should always be provided medication with the kit ID(s) allocated by the IVRS/IWRS. If a patient receives the incorrect randomised treatment at any time during the study, this must be corrected as soon as discovered after discussing with study physician.

## 3.6 Methods for ensuring blinding

This study is double-blind and double-dummy technique will be used. The active tablets and their matching placebo tablets will be provided see Section 7.1 identical in appearance and with the same number and packaging of the tablets. The bottles with IPs will be labelled with unique identification numbers allocated from the IVRS/IWRS, but it will not indicate treatment allocation to the Investigator.

The PRU value obtained from VerifyNow system will be kept strictly blinded to safeguard the integrity of the blinding of Investigators and patients, and hence to minimize any possible bias in data handling.

No member of the study team at AZ or representative, personnel at study centres or any clinical research organisation (CRO) handling data will have access to the randomisation scheme during the conduct of the study, with the exception of the AZ personnel generating the randomisation scheme and the bioanalysis personnel analysing the PK samples as well as AZ Supply Chain, the Patient Safety data entry site and the CRO companies providing the IVRS/IWRS and carrying out the packaging and labelling of IPs. This documentation will be kept in a secure location until the end of the study.

## 3.7 Methods for unblinding

Individual treatment codes, indicating the treatment randomisation for each randomised patient, will be available to the Investigator(s) or pharmacists from the 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 randomisation. The AZ physician or delegate should be consulted whenever possible prior to the Investigator breaking the blind. The Investigator documents and reports the action to AZ, without revealing the treatment given to patient to the AZ 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 drug should be continued if considered appropriate.

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

## 3.8 Restrictions

The following recommendations will be applied for patients participating in the study:

- Patients may not participate in another clinical study that involves an IP (active or placebo) or device during this study.
- Females of child bearing potential are not allowed to be included in this study unless they use a highly effective method of contraception, and must refrain from becoming pregnant from 1 month following the last dose. A highly effective method is defined as the one which results in a low failure rate (i.e., less than 1% per year) when used consistently and correctly. Examples of highly effective methods include implants, injectables, combined oral contraceptives, some intrauterine devices, sexual abstinence or vasectomised partner. There are no restrictions against fathering a child when treated with ticagrelor. For further details, please see Section 6.6.
- Grapefruit juice must not be consumed during the study.
- Patients are not allowed to eat 2 hours before and 1 hour after dosing at Visit 2 and 3.
- For concomitant medications which are restricted during the study, please see Section 7.7.

## 3.9 Discontinuation of investigational product

Patients will be discontinued from investigational product (IP) in the following situations:

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment
- AE, as judged by Investigator
- Severe non-compliance with the study protocol, as judged by Investigator and/or AZ
- Any major bleeding, as judged by Investigator
- Risk to patient as judged by Investigator

- Pregnancy

**NB.** Discontinuation of IP does not mean discontinue of follow-up or termination of study participation.

### 3.9.1 Procedures for discontinuation of a patient from IP

At any time, patients are free to discontinue IP or withdraw from the study (i.e., investigational product and assessments – see Section 3.10 without prejudice to further treatment. A patient that decides to discontinue IP will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by an Investigator(s). All end of treatment (Visit 5) procedures will be followed in addition to safety follow-up (Visit 6). AEs will be followed up (see Section 6); electronic devices for Patient Reported Outcomes (ePRO) and all study drugs should be returned by the patient.

If a patient is withdrawn from study, see Section 3.10.

### 3.9.2 Procedure for management of dyspnea associated with investigational product

If a patient develops new, prolonged, or worsened dyspnea during treatment with ticagrelor, exclude underlying diseases that may require treatment. If dyspnea is determined to be related to ticagrelor, no specific treatment is required.

### 3.9.3 Procedure for management of elevated serum creatinine

Serum creatinine may initially increase and then decrease on continued treatment. These increases typically do not progress with ongoing treatment and often decrease with continued therapy.

If a 50% increase in serum creatinine is observed, the patient should be monitored closely, but this value may decrease with continued therapy. However, if the serum creatinine is 2x ULN and other causes are ruled out and the value does not improve on continued therapy, then discontinuation should be considered.

### 3.9.4 Procedure for management of elevated liver function tests

Subjects with grade 3 elevations in liver function tests (LFTs; >5x ULN) should have their LFTs repeated. If LFTs remain >5x ULN, and/or elevated total bilirubin >2 mg/dl (and sickle cell-related causes are excluded) and thought to be related to ticagrelor, stopping the study drug should be considered.

## 3.10 Criteria for withdrawal

### 3.10.1 Screen failures

Screening failures are patients who do not fulfil the eligibility criteria for the study, and therefore must not be randomised. These patients should have the reason for study withdrawal recorded as ‘Eligibility criteria not fulfilled’ (i.e., patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (not randomised patients).

### 3.10.2 Withdrawal of the informed consent

Patients are free to withdraw from the study at any time (IP and assessments), without prejudice to further treatment.

A patient who withdraws consent will always be asked about the reason(s) and the presence of any AEs. The Investigator will follow up AEs outside of the clinical study. The patient will return ePRO devices.

If a patient withdraws from participation in the study, then his/her enrolment/randomisation code cannot be reused. Withdrawn patients will not be replaced after randomisation.

**Withdrawal of informed consent for donated biomarker samples**

As collection of the blood biomarker samples is a voluntary part of the study, if patients withdraw consent for use then the patient may continue in the study. Patients may withdraw from optional exploratory research at any time, without prejudice to further treatment and independent of any decision concerning participation in other aspects of the main study. Procedures for withdrawal from the exploratory research are outlined in Section 5.7.4.

## 3.11 Discontinuation of the study

The study may be stopped if, in the judgment of AZ, trial patients are placed at undue risk because of clinically significant findings that:

- Are assessed as causally related to study drug,
- Are not considered to be consistent with continuation of the study

Regardless of the reason for termination, all data available for the patient at the time of discontinuation of follow-up must be recorded in the electronic case report form (eCRF). All reasons for discontinuation of treatment must be documented.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the patients' interests.

# 4. STUDY PLAN AND TIMING OF PROCEDURES

## Table 1 Study Plan Detailing the Procedures

| **Study Period** | **Screening period** | **Treatment period** | | | | **Follow-up period** | **For details see Protocol Section** |
|---|---|---|---|---|---|---|---|
| **Visit** | **Enrolment** | **Rando-misation** | **Treat-ment** | **Treat-ment** | **End of treatment** | **Phone contact** | |
| **Visit Number** | **1** | **2** | **3** | **4[a]** | **5** | **6** | |
| **Week** | **-4** | **0** | **1** | **4** | **12** | **14** | |
| **Day** | **-28** | **0** | **7** | **28** | **84** | **98** | |
| **Visit Window** | **-35 to -28** | **Not Applicable** | **±3 days** | **±7 days** | **±7 days** | **±7 days** | |
| Signed and Dated Informed consent | ✓ | | | | | | 10.4 |
| Inclusion/Exclusion Criteria | ✓ | ✓[b] | | | | | 3.1 and 3.2 |
| Allocation of E-code via IVRS/IWRS | ✓ | | | | | | 3.3 |
| Randomisation via IVRS/IWRS | | ✓ | | | | | 3.3 and 3.5 |
| Electronic Diary Assessment[c]:<br>– Pain (worst/ average/ right now), daily<br>– Analgesic use, daily<br>– Absence school/ work, weekly<br>– PGIC, end of treatment | ← | — | — | — | → | | 5.1.1 |
| Medical and Surgical History | ✓ | | | | | | 4.1 |
| Demographics | ✓ | | | | | | 4.1 |
| Vital Signs (BP and Pulse Rate) | ✓ | ✓ | ✓ | ✓ | ✓ | | 5.2.4 |
| Weight and Height | ✓ | | | | ✓[d] | | 5.2.4 |
| Physical Examination | ✓ | | | | ✓ | | 5.2.2 |
| 12-Lead ECG | ✓ | | | | | | 5.2.3 |
| Ophthalmology examination (if not performed within previous 12 months | ✓ | | | | | | 4.1 |

| **Study Period** | **Screening period** | **Treatment period** | | | | **Follow-up period** | **For details see Protocol Section** |
|---|---|---|---|---|---|---|---|
| **Visit** | **Enrolment** | **Rando-misation** | **Treat-ment** | **Treat-ment** | **End of treatment** | **Phone contact** | |
| **Visit Number** | **1** | **2** | **3** | **4[a]** | **5** | **6** | |
| **Week** | **-4** | **0** | **1** | **4** | **12** | **14** | |
| **Day** | **-28** | **0** | **7** | **28** | **84** | **98** | |
| **Visit Window** | **-35 to -28** | **Not Applicable** | **±3 days** | **±7 days** | **±7 days** | **±7 days** | |
| Blood samples for Hematology and Clinical Chemistry | ✓ | | | ✓ | ✓ | | 5.2.1 |
| Blood samples for coagulation (INR and PTT) | ✓ | | | | | | 5.2.1 |
| Virology screen (HIV, HBsAg, and HCV) | ✓ | | | | | | 5.2.1 |
| Urinalysis (dipstick) | ✓ | | | ✓ | ✓ | | 5.2.1 |
| Pregnancy Test[e] | ✓ | ✓ | | ✓ | ✓ | | 5.2.1 |
| Platelet aggregation (PRU) (VerifyNow)[f] | | ✓ | ✓ | | | | 5.5.1 |
| Blood sampling for Biomarkers (optional) | | ✓[g] | ✓ | ✓ | | | 5.7 |
| Blood sampling for Pharmacokinetics[h] | | ✓ | ✓ | | | | 5.4 |
| Dispense IP | ✓[i] | ✓ | | ✓ | | | 7 |
| Administration of IP in Clinic | ✓[i] | ✓ | ✓ | | | | 7 |
| Return IP and Drug Accountability | | ✓ | | ✓ | ✓ | | 7.5 and 7.6 |
| Vaso-occlusive crisis | ✓[j] | ✓ | ✓ | ✓ | ✓ | | 5.1.2 |
| Concomitant Medications | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 7.7 |
| Adverse Event review (AEs and SAEs) including bleeding events | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 6 |

AE adverse event; β-hCG beta-human chorionic gonadotropin; BP blood pressure; ECG electrocardiogram; HBsAg hepatitis B surface antigen; HCV hepatitis C virus; HIV human immunodeficiency virus; INR international normalized ratio; IVRS Interactive Voice Response System; IWRS Interactive Web Response System; IP investigational product; PTT Partial Thromboplastin Time; SAE serious adverse event.

[a] Patients should be contacted by telephone between Visits 4 and 5 (at Week 8 at a minimum), and Investigators are expected to follow subjects per local institutional guidelines during this period. If unscheduled visits are required for AEs or medical complications, please see Section 4.2.5.

[b] Confirm patient still meets inclusion and exclusion criteria prior to receiving first dose of study drug.

[c] Electronic diary will be dispensed to patient at Visit 1.

[d] Only weight will be measured.

[e] For females of child bearing potential. At Screening (Visit 1), serum β-hCG; at all other visits, urine dipstick.

[f] PRU will be assessed at 0 (pre-dose) and 2 hours post-dose at Visits 2 and 3.

[g] Optional Biomarker sample needs to be collected only if patient agrees to consent for additional optional Biological Samples Research Addendum to Informed Consent Form. Blood sample must be taken prior to first dose of study drug at Visit 2.

[h] PK will be measured 2 hours post-dose at Visit 2, and at 0 (pre-dose) and 2 hours post-dose at Visit 3.

[i] At Screening, patients will be given matching placebo tablets for the 10 mg and 45 mg doses and starting at Visit 2, patients will be randomly assigned to 1 of 3 treatment regimens.

[j] At Screening, history of VOC over previous 12 months will be recorded.

## 4.1 Enrolment/Screening Period

Procedures will be performed according to the Study Plan Table 1.

At Screening, consenting patients are assessed to ensure that they meet eligibility criteria. Patients who do not meet these criteria must not be enrolled in the study.

The below assessments to be performed for all enrolled patients at Visit 1:

- Contact IVRS/IWRS to obtain unique patient enrolment number
- Perform an ophthalmology examination (if not performed within previous 12 months)
- Review and confirm the patient's eligibility for the study by assessing inclusion and exclusion criteria listed in Sections 3.1 and 3.2
- Dispense patient electronic diary and provide instruction on recording the values
- Patient medical and surgical history (including VOC over previous 12 months) as well as medication history (last 3 months) will be obtained with the review of selection criteria
- Record demographics (including sex, date of birth, race, ethnic group)
- Obtain vital signs (pulse rate and blood pressure [BP]), body weight and height
- Perform standard physical examination
- Perform 12-lead electrocardiogram (ECG). ECG must be obtained and reviewed with no significant abnormalities prior to randomisation
- Obtain specimens (blood) for safety laboratory panel and virology screen, and perform serum pregnancy test for females of child bearing potential
- Obtain specimen for urinalysis
- Review concomitant medications and AEs including bleeding events
- Obtain study drug dispensing bottles assignment numbers by accessing IVRS/IWRS and dispense the study drug bottles
- The patient will take his/her first dose of the run-in period study drug

Dispense the patient participation card and schedule the Visit 2 date. Remind patient to bring electronic diary (eDiary) during their next scheduled visit. Patients should be instructed to not take their dose at home in the morning of Visit 2 and to return the unused study drug.

## 4.2 Treatment period

Descriptions of the procedures for this period are included in the Study Plan Table 1. The specific requirements to be followed during treatment period are mentioned below:

### 4.2.1 Visit 2, Randomisation

- Review and confirm inclusion/exclusion criteria for randomisation
- Patient eDiary will be collected from those who do not qualify for randomization
- Review concomitant medications and AEs including bleeding events
- Collect and assess compliance with run-in study drug based on tablet count
- Obtain vital signs (pulse rate and BP)
- Perform urine pregnancy test for females of child bearing potential
- Perform platelet aggregation measurement by using VerifyNow™ P2Y12 assay and reported as PRU (prior and 2 hours post-dose)
- Obtain specimens (blood) for biomarker analysis prior to study drug dispensing (only if patient agrees to consent for optional biomarker research)
- Contact IVRS/IWRS to randomise patient and obtain study drug dispensing bottles assignment number and dispense the study drug bottles
- Patient will be administered his/her first dose of the double-blind treatment at site
- A PK sample will be collected 2 hours post-dose

Schedule the Visit 3 date. Remind patient to bring eDiary in the next scheduled visit and instruct to not take their dose at home in the morning of Visit 3 and bring the study drug to clinic. After all the above assessments patients are allowed to leave the clinic.

### 4.2.2 Visit 3, treatment visit

- A PK sample will be collected 0 hr (pre-dose) and at 2 hours post-dose
- Review concomitant medications and AEs including bleeding events
- Obtain vital signs (pulse rate and BP)
- Perform platelet aggregation measurement by using VerifyNow™ P2Y12 assay and reported as PRU (prior and 2 hours post-dose)
- Obtain specimens (blood) for biomarker analysis

- Patient will be administered his/her Visit 3 morning dose at site

Schedule the Visit 4 date. Remind patient to bring eDiary and to return the unused study drug during their next scheduled visit.

### 4.2.3 Visit 4, treatment visit

- Review concomitant medications and AEs including bleeding events
- Collect and assess compliance with study drug based on tablet count
- Obtain vital signs (pulse rate and BP)
- Obtain specimen for urinalysis and perform urine pregnancy test for females of child bearing potential
- Obtain specimens (blood) for safety laboratory panel and biomarker analysis
- Contact IVRS/IWRS to obtain study drug dispensing bottles assignment number and dispense the study drug bottles

Schedule the Visit 5 date. Remind patient to bring eDiary and to return the unused study drug during their next scheduled visit.

Patients should be contacted by telephone between Visits 4 and 5 (at Week 8 at a minimum), and Investigators are expected to follow subjects per local institutional guidelines during this period. If unscheduled visits are required for AEs or medical complications, please see Section 4.2.5.

### 4.2.4 Visit 5, End of treatment visit

- Patient eDiary will be collected
- Review concomitant medications and AEs including bleeding events
- Obtain vital signs (pulse rate and BP), body weight
- Perform standard physical examination
- Obtain specimens (blood) for safety laboratory panel
- Obtain specimen for urinalysis and perform urine pregnancy test for females of child bearing potential
- Collect and assess compliance with study drug based on tablet count

Instruct the patient that they will be contacted for safety assessment through telephone after 2 weeks.

### 4.2.5 Unscheduled visits

Patients may return to the clinic for an unscheduled visit. At these visits, patients should be evaluated according to the Investigator's standard practice, and the Investigator will determine whether the patient is well and stable enough to continue on study medication. The Investigator's evaluation should be documented in the source documents. Unscheduled visits should not affect the regular visit schedule and assessments.

The following are suggested to be performed at unscheduled visits, per the Investigator's discretion, and entered in the eCRF:

- Review concomitant medications and AEs including bleeding events
- Perform standard physical examination
- Obtain specimens (blood) for safety laboratory panel
- Perform other diagnostic tests as needed based on the patient's condition

## 4.3 Follow-up period

Visit 6 is safety follow-up visit, during which all patients will be contacted by telephone by site personal to check their concomitant medications and for any AEs including bleeding events.

# 5. STUDY ASSESSMENTS

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

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

## 5.1 Efficacy assessments

Clinical efficacy events will be collected in the eCRF and by using a daily eDiary. These events will be identified using standard questioning of the patient at each visit, by information collected in the eDiary or by information that the Investigator may receive as part of standard medical practice.

### 5.1.1 PRO

Pain is commonly reported in clinical trials by having patients provide a rating of their own pain, i.e., it is patient reported.

The primary efficacy variable is change from baseline in number of days with pain. Secondary and exploratory variables include intensity of Worst Pain and use of analgesics. Patient reported data regarding Average Pain, Pain Right Now and Absence from school/work are exploratory variables.

#### 5.1.1.1 Pain due to SCD

Pain assessment will be captured daily using an eDiary and will be collected in the evening from enrolment to end of treatment. After the enrolment part only patients with ≥4 days of pain during last 4 weeks of the run-in period will be eligible for randomisation.

At the start of the study, Visit 1, patients will be issued an eDiary. The numerical rating scale (NRS) asks the patient to rate the intensity of his/her worst pain and average pain during the past 24 hours and pain right now, using an 11-point scale where 0 represents "no pain" and 10 represents "pain as bad as you can imagine". The patient will indicate his/her pain intensity by tapping a number on the NRS scale on the screen in the eDiary. If a patients reports 0 (no pain) that will be recorded as a pain free day, whereas a report between 1-10 will be recorded as a day with pain.

The validity of the NRS has been well documented in different pain populations. The NRS demonstrates positive and significant correlations with other measures of pain intensity (Jensen et al 1986, Jensen et al 1989, Kremer et al 1981, Seymour 1982, Wilkie et al 1995). It has also demonstrated sensitivity to treatments that are expected to have an impact on pain intensity (Chapman et al 2001, Paice et al 1997, Stenn et al 1979).

If the patient answers that he/she has pain, a body outline diagram will be presented and the patient will be asked to indicate the location of the pain.

#### 5.1.1.2 Use of Analgesics

During both the enrolment and treatment part, patients will be asked about their use of analgesics. The question 'Have you taken any medication because of your SCD pain today' will be administered daily in the electronic device. Response options will be dichotomous, i.e., 'Yes' or 'No'. The question is presented in the eDiary and should be answered daily in the evening. Specification of whether analgesics have been opioid or non-opioid will be done at follow-up site visit.

#### 5.1.1.3 Absence from school/work

Absence from school/work will be recorded in the eDiary weekly by asking the question 'Have you been at home from school/work the last 7 days because of your disease'. If the reply is 'Yes' the patient will be prompted to answer how many days he/she has been absent. Days off school/work due to study visits will not be recorded.

#### 5.1.1.4 Patient Global Impression of Change (PGIC)

The PGIC is a global measure indicating the degree of change in SCD related pain compared to the start of treatment, as evaluated by the patient. Patients will be asked to evaluate "Since

the start of the treatment I have received in this study, my sickle cell pain is" and response options are a 7-point Likert response scale with the following categories: Very much improved; Much improved; Minimally improved; No change; Minimally worse; Much worse and; Very much worse (Dworkin et al 2005).

The patient will be asked to fill in the PGIC at end of treatment in the eDiary.

### 5.1.2 Vaso-occlusive crisis (VOC)

At each visit, patients will be questioned regarding any painful sickle cell crises occurring. For each event, the Investigator will complete necessary information in the eCRF. VOC is defined as a composite endpoint of painful sickle cell crisis or acute chest syndrome. Acute chest syndrome is defined as an acute illness characterized by fever and/or respiratory symptoms, accompanied by a new pulmonary infiltrate on a chest X-ray. A painful sickle cell crisis is defined as an onset of moderate to severe pain (that has no other explanation than VOC) that lasts at least 2 hours and requires medical intervention including oral or parenteral opioids or parenteral NSAIDs in any of the following settings:

- In-patient hospitalisation
- Emergency department
- Short-stay outpatient unit
- Medical clinic outpatient
- Medically supervised outpatient treatment with escalated pain medication (e.g. management by telephone)
- Self-treated (no consultation with medical personnel prior to escalation of pain medication)

The occurrence of a VOC event is considered an efficacy event of the disease under study primarily reported on the eCRF VOC module and should not be recorded as an AE. If a VOC event fulfils any criteria of an SAE according to the definition (see Appendix B) or result in discontinuation of IP, it should be reported both on the eCRF VOC module and as an SAE or AE respectively. See Section 6.3.

## 5.2 Safety assessments

### 5.2.1 Laboratory safety assessments

Blood and urine samples for determination of clinical chemistry, haematology, virology (only at Visit 1), coagulation (only at Visit 1), and urinalysis will be taken at the times indicated in the Study Plan (see Section 4). Additional safety samples for central lab assessment may be collected during unscheduled visits if clinically indicated at the discretion of the Investigator. The date, time of collection and results (values, units and reference ranges) will be recorded on the appropriate eCRF module.

The clinical chemistry, haematology, virology and coagulation will be performed at a central laboratory. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site but it is crucial that the blood volume is not exceeding the volume stated in Table 3.

Urinalysis is to be performed at the investigational site by dipstick. A serum pregnancy test (β-hCG) will be taken at Visit 1 and a urine pregnancy test will be taken at Visit 2, Visit 4 and Visit 5 in females of child bearing potential. If female patients achieve menarche during the study, a urine pregnancy test should be performed before any study procedures at the next visit. The following laboratory variables will be measured:

**Table 2 Laboratory Safety Variables**

| **Haematology/Haemostasis (whole blood)** | **Clinical Chemistry (serum)** |
|---|---|
| B-Haemoglobin (Hb) | S-Creatinine |
| B-Haematocrit | S-Bilirubin, total |
| B-Leukocyte count | S-Bilirubin, direct |
| B-Leukocyte differential count (absolute count) | S-Alkaline phosphatase (ALP) |
| B-Platelet count | S-Aspartate transaminase (AST) |
| | S-Alanine transaminase (ALT) |
| **Urinalysis** (dipstick) | S-Lactate dehydrogenase (LDH) |
| U-Hb/Erythrocytes/Blood | S-Uric Acid |
| U-Protein/Albumin | S-Blood Urea Nitrogen (BUN) |
| U-Glucose | S-Albumin |
| U-beta-human chorionic gonadotropin (β-hCG) | S-Potassium |
| | S-Chloride |
| **Virology Screen**[a] | S-Sodium |
| Hepatitis B surface antigen (HBsAg) | S-Glucose |
| Hepatitis C virus (HCV) | S-Carbon Dioxide |
| HIV | S-Haptoglobin |
| | S-β-hCG (Screening only) |
| | |
| | **Coagulation**[a] |
| | International normalized ratio (INR) |
| | Partial Thromboplastin Time (PTT) |

[a] Virology screen and coagulation will be conducted at the Screening Visit only.
Prefix: B for blood; S for serum; U for urine.

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at centre as source data for laboratory variables. For information on how AEs based on laboratory tests should be recorded and reported, see Section 6.3.

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

### 5.2.2 Physical examination

A complete physical examination will be performed at enrolment (Visit 1) and at the end of treatment visit (Visit 5) and include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculo-skeletal (including spine and extremities) and neurological systems.

### 5.2.3 ECG

#### 5.2.3.1 Resting 12-lead ECG

A 12-lead ECG (standard ECG with a paper speed of 25 or 50 mm/second covering at least 6 sequential beats) will be recorded at enrolment (Visit 1) after the patient has been lying down to rest for up to 5 minutes. After paper ECG has been recorded, the Investigator or designated physician will review each of the ECGs for patient eligibility and entered as 'Normal' or 'Abnormal' in the eCRF. If the ECG is evaluated as "Abnormal" the Investigator should document the specific abnormality. Follow-up ECG will be performed during study only if clinically indicated. A standardised ECG machine should be used and a paper copy of ECG tracing should be filed in the patient's medical records.

### 5.2.4 Vital signs

**Blood pressure and pulse rate**

Pulse rate and systolic and diastolic blood pressure (BP) will be assessed using non-invasive equipment after the patient has been sitting at rest for 5 minutes. Results will be recorded in the eCRF. Pulse rate and BP will be measured at every visit (except Visit 6).

**Weight and Height**

Weight and Height assessments will be performed at the visits as shown in Table 1. Results will be recorded in the eCRF.

## 5.3 Other assessments (Not Applicable)

## 5.4 Pharmacokinetics

### 5.4.1 Collection of samples

Blood samples for determination of ticagrelor and its active metabolite in plasma will be taken at the times presented in the study plan Table 1. The actual date and time will be collected in the eCRF.

Samples will be collected, labelled stored and shipped as detailed in the Laboratory Manual. A central laboratory will be used for the logistic arrangements.

### 5.4.2 Determination of drug concentration

Samples for determination of ticagrelor and its active metabolite (AR-C124910XX) in plasma will be analysed by Covance on behalf of Clinical Bioanalysis Alliance AZ R&D, using an appropriate bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report.

All samples still within the known stability of the analytes of interest (i.e., ticagrelor and its active metabolite), at the time of receipt by the bioanalytical laboratory, will be analysed.

### 5.4.3 Storage and destruction of pharmacokinetic samples

Pharmacokinetic (PK) samples will be disposed of after the Bioanalytical Report finalization or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless requested for future analyses.

PK samples may be disposed of or destroyed and anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the clinical study report (CSR).

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the CSR but separately in a Bioanalytical Report. PK samples will be destroyed once CSR is finalized.

For each placebo subject, samples will only be analysed on a 'for cause' basis, e.g., if no quantifiable concentrations were observed in a subject's samples when the drug was expected to be present.

## 5.5 Pharmacodynamics

### 5.5.1 VerifyNow™ P2Y12 assay

The VerifyNow™ P2Y12 test is a whole blood test used in the point-of-care setting to measure the level of platelet $P2Y_{12}$ receptor blockade. Light transmittance increases as activated

platelets bind and aggregate fibrinogen-coated beads. The instrument measures this change in optical signal and reports results in PRU.

### 5.5.2 Collection of samples

Blood samples for determination of PRU in whole blood will be taken at the time presented in Table 1. The actual date and time will be collected in the eCRF. VerifyNow™ P2Y12 assay will be used. PRU values will be blinded to avoid any possible bias. At the end of the study PRU values will be unblinded and reconciled by an acceptable third party for analysis.

Samples will be collected and labelled as detailed in the Laboratory Manual.

## 5.6 Pharmacogenetics (Not Applicable)

## 5.7 Biomarker analysis

The patient's consent to the use of donated biological samples is optional.

Biological samples (e.g., plasma, serum samples) will be collected (see Table 1 and Section 5.8) and may be analysed for exploratory biomarkers (sP-selectin, sCD40L and TXB2) to assess correlations with disease activity, effects of study drug, clinical outcomes and toxicity.

### 5.7.1 Storage, re-use and destruction of biological samples

Samples will be stored for a maximum of 15 years from the date of the Last Patient's Last Visit, after which they will be destroyed. The results of this biomarker research will be reported either in the CSR itself or as an addendum, or separately in a scientific report or publication. The results of this biomarker research may be pooled with biomarker data from other studies with the study drug to generate hypotheses to be tested in future research.

### 5.7.2 Labelling and shipment of biological samples

The Principal Investigator (PI) ensures that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix C 'IATA 6.2 Guidance Document'.

Any samples identified as Infectious Category A materials are not shipped and no further samples will be taken from the patient unless agreed with AZ and appropriate labelling, shipment and containment provisions are approved.

### 5.7.3 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The PI at each centre keeps full traceability of collected biological samples from the patients while in storage at the centre until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

AZ keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

Samples retained for further use are registered in the AZ Biobank during the entire life cycle.

### 5.7.4 Withdrawal of Informed Consent for donated biological samples

If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analysed, AZ is not obliged to destroy the results of this research.

The Principal Investigator:

- Ensures patients' withdrawal of informed consent to the use of donated samples is notified immediately to AZ
- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the signed document returned to the study site
- Ensures that the patient and AZ are informed about the sample disposal.

AZ ensures the central laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

## 5.8 Volume of blood

The total volume of blood that will be drawn from each patient for this study is listed in Table 3 below. The collection of additional samples is performed locally at the discretion of the investigator and recorded in the eCRF as appropriate, thus requiring additional sample volumes.

**Table 3 Volume of blood to be withdrawn from each patient**

| Assessment | Sample Volume (mL) | No. of samples Visit 1 | Total volume Visit 1 (mL) | No. of samples Visit 2 | Total volume Visit 2 (mL) | No. of samples Visit 3 | Total volume Visit 3 (mL) | No. of samples Visit 4 | Total volume Visit 4 (mL) | No. of samples Visit 5 | Total volume Visit 5 (mL) | Total (mL) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Haematology | 5 | 1 | 5 | 0 | 0 | 0 | 0 | 1 | 5 | 1 | 5 | 15 |
| Clinical Chemistry | 5 | 1 | 5 | 0 | 0 | 0 | 0 | 1 | 5 | 1 | 5 | 15 |
| Coagulation | 3 | 1 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 03 |
| Virology Screen | 4 | 1 | 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 04 |
| PRU | 4 | 0 | 0 | 2 | 8 | 2 | 8 | 0 | 0 | 0 | 0 | 16 |
| Pharmacokinetic | 2 | 0 | 0 | 1 | 2 | 2 | 4 | 0 | 0 | 0 | 0 | 06 |
| Biomarkers | 8.5 | 0 | 0 | 1 | 8.5 | 1 | 8.5 | 1 | 8.5 | 0 | 0 | 25.5 |
| Total | | | 17 | | 18.5 | | 20.5 | | 18.5 | | 10 | 84.5 |

# 6. SAFETY REPORTING AND MEDICAL MANAGEMENT

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

## 6.1 Definition of adverse events

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., 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.

## 6.2 Definitions of serious adverse event

A serious adverse event (SAE) is an AE occurring during any study phase (i.e., run-in, treatment, follow-up), that fulfils 1 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 1 of the outcomes listed above.

For further guidance on the definition of a SAE, see Appendix B to the Clinical Study Protocol.

## 6.3 Recording of adverse events

### 6.3.1 Time period for collection of AEs

AEs and SAEs will be collected from the time of informed consent and throughout the study including follow-up period (up to Visit 6).

### 6.3.2 Follow-up of unresolved adverse events

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

### 6.3.3 Variables

The following variables will be collect for each AE;

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

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

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

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Section 6.2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Section 6.2.

The 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)

### 6.3.4 Causality collection

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

For SAEs causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B to the Clinical Study Protocol.

### 6.3.5 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or care provider 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.

### 6.3.6 Adverse events based on examinations and tests

The results from protocol mandated laboratory tests and vital signs will be summarised in the CSR. Deterioration as compared to baseline in protocol-mandated laboratory values, 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 IP.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE 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 (e.g., anaemia versus low haemoglobin [Hb] value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

### 6.3.7 Hy's Law

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3xULN together with total bilirubin ≥ 2xULN may need to be reported as SAEs. Please refer to Appendix D for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

### 6.3.8 Assessment of bleeding events

One of the safety objectives in this study is to determine the percent of patients with haemorrhagic events requiring medical intervention. Bleeding events will be recorded as AEs. The investigator will do the classification of bleeding events; there will be no committee for adjudication of these events.

Bleeding events will be recorded in the bleeding event eCRF.

For patients experiencing a bleeding event that fulfils criteria in more than 1 category, the bleed will be assigned to the most severe category. The bleeding definitions (Mitchell et al 2011) are:

**Major bleeding:** defined as any fatal bleeding, clinically overt bleeding associated with a decrease in Hb of at least 20 g $L^{-1}$ (2 g $dL^{-1}$), bleeding that is retroperitoneal, pulmonary, intracranial, or otherwise involves the central nervous system or bleeding that requires surgical intervention in an operating suite.

**Clinically relevant non-major bleeding:** defined as overt bleeding for which a blood product is administered and which is not directly attributable to the patient's underlying medical condition, and bleeding that requires medical or surgical intervention to restore hemostasis, other than in an operating suite.

**Minor bleeding:** defined as any overt or macroscopic evidence of bleeding that does not fulfil the above criteria for either major bleeding or clinically relevant, non-major bleeding. Menstrual bleeding resulting in a medical consultation and/or intervention will be classified as a minor bleeding event.

### 6.3.9 Vaso-occlusive crisis (VOCs)

If a VOC event fulfils any criteria of an SAE according to the definition (see Appendix B) or result in discontinuation of IP, it should be reported both on the eCRF VOC module and as an SAE or AE respectively. For reporting and definition of VOC see Section 5.1.2.

## 6.4 Reporting of serious adverse events

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

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate AZ representatives within 1 day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AZ representative works with the Investigator to ensure that all the necessary information is provided to the AZ Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

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

Once the Investigators or other site personnel indicate an AE is serious in the WBDC system, an automated email alert is sent to the designated AZ representative.

If the WBDC system is not available, then the Investigator or other study site personnel reports a SAE to the appropriate AZ representative by telephone.

The AZ representative will advise the Investigator/study site personnel how to proceed.

The reference document for definition of expectedness/listedness is the IB for the AZ drug.

## 6.5 Overdose

An overdose is considered any dose greater than that specified in the protocol.

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

In healthy adults, ticagrelor is well tolerated in single doses up to 900 mg. Gastrointestinal toxicity (nausea, vomiting, diarrhoea) was dose-limiting in healthy adults following ascending single doses. Other clinically meaningful adverse effects, which may occur with overdose, include dyspnoea and ventricular pauses. In the event of overdose, observe for these potential adverse effects, and consider ECG monitoring. Measure platelet inhibition with VerifyNow to determine the extent and duration of excessive platelet inhibition.

- 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 AZ study drug occurs in the course of the study, then the Investigator or other site personnel inform appropriate AZ representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AZ representative works with the Investigator to ensure that all relevant information is provided to the AZ Patient Safety data entry site.

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 6.4. For other overdoses, reporting must occur within 30 days.

## 6.6 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AZ representatives.

### 6.6.1 Maternal exposure

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

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

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AZ representatives within 1day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AZ representative works with the Investigator to ensure that all relevant information is provided to the AZ Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 6.4) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

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

## 6.7 Management of IP related toxicities

Please see Section 3.9.2.

## 6.8 Study governance and oversight

There will be no Independent Data Monitoring Committee in this study. The safety of all AstraZeneca clinical studies is closely monitored on an on-going basis by AstraZeneca

representatives in consultation with Patient Safety. Issues identified will be addressed; for instance this could involve amendments to the study protocol and letters to Investigators.

# 7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

## 7.1 Identity of investigational product(s)

| Investigational product | Dosage form and strength | Manufacturer |
|---|---|---|
| Ticagrelor 10 mg tablet | Plain, round, biconvex, white/off-white, tablet, 10 mg | AstraZeneca |
| Ticagrelor 45 mg film-coated tablet | Plain, round, biconvex, yellow, film-coated tablet, 45 mg | AstraZeneca |
| Placebo for ticagrelor 10 mg tablet | Plain, round, biconvex, white/off-white, tablet containing no active ingredient | AstraZeneca |
| Placebo for ticagrelor 45 mg film-coated tablet | Plain, round, biconvex, yellow, film-coated tablet containing no active ingredient | AstraZeneca |

Ticagrelor tablets of 10 mg, 45 mg and their matching placebos will be packed in high-density polyethylene bottles.

## 7.2 Dose and treatment regimens

**Treatment during single-blind run-in period**

During the 4 week single-blind run-in treatment period eligible patients will receive:

- Matching placebo for ticagrelor 10 mg + matching placebo for ticagrelor 45 mg, 1 tablet bid given orally from each bottle

Study drug bottles will be managed via the IVRS/IWRS and at Visit 1 first dose of the study drug from each bottle will be administered at the clinic by site staff. Subsequent doses should be taken morning and evening, at approximately 12 hour intervals.

**Treatment during double-blind randomisation period**

Randomisation to bid double-blind treatment with ticagrelor or placebo will occur at Visit 2 via the IVRS/IWRS. Eligible patients will be randomly assigned to 1 of 3 treatment regimens:

- Ticagrelor 10 mg + matching placebo for ticagrelor 45 mg, 1 tablet bid given orally from each bottle

- Ticagrelor 45 mg + matching placebo for ticagrelor 10 mg, 1 tablet bid given orally from each bottle

- Matching placebo for ticagrelor 10 mg + matching placebo for ticagrelor 45 mg, 1 tablet bid given orally from each bottle

At Visit 2, the first dose of the study drug from each bottle will be administered at the clinic by site staff as soon as possible after randomisation. Subsequent doses should be taken morning and evening, at approximately 12 hour intervals.

At Visit 3 patient should not take their morning dose at home and it should be administered after obtaining the '0' hour (Pre-dose) PRU and PK samples.

Study drug should be swallowed whole with water. Study drug should not be altered (e.g., crushed, put in another vehicle) and should not be given by other routes.

## 7.3 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.

## 7.4 Storage

All study drugs should be kept in a secure place under appropriate storage conditions and in original container. The study drug label on the bottle specifies the appropriate storage.

## 7.5 Compliance

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

Each time study drug is dispensed, compliance will be reinforced. When study drug is returned, compliance will be assessed based upon an interview with the subject and a count of the tablets returned which should be ≥80% of that prescribed. Noncompliance with study drug will be considered as protocol deviations. Missed doses of ticagrelor or placebo blinded study drug should not be compensated (i.e., if a dose is missed the next regularly scheduled dose should be taken and should not be doubled).

## 7.6 Accountability

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

Patient will be asked to bring all unused study drug and empty bottles to the study site at each on-site visit. The Investigator or delegate will enter the amount of returned tablets in the eCRF (except Visit 3) and make an assessment regarding patient treatment compliance. Any patient found to be noncompliant would be counselled on the importance of taking their study drug as prescribed.

Study site personnel or the AZ delegated monitor will account for all study drugs received at the site, unused study drugs and for appropriate destruction. Certificates of delivery, destruction and return should be signed.

## 7.7 Concomitant and other treatments

Use of ADP receptor blockers (e.g., clopidogrel, prasugrel, ticlopidine), dipyridamole and cilostazol is not allowed in the study.

Treatment with oral or parenteral anticoagulants, and daily aspirin or non-steroidal anti-inflammatory agents (requiring treatment >3 days/week) is not allowed in the study except for prophylactic doses of heparins, e.g., flushing of catheters (see exclusion criteria in Section 3.2).

**CYP3A4 inhibitors**

Concomitant use of strong inhibitors of CYP3A4 (e.g., atanazavir, boceprevir, clarithromycin, [but not erythromycin or azithromycin], conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole) is not allowed.

**CYP3A4 substrates or inducers**

Co-administration of CYP3A4 substrates with a narrow therapeutic index is not allowed. Co-administration of strong inducers of CYP3A4 (e.g., rifampin/rifampicin, rifabutin, phenytoin, carbamazepine, phenobarbital, avasimibe, St. John's wort) is not allowed.

**P-glycoprotein interactions**

Ticagrelor is a weak inhibitor of P-glycoprotein (P-gp), a drug efflux transporter. Digoxin is a substrate of P-gp and concurrent treatment with ticagrelor modestly increases digoxin levels. If the patient is receiving digoxin, levels should be monitored closely following initiation of IP and with any change in IP.

### 7.7.1 Blood transfusions

If a patient requires any blood transfusion during the study, this information will be captured in the eCRF.

### 7.7.2 Other concomitant treatment

If a patient is taking HU, they must have been on the drug for 6 months or more and the dose stabilised for at least 3 months, and the dosing should not be altered or terminated throughout the 16-week study treatment period, other than for safety reasons.

If a patient is taking erythropoietin at Screening, they must have been on the drug for 6 months or more and the dose stabilised for at least 3 months.

Other medication other than that described above, 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. The entry must include the dose, regimen, route, indication, and dates of use.

Patients may not participate in any other interventional drug study for at least 30 days prior to starting this study and may not participate in any other interventional drug study throughout the study period.

## 7.8 Post Study Access to Study Treatment (Not Applicable)

# 8. STATISTICAL ANALYSES BY ASTRAZENECA OR DELEGATE

## 8.1 Statistical considerations

A comprehensive Statistical Analysis Plan (SAP) will be prepared prior to first patient in and any subsequent amendments will be documented, with final amendments completed prior to unblinding of the data. The analysis of this study will be performed by AZ or AZ delegate.

## 8.2 Sample size estimate

A sample size of 30 patients per group provides the ability to detect a difference in proportion of days with pain of 0.17 (17 percentage points) by use of a 90% confidence interval. Basis for this assumption is a placebo level of 0.56 with a SD of approximately 0.4 (PISCES and a prasugrel study in both cases – Wun et al 2013, Smith et al 2008).

## 8.3 Definitions of analysis sets

### 8.3.1 Efficacy analysis set

All randomised patients with at least 1 eDiary record post-dose will be included in the efficacy analysis set. Patients will be analysed according to their randomised study drug.

### 8.3.2 Safety analysis set

All patients who received at least 1 single dose of randomised IP, ticagrelor or placebo, and for whom any post-dose data are available, will be included in the safety analysis set. Erroneously treated patients (e.g., those randomised to treatment A but actually given treatment B) will be accounted for in the actual treatment group.

### 8.3.3 PK analysis set

The PK analysis set is a subset of the safety analysis set, including all patients having at least 1 post-dose PK variable calculated.

### 8.3.4 PD analysis set

The PD analysis set is a subset of the safety analysis set, including all patients having at least 1 post-dose PD variable calculated.

## 8.4 Outcome measures for analyses (Not Applicable)

## 8.5 Methods for statistical analyses

No statistical comparisons are planned for the primary objective. PRO and safety measures will be summarized descriptively using respective analysis set.

In general, all efficacy, safety, plasma concentrations of ticagrelor and active metabolite, PRU and PRO variables will be presented using descriptive statistics and graphs as appropriate. Continuous variables will be presented with descriptive statistics (n, mean, standard deviation [SD], median, min, max), within treatment group. Geometric mean and coefficient of variation (CV) will be used instead of arithmetic mean and SD, if appropriate, with CV(%) calculated as:

$$100 \cdot \sqrt{\left(\exp\left(s^2\right)-1\right)}$$

where s is the SD of the data on a log scale.

Categorical variables will be summarized in frequency tables (number of patients and percentage), by treatment group. Data will also be presented in individual patient listings.

The presentation of pain, intensity of pain and days of analgesic use due to SCD, will be presented by week. They will also be presented by subgroup of PGIC, divided into 3 groups, improved (1 and 2), no change (3, 4 and 5) and worse (6 and 7).

In general, baseline values will be the closest observation prior to the first administration of randomised IP. For the baseline value of pain, intensity of pain and days of analgesic use, a mean value for the 4 weeks in the Screening period will be calculated.

The number of days with pain due to SCD and the analysis of analgesic use due to SCD will be analysed using an ANCOVA model, with treatment, country, baseline average value, and baseline hydroxyurea (HU) use as explanatory variables, and treatment and HU as fixed effects and centre as a random effect. Least squares differences in means between ticagrelor 45 mg and placebo and ticagrelor 10 mg and placebo with corresponding 90% confidence interval will be presented. The objectives will be analysed as a proportion of days, during the whole treatment period. A sensitivity analysis of pain and analgesic use will be performed using the ANCOVA model but excluding country and baseline HU use.

The relationship between ticagrelor dose, plasma concentration and PRU may be explored using a population PK and PK/PD modelling approach (i.e., non-linear mixed effect modelling). Data may be pooled with other appropriate ticagrelor studies for selection of doses in the planned ticagrelor SCD paediatric phase III program.

# 9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA

## 9.1 Training of study site personnel

Before the first patient is entered into the study, an AZ or its representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigator site staff and also train them in any study specific procedures and the WBDC and ePROs system(s) utilised.

The PI will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The PI will maintain a record of all individuals involved in the study (medical, nursing and other staff).

## 9.2 Monitoring of the study

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

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the eCRFs 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 (e.g., clinic charts)
- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient

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

### 9.2.1 Source data

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

### 9.2.2 Study agreements

The PI at each/the 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 Clinical Study Protocol and the CSA, the terms of Clinical Study Protocol 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 AZ delegate and the PI should be in place before any study-related procedures can take place, or patients are enrolled.

### 9.2.3 Archiving of study documents

The Investigator follows the principles outlined in the CSA.

## 9.3 Study timetable and end of study

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

The study is expected to start in Q2 2015 and to end by Q3 2016.

The Sponsor will notify the PI(s) when recruitment is complete.

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

## 9.4 Data management by AstraZeneca or delegate

Data management will be performed by the AZ delegate.

Data will be entered into the WBDC system at the study site. Trained site staff will be entering the data as specified in the protocol and according to the eCRF instructions. Data entered into 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.

AEs and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the AZ Drug Dictionary. All coding will be performed by the AZ delegate.

The PI is responsible for signing the eCRF and this may be delegated to a trained Investigator.

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

responsibilities of the various functions and personnel involved in the data management process.

When all data have been coded, validated, signed and locked, clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked. A copy of the eCRF will be archived at the study site when the study is completed.

**Serious Adverse Event (SAE) Reconciliation**

SAE reconciliation reports are produced and reconciled with the Patient Safety database and/or the investigational site.

**Data associated with human biological samples**

Data associated with biological samples will be transferred from laboratory(ies) internal or external to AZ.

**Management of external data**

Data Management determines the format of the data to be received from external vendors and coordinates the flow of data to the clinical database. Data Management will assure that the data collection tools for eDiary and IVRS are tested and validated. External data reconciliation will be done with the clinical database as defined in the Data Management Plan.

# 10. ETHICAL AND REGULATORY REQUIREMENTS

## 10.1 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 AZ policy on Bioethics and Human Biological Samples.

## 10.2 Patient data protection

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

## 10.3 Ethics and regulatory review

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

The opinion of the EC/IRB should be given in writing. The Investigator should submit the written approval to AZ or its representatives before enrolment of any patient into the study.

The EC/IRB should approve all advertising used to recruit patients for the study.

AZ should approve any modifications to the ICF that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the EC/IRB annually.

Before enrolment of any patient into the study, the final study protocol, including the final version of the ICF, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AZ will handle the distribution of any of these documents to the national regulatory authorities.

AZ will provide Regulatory Authorities, EC/IRB and PIs with safety updates/reports according to local requirements.

Each PI is responsible for providing the EC/IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. AZ or its representatives will provide this information to the PI so that he/she can meet these reporting requirements.

## 10.4 Informed consent

This study consists of 2 ICFs, the main ICF that allows patient to participate in the main study and the other optional ICF that allows subjects to participate in optional biomarker research. The subject may participate in the main study without participating in the optional component. To participate in the optional component of the study the subject must sign and date both the consent forms for the main study and the optional component of the study. Enrolment code must be obtained from IVRS/IWRS. The principal investigator(s) is responsible for ensuring that consent is given freely and that the subject understands that they may freely discontinue the optional biomarker aspect of the study at any time.

The PI(s) at each centre will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each patient is notified that they are free to discontinue from the study at any time
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed 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 EC/IRB.

## 10.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the PI and AZ or AZ delegate.

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 EC/IRB and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

AZ or AZ delegate will distribute any subsequent amendments and new versions of the protocol to each PI(s). For distribution to EC/IRB see Section 10.3.

If a protocol amendment requires a change to a centre's ICF, AZ or AZ delegate and the centre's EC/IRB are to approve the revised ICF before the revised form is used.

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

## 10.6 Audits and inspections

Authorised representatives of AZ, a regulatory authority, or an EC 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 AZ or AZ delegate immediately if contacted by a regulatory agency about an inspection at the centre.

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**Clinical Study Protocol Appendix B**

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| Drug Substance | Ticagrelor |
| Study Code | D5136C00008 |
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| Date | 10 April 2015 |

# 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 (e.g., 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 (e.g., 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.

- 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 (e.g., neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse

# A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

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

- Time Course. Exposure to suspect drug. Has the 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?

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

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

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

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

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

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

- Is there a known mechanism?

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

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

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

**Clinical Study Protocol Appendix C**

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# Appendix C
# International Airline Transportation Association (IATA) 6.2 Guidance Document

# LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm).** For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and categories A and B.

**Category A Infectious Substances** are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are eg, Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

**Category B Infectious Substances** are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

**Exempt** - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)**
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable

- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

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| Clinical Study Protocol Appendix D | |
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# Appendix D
# Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

# TABLE OF CONTENTS PAGE

# 1. INTRODUCTION

This Appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

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) **together with** Total Bilirubin (TBL) ≥ 2xULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

**Hy's Law (HL)**
AST or ALT ≥ 3x ULN **together with** TBL ≥ 2xULN, where no other reason, other than the IMP, can be found to explain the combination of increases, e.g., elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (i.e. on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

# 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

When a patient meets any of the identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the Investigator (also sent to AstraZeneca representative).

The Investigator will also remain vigilant for any local laboratory reports where the identification criteria are met, where this is the case the Investigator will:

- Notify the AstraZeneca representative
- Request a repeat of the test (new blood draw) by the central laboratory
- Complete the appropriate unscheduled laboratory eCRF module(s) with the original local laboratory test result

When the identification criteria are met from central or local laboratory results the Investigator will without delay:

- Determine whether the patient meets PHL criteria (see Section 2 of this Appendix for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

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

- Notify the AstraZeneca representative
- Determine whether the patient meets PHL criteria (see Section 2 of this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory eCRF

# 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 eCRF 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 eCRF

- If the alternative explanation is an AE/SAE, record the AE /SAE in the eCRF 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

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| Clinical Study Protocol Appendix E | |
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| Date | 10 April 2015 |

# Appendix E
# Child-Pugh Classification

# 1. CHILD-PUGH CLASSIFICATION

The Child-Pugh score is a FDA-recommended classification for assessing hepatic impairment. Drugs that are predominantly metabolized by the liver must be studied in a controlled trial with patients who have varying degrees of liver impairment. Dosage modifications due to hepatic impairment may be based on the Child-Pugh score[1].

**Table 1 Child-Pugh Classification[2] (modified from Pugh 1973)**

| Clinical and Biochemical Markers | Points scored for observed findings | | |
|---|---|---|---|
| | 1 | 2 | 3 |
| Hepatic encephalopathy (grade)* | Absent | Moderate (1 or 2) | Severe (3 or 4) |
| Ascites | Absent | Slight | Moderate |
| Bilirubin (mg/dL) | < 2.0 | 2.0 - 3.0 | > 3.0 |
| Serum albumin (g/dL) | > 3.5 | 2.8 - 3.5 | < 2.8 |
| Prothrombin time (seconds prolonged)<br>or<br>Prothrombin time (INR) | < 4<br><br>< 1.7 | 4 - 6<br><br>1.7 - 2.3 | > 6<br><br>> 2.3 |

**Total Child-Pugh Scoring**

| Total Points | Grade | Description |
|---|---|---|
| 5-6 | A | Mild: well-compensated disease |
| 7-9 | B | Moderate: significant functional compromise |
| 10-15 | C | Severe: decompensated disease |

*Grade 0: normal consciousness, personality, neurological examination, electroencephalogram.

Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cycles per second (cps) waves.

Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves.

Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves.

Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2-3 cps delta activity.

## References

[1] US Department of Health and Human Services Food and Drug Administration. Guidance for industry: pharmacokinetics in patients with impaired hepatic function: study design, data analysis, and impact on dosing and labeling. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072123.pdf. Updated May 30, 2003. Accessed March 21, 2011.

[2] Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC and Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973;60(8):646-9.

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| Clinical Study Protocol Appendix F | |
|---|---|
| Drug Substance | Ticagrelor |
| Study Code | D5136C00008 |
| Edition Number | 1.0 |
| Date | 10 April 2015 |

# Appendix F
# Patient Reported Outcomes

# SICKLE CELL DISEASE PAIN

**NB:** These questions will be administered via an electronic device.

### Instructions for site staffs

Immediately after patient enrolment on visit 1, dispense the electronic diary containing questions and train the patients on how to use the electronic diary.

### NRS

1. **Please rate your sickle cell pain by selecting the one number that best describes your worst pain in the last 24 hours**

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| No pain | | | | | | | | | | Pain as bad as you can imagine |

2. **Please rate your sickle cell pain by selecting the one number that best describes your average pain in the last 24 hours**

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| No pain | | | | | | | | | | Pain as bad as you can imagine |

3. **Please rate your sickle cell pain by selecting the one number that best describes your pain right now**

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| No pain | | | | | | | | | | Pain as bad as you can imagine |

## USE OF ANALGESICS

**NB:** This question will be administered via an electronic device.

1. **Have you taken any medication because of your sickle cell pain today?**

   **Yes No**

# DAYS MISSED FROM SCHOOL/WORK

**NB:** This question will be administered via an electronic device.

1. **Have you been at home from school/work the last 7 days because of your disease?**

   **Yes No**

   **If yes, how many days?**

## PATIENT'S GLOBAL IMPRESSION OF CHANGE (PGIC)

**NB:** This question will be administered via an electronic device.

**1. Since the start of the treatment I have received in this study, my sickle cell pain is:**

| **1** | **2** | **3** | **4** | **5** | **6** | **7** |
|---|---|---|---|---|---|---|
| Very much improved | Much improved | Minimally improved | No change | Minimally worse | Much worse | Very much worse |