AstraZeneca

Revised Clinical Study Protocol	
Drug Substance	Ticagrelor
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Multicenter, open-label, randomised, pharmacokinetic (PK) and pharmacodynamic (PD) dose-ranging Phase II study of ticagrelor followed by a double-blind, randomised, parallel-group, placebo-controlled 4 weeks extension phase in paediatric patients with sickle cell disease

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

[redacted]

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	23 April, 2014		
2	05 March 2015		
3	22 December 2015		
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PROTOCOL SYNOPSIS

Multicenter, open-label, randomised, pharmacokinetic (PK) and pharmacodynamic (PD) dose-ranging Phase II study of ticagrelor followed by a double-blind, randomised, parallel-group, placebo-controlled 4 weeks extension phase in paediatric patients with sickle cell disease

Study site(s) and number of subjects planned

This study is planned to be conducted in approximately 6-10 countries in North America, Europe, Middle East and Africa at approximately 30 - 37 sites, with a minimum of 36 patients and a maximum of 50 patients (including the patients already randomised to date) to be randomised in the study, depending on how many patients are required in order to have 36 evaluable patients. Of these 36 evaluable patients, at least 12 patients must be 2 to 11 years of age and 12 patients must be 12 to 18 years. In addition, a minimum of 12 evaluable patients must complete Part B (through Visit 8).

Study period		Phase of development
Estimated date of first subject enrolled	Q3 2014	II
Estimated date of last subject completed	Q1 2017	

Study design

This is a multicenter, open-label, dose-ranging study of ticagrelor followed by a double blind, placebo-controlled extension phase in paediatric patients with sickle cell disease (SCD).

Part A: Patients will be randomised 1:1 to receive one of two dosing schedules. All patients will receive 0.75 mg/kg as their initial dose, followed 7 days later by 1.125 mg/kg or 2.25 mg/kg with determination of pharmacokinetic (PK) parameters and pharmacodynamic (PD) platelet inhibition following each dose. The PK and platelet aggregation data are intended to support modelling-based selection of a weight-based dose for Phase III. Platelet aggregation will be measured using the VerifyNow™ P2Y12 assay and reported as $P2Y_{12}$ reaction units (PRU).

Following the 2 single doses, all patients will receive open-label one-week treatment with ticagrelor 0.75 mg/kg twice daily to determine tolerability prior to randomisation into Part B.

Part B: Part B will be optional for patients. The investigator should present Part B to each patient and the decision to participate in Part B should be made by the patient (or parents/legal guardian). In this part patients will be randomised (2:1 ratio) to ticagrelor 0.75 mg/kg twice

daily or placebo for a 4-week treatment phase. In some countries, Part B will not be performed.

During the study, patients will be followed for the occurrence of vaso-occlusive crisis (VOC) and for other disease manifestations such as daily pain, analgesic use and complications of SCD.

For safety reasons the dosing schedule will be modified for individual patients as follows: If PRU at 2 hr following dosing of 0.75 mg/kg is <95, the subsequent maximum dose for this patient will be 0.563 mg/kg throughout the study. If PRU <95 following dosing of 0.563 mg/kg, the patient will be discontinued from further study drug.

Since Part A of the study is open label, the PK and PD results will be monitored as the study proceeds and the doses may be further adjusted in both Part A and B based on emerging PK and PD results. Doses may be adjusted following assessment by AstraZeneca and the Steering Committee of open label Part A results in the first 6-12 patients randomised under this amendment. Dose adjustment decisions will be based upon a review of PK, PD and adverse events (see Section 8.6).

Objectives

Primary Objective:	**Outcome Measure:**
To characterise the relationship between ticagrelor dose and inhibition of platelet aggregation in paediatric patients with SCD, using PK-PD modelling, to support dose selection for Phase III	PRU, Maximum Plasma Concentration (C_{max}) and Area Under the Plasma Concentration Time Curve (AUC)

Secondary Objective:	**Outcome Measure:**
To determine the PK properties of ticagrelor and its active metabolite in paediatric patients with SCD and to assess impact of weight, age and other demographic on the ticagrelor pharmacokinetics	Concentrations of ticagrelor and its active metabolite. Population PK parameters (Oral Clearance (CL/F) and AUC)
Investigation of efficacy of ticagrelor vs. placebo in paediatric patients with SCD in reducing:	Number of VOC* Number of VOC requiring hospitalization or emergency department visits Days hospitalized for VOC or other complications of SCD Days with pain (ages ≥4 years only) Intensity of pain (ages ≥4 years only) Days of analgesic use (ages ≥4 years only) Days of opioid analgesic use Days of absence from school or work (ages ≥6 years only)

Safety Objective:	**Outcome Measure:**
To assess safety and tolerability of single and multiple doses of ticagrelor in paediatric patients with SCD	Adverse Events (AE)/Serious Adverse Events (SAEs) Vital signs, laboratory safety samples
To determine the percent of patients with haemorrhagic events requiring medical intervention	Haemorrhagic events**

* VOC is defined as a painful sickle cell crisis requiring medical intervention including any of the following (1) hospitalization (2) emergency department or clinic visit (3) medically supervised outpatient treatment with escalated doses of drugs for management of painful crisis (may include oral or parenteral opioids or non-steroidal anti-inflammatory drugs).

** A haemorrhagic event is defined as bleeding prompting an unscheduled visit or call to a medical provider and resulting in therapy or further investigation.

Exploratory Objective:	**Outcome Measure:**
Investigation of efficacy of ticagrelor vs. placebo in paediatric patients with SCD in reducing:	Days with pain (ages <4 years only) Intensity of pain (ages <4 years only)

Target subject population

Patients eligible for this study include all children aged ≥2 to <18 years of age (age from birth to Visit 1) who are diagnosed with sickle cell disease [homozygous sickle cell (HbSS) or sickle beta-zero-thalassemia (HbS/β^0).

Duration of treatment

In Part A the treatment period consists of 2 single doses (separated by at least 7 days) followed by 7 days open label ticagrelor treatment twice daily. In Part B patients will be randomised to 4 weeks twice-daily treatment. There is no washout period between Part A and Part B. The total expected study duration for an individual patient participating in both Part A and Part B is approximately 3 months (including 30 days follow-up after last dose) and approximately 2 months for an individual patient participating in only Part A (including 30 days follow-up after last dose).

Investigational product, dosage and mode of administration

Part A:

Ticagrelor 0.563 mg/kg, 0.75 mg/kg, 1.125 mg/kg or 2.25 mg/kg given as oral single doses.

Ticagrelor 0.563 mg/kg or 0.75 mg/kg twice daily given orally.

These doses may be adjusted based upon evaluation of PK/PD data as described in Appendix E.

Part B:

Ticagrelor 0.563 mg/kg or 0.75 mg/kg twice daily given orally and matching placebo.

These doses may be adjusted based upon evaluation of PK/PD data as described in Appendix E.

The investigational product (active or placebo) will be granules for oral suspension supplied in glass bottles. Before each dosing occasion the granules will be constituted with 10 mL of purified water in the glass bottle to form a suspension suitable for oral dosing.

Statistical methods

The relationship between ticagrelor dose, plasma concentration and PRU will be characterized using a population PK/PD approach (i.e non-linear mixed effect modeling). This analysis will be based on all available PK and PRU data from which complete dosing and sampling history is collected.

No statistical comparisons are planned for the primary objective. PK, PD and safety measures will be summarized descriptively.

A statistical analysis will be done comparing ticagrelor and placebo for each of the following variables:

- Percentage of days with pain (ages ≥4 years only)
- Percentage of days of opioid analgesic use
- Percentage of days of analgesic use (ages ≥4 years only)
- Percentage of days hospitalized for VOC or other complications of SCD
- Percentage days of absence from school or work (ages ≥6 years only)

A t-test will be performed for each of these variables at 5% significance level, provided that the efficacy analysis set contains at least 30 patients, otherwise only descriptive statistics will be used. The p-value and a 95% confidence interval for the difference between ticagrelor and placebo will be reported. There will be no adjustment for multiple comparisons. If it is

inappropriate to assume a normal distribution, a Wilcoxon rank sum test may be performed. Number of VOC requiring hospitalization and intensity of pain will be summarized descriptively.

TABLE OF CONTENTS PAGE

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

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
ALT	Alanine transaminase
AST	Aspartate transaminase
ATP	Adenosine Triphosphate
AUC	Area Under the Plasma Concentration Time Curve
BP	Blood pressure
CL/F	Oral Clearance
CNS	Central Nervous System
C_{max}	Maximum Plasma Concentration
CPTP	Cyclopentyltriazolopyrimidines
CRF	Case Report Form (electronic/paper)
CRO	Contract Research Organization
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CVA	Cerebrovascular accident
EC	Ethics Committee, synonymous with Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ENT-1	Equilibrative nucleoside transporter-1
ePRO	Electronic devices for Patient Reported Outcomes
FHS	Faces Hedonic Scale
FLACC	Face, Legs, Activity, Cry, Consolability scale
FPS-R	Faces Pain Scale - Revised
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GRand	Global Randomisation system
HbSS	homozygous sickle cell anemia
HbS/β^0	sickle beta-zero-thalassaemia
ICH	International Conference on Harmonisation

Abbreviation or special term	Explanation
ICF	Informed consent form
INR	International Normalised Ratio
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.
IPA	Inhibition of platelet aggregation
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
NSAIDs	Non-steroidal anti-inflammatory drug
OSE	Office of Surveillance and Epidemiology
PD	Pharmacodynamic
P-gp	P-glycoprotein
PI	Principal Investigator
PK	Pharmacokinetic
PRO	Patient reported outcomes
PRU	$P2Y_{12}$ reaction units
PTT	Partial Thromboplastin Time
RBC	Red Blood Cells
SAE	Serious adverse event
SC	Steering Committee
SCD	Sickle Cell Disease
SOC	Standard of care
TAMMV	Time averaged mean of the maximum velocity
TCD	Transcranial Doppler
TCDi	Imaging Transcranial Doppler
TIA	Transient ischemic attack
t_{max}	Time to maximum plasma concentration
ULN	Upper Limit of Normal
UK	United Kingdom
US	United States
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). The ticagrelor development program to date has focused on adult patients since there is no paediatric correlate for the adult condition of 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.

Inhibition of platelet activation has been proposed as a potential therapeutic option in the treatment of children and adults with SCD. 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.

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 although platelets do not initiate VOC, they 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. A low level of platelet inhibition with prasugrel for at least 9 months in children with SCD showed numerical reductions in rate of VOC's and pain crises, but differences were not statistically significant compared to placebo (Heeney et al 2015).

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.

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 two 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 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 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 the Area Under the Plasma Concentration Time Curve (AUC) of ticagrelor 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%). 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 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 P2Y12 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 paediatric study is intended to determine appropriate dosing and tolerability in patients with SCD in preparation for a subsequent paediatric Phase III study. In addition, the current study will collect data on clinical manifestations such as pain and analgesic use to inform the choice of clinical outcome measures in the subsequent study and for exploratory efficacy.

Although the manifestations of SCD begin in childhood and evolve with age, the unique circumstances of childhood SCD indicate that dosing strategies and assessment of efficacy and safety in adults with SCD are not directly applicable to children. As patients with SCD age, lesions are acquired that contribute to the risk of serious bleeding (central nervous system (CNS) and other organ infarction, retinopathy). For these risks, which are presumably cumulative over a lifetime, adults may be at greater risk of serious bleeding than children.

With respect to efficacy, there are considerable data to indicate that the physiology of SCD pain in children may be different than in adults. Sickling pain in children is believed to be mostly ischemic in origin, and more likely to be impacted by inhibition of platelet aggregation. In contrast, painful crises in adults are more complicated, and may have ischemic and neuropathic components (Ballas 2007). Platelet inhibition may be less likely to influence painful crises in adults due to the multifactorial origin of the pain. Thus a well-designed study in paediatric SCD is likely to provide the most relevant, rigorous and scientific answer regarding the efficacy and safety of reversible $P2Y_{12}$ platelet inhibition in the prevention of VOC in children with SCD.

1.2.2 Study design

The current study will randomise a minimum of 36 patients with SCD aged ≥2 years to <18 years. An open-label, randomised pharmacokinetic (PK) and pharmacodynamic (PD) evaluation of 2 single doses will be followed by one week of treatment with ticagrelor twice daily to determine tolerability. This will be followed by an optional 4-week randomised, double blind placebo-controlled treatment with twice-daily ticagrelor or placebo. There is no washout period between Part A and Part B. All patients will receive 2 single open-label doses of ticagrelor separated by at least 7 days, with determination of PK parameters and PD (inhibition of platelet activation) after each dose, to support modelling-based selection of a weight-based dose for the subsequent Phase III study. The current study is designed to provide PK and PD data on ticagrelor in children, and to provide initial experience with chronic daily dosing.

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 study endpoint is the evaluation of the PK and PD properties of ticagrelor and its active metabolite in children after administration as single doses and after attainment of steady-state following twice-daily administration of ticagrelor. PK will be determined using standard methodologies. The PD measure employed will be the VerifyNow P2Y12 assay (Jeong et al 2012) that is a well-validated and commercially available point-of-care assay to assess inhibition of the $P2Y_{12}$ platelet receptor.

The secondary PK objectives are to determine the PK properties of ticagrelor and its active metabolite and to access the impact of demographic characteristics on the PK of ticagrelor. Outcome measures including:

- Concentrations of ticagrelor and its active metabolite.
- Population PK parameters (Oral Clearance (CL/F) and AUC)

The secondary efficacy objectives will include a daily diary and data collection during clinic Visits to assess disease burden including the following:

- Occurrence of VOC
- VOC requiring hospitalization or emergency department visits
- Days hospitalized for VOC or other complications of SCD
- Days with pain (ages ≥4 years only)
- Intensity of pain (ages ≥4 years only)
- Days of analgesic use (ages ≥4 years only)
- Days of opioid analgesic use
- Days of absence from school or work (ages ≥6 years only)

The secondary safety endpoints will include caregiver or patient reports of adverse events (AEs) including bleeding.

1.2.4 Dose and study duration

Assessment of the first 12 randomised patients indicates that higher doses are needed in order to accomplish the primary study objective of characterising the relationship between ticagrelor dose and inhibition of platelet aggregation to support dose selection for Phase III. This amendment provides for the following revised doses: The initial single dose will be a 0.75 mg/kg (weight-based dose equivalent to 60 mg in adults). The second single dose of ticagrelor will be 1.125 mg/kg or 2.25 mg/kg (weight-based dose equivalent to 90 or 180 mg in adults).

For safety reasons the dosing schedule will be modified for individual patients as follows: If PRU at 2 hr following dosing of 0.75 mg/kg is <95, subsequent maximum dose for this patient will be 0.563 mg/kg throughout the study. If PRU is <95 following dosing of 0.563 mg/kg, the patient will be discontinued from further study drug.

Dose selection in this study is informed by the interim data from 12 first patients in this study as well as the substantial clinical pharmacology programme for ticagrelor in adults, which included 41 studies in approximately 1000 subjects examining the exposure-response relationship, safety, and drug interactions. The dose range of ticagrelor administered during these studies was 0.1 to 1260 mg, and 900 mg was established as the maximum tolerated dose (MTD) in healthy volunteers. The approved dose regimen in adults with ACS consists of a loading dose of 180 mg followed by 90 mg twice daily for up to one year. In adult patients with prior myocardial infarction, a dose of 60 mg twice daily is approved by the US FDA and is under review in Europe and additional countries.

The 4-week duration of the second part of the study is intended to provide preliminary data on tolerability of daily dosing in children, without imposing a large burden on the patients but providing a period of potential benefit.

For potential further dose adjustments after monitoring of PK and PD please see Appendix E

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 hospitalisation and treatment with opioids, only one 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. Until a genetic cure is available, there is a clear unmet need for additional therapies that are better tolerated, safer, and more effective than available treatments.

Antiplatelet therapies have an established role in the treatment of many paediatric diseases, including thromboprophylaxis of stents, valves, shunts, and ventricular assist devices, and Kawasaki disease (Giglia et al 2013). Clinical experience with $P2Y_{12}$ inhibitors such as clopidogrel and prasugrel is relevant to the proposed ticagrelor paediatric program. Clopidogrel has been marketed in the United States (US) since 1997, and there is substantial clinical experience in paediatric patients. Completed studies in adults and children with SCD treated with prasugrel provide evidence that targeting inhibition of platelet aggregation (IPA) of 30% to 60% with a $P2Y_{12}$ platelet aggregation inhibitor does not pose an unacceptable safety risk to either adults or children with SCD enrolled in a well-controlled clinical study (Styles 2012, Wun et al 2013). Collectively these data provide substantial reassurance that 30%-60% IPA produced by treatment with a $P2Y_{12}$ inhibitor, the same degree of platelet inhibition targeted in the current Phase II ticagrelor study, is well tolerated in children and in patients with SCD.

Two randomised studies of clopidogrel in paediatric patients have been performed in infants with cyanotic congenital heart disease palliated with a systemic-to-pulmonary artery shunt, with the objective of prevention of shunt thrombosis. The largest study, CLARINET, was a randomised, double-blind, study in 906 infants aged 92 days or younger randomised to receive clopidogrel 0.2 mg/kg/day versus placebo for a median duration of 5.8 months, in addition to standard of care (Wessel et al 2013). This dose provides a level of platelet inhibition similar to that provided by a 75 mg dose in an adult (30% to 50% inhibition after stimulation with 5 μM ADP). Aspirin was administered concomitantly to 88.7% of patients in the clopidogrel group and 87.0% of patients randomised to placebo. Serious bleeding occurred in 6.5% in the clopidogrel group and 7.3% in the placebo group. These data provide substantial reassurance that 30%-50% IPA produced by treatment with a $P2Y_{12}$ inhibitor is well tolerated even in a very young and vulnerable paediatric population. The DOVE study was a randomised, placebo controlled study of the P2Y12 inhibitor prasugrel in children with sickle cell disease evaluating doses of prasugrel providing a mean platelet inhibition of approximately 25%. This treatment was well tolerated with no significant differences in safety results compared to placebo, and numerical reduction in rate of pan crises although differences were not statistically significant compared to placebo (Heeney et al 2015).

The FDA Office of Surveillance and Epidemiology (OSE) recently evaluated post-market reports of AEs in paediatric patients (ages 0-17 years) treated with clopidogrel (FDA Office of Surveillance and Epidemiology report, 2013). The report concludes that there was no new safety concerns identified with the use of clopidogrel in paediatric patients.

Prior to current study, there are no safety data regarding ticagrelor treatment in patients younger than 18 years. However, more than 25,000 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.

The proposed ticagrelor Phase II study design is focused on minimization of risk, including a low starting dose and conservative dose-ranging strategy, exclusion of patients with ocular or CNS clinical findings which might predispose to significant bleeding, and incorporating other exclusion criteria to minimize the bleeding risk. The potential benefit of ticagrelor is reduction

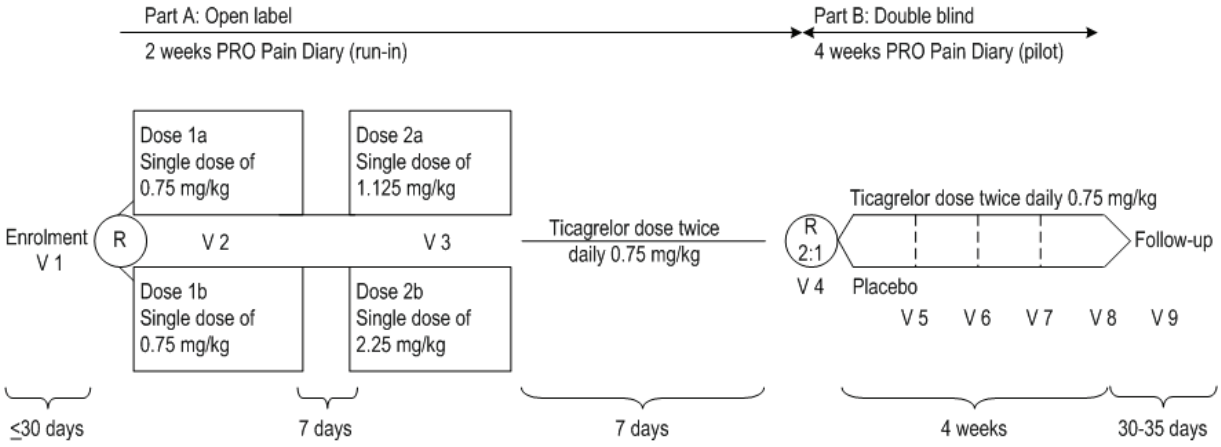
of the occurrence of VOC, based on its mechanism of action as a potent $P2Y_{12}$ inhibitor and the potential to reduce the occurrence of VOC, although vascular occlusion in SCD is multifactorial and it is not known whether antiplatelet therapy will be beneficial.

However, in the context of the unmet need for treatment of painful VOC in children with SCD, the benefit-risk balance for the program is believed to be favourable.

1.4 Study Design

This study is planned to be conducted in approximately 6-10 countries in North America, Europe, Middle East and Africa at approximately 30-37 sites, with a minimum of 36 patients and a maximum of 50 patients (including the patients already randomised to date) to be randomised in the study, depending on how many patients are required in order to have 36 evaluable patients. Of these 36 evaluable patients, at least 12 patients must be 2 to 11 years of age and 12 patients must be 12 to 18 years. In addition, a minimum of 12 evaluable patients must complete Part B (through Visit 8).

Figure 1 Study flow chart



R = randomisation; PRO = patient reported outcome

For safety reasons the dosing schedule will be modified for individual patients based on their PRU at Visit 2, 3 and 4 (see Figure 2). The dose modifications may occur at Visit 2, 3 and 4.

2. STUDY OBJECTIVES

2.1 Primary objective

Primary Objective:	Outcome Measure:
To characterise the relationship between ticagrelor dose and inhibition of platelet aggregation in paediatric patients with SCD, using PK-PD modelling, to support dose selection for Phase III	PRU, Maximum Plasma Concentration (C_{max}) and Area Under the Plasma Concentration Time Curve (AUC)

2.2 Secondary objectives

Secondary Objective:	Outcome Measure:
To determine the PK properties of ticagrelor and its active metabolite in paediatric patients with SCD and to assess impact of weight, age and other demographic on the ticagrelor pharmacokinetics	Concentrations of ticagrelor and its active metabolite. Population PK parameters (Oral Clearance (CL/F) and AUC)
Investigation of efficacy of ticagrelor vs. placebo in paediatric patients with SCD in reducing:	Number of VOC* Number of VOC requiring hospitalization or emergency department visits Days hospitalized for VOC or other complications of SCD Days with pain (ages ≥4 years only) Intensity of pain (ages ≥4 years only) Days of analgesic use (ages ≥4 years only)Days of opioid analgesic use Days of absence from school or work (ages ≥6 years only)

2.3 Safety objectives

Safety Objective:	Outcome Measure:
To assess safety and tolerability of single and multiple doses of ticagrelor in paediatric patients with SCD	AEs/Serious Adverse Events (SAE)s Vital signs, laboratory safety samples
To determine the percent of patients with haemorrhagic events requiring medical intervention	Haemorrhagic events**

* VOC is defined as a painful sickle cell crisis requiring medical intervention including any of the following (1) hospitalization (2) emergency department or clinic visit (3) medically supervised outpatient treatment with escalated doses of drugs for management of painful crisis (may include oral or parenteral opioids or non-steroidal anti-inflammatory drugs).

** A haemorrhagic event is defined as bleeding prompting an unscheduled visit or call to a medical provider and resulting in therapy or further investigation for definitions, please see Section 6.3.8.

2.4 Exploratory objectives

Exploratory Objective:	Outcome Measure:
Investigation of efficacy of ticagrelor vs. placebo in paediatric patients with SCD in reducing:	Days with pain (ages <4 years only) Intensity of pain (ages <4 years only)

3. SUBJECT 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. Children aged ≥2 to <18 years* of age and body weight >16 kg diagnosed with homozygous sickle cell (HbSS) or sickle beta-zero-thalassaemia (HbS/β^0)
2. If ≤16 years, must have had transcranial Doppler (TCD) within the past year prior to Visit 1. If this is not the case, a TCD examination must be done before proceeding in the study.
3. If ≥6 years old, must have had an ophthalmological examination within the past year prior to Visit 1. If this is not the case, the patient must be examined by an ophthalmologist before proceeding in the study.
4. If treated with an anti-sickling agent such as hydroxyurea, the weight-adjusted dose must be stable for 1 month before enrolment
5. Suitable venous access for the study-related blood sampling
6. Provision of signed and dated written informed consent prior to any study specific procedures not part of standard medical care, (local regulations and international guidelines are to be followed in determining the assent/consent requirements for children)

* Age from birth to Visit 1.

3.2 Exclusion criteria

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

1. Previous history of transient ischemic attack (TIA) or clinically overt cerebrovascular accident (CVA) (ischemic or haemorrhagic), severe head trauma, intracranial haemorrhage, intracranial neoplasm, arteriovenous malformation, aneurysm, or proliferative retinopathy

2. Findings on TCD: Current or previous values for time averaged mean of the maximum velocity (TAMMV) that are Conditional or Abnormal*.

   Conditional TAMMV values are ≥153 cm/sec using imaging TCD (TCDi) technique (corresponding to ≥170 cm/sec by the non-imaging technique). Both the middle cerebral artery and the internal carotid artery should be considered. Abnormal TAMMV values are ≥180 cm/sec using TCDi (corresponding to ≥200 cm/sec by the non-imaging technique) and are an indication for chronic transfusions because of a high stroke risk. Any other criteria that would locally be considered as TCD indications for chronic transfusion would also exclude the patient.

3. Undergoing treatment with chronic RBC transfusion therapy

4. Use of non-steroidal anti-inflammatory drugs (NSAIDs) >3 days per week

5. Receiving chronic treatment with anticoagulants or antiplatelet drugs that cannot be discontinued.

6. Moderate or severe hepatic impairment, defined as Child-Pugh Class B or C (see Appendix H) or renal failure requiring dialysis

7. Active pathological bleeding or increased risk of bleeding complications according to Investigator

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

9. Concomitant oral or intravenous therapy (see Restrictions) with strong CYP3A4 inhibitors**, CYP3A4 substrates with narrow therapeutic indices, or strong CYP3A4 inducers**, which cannot be stopped at least five half-lives, but not shorter than 10 days, before enrolment

10. Surgical procedure planned to occur during the study

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

12. Females (if after menarche) who are not willing to use a highly effective method of contraception which results in a low failure rate (i.e. less than 1% per year)

13. Known hypersensitivity or contraindication to ticagrelor

14. Concern for the inability of the patient or parents to comply with study procedures and/or follow-up

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

16. Previous randomization in the present study***

17. Participation in another clinical study with an investigational product or device during the last 30 days preceding enrolment.

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

* According to STOP study thresholds for non-imaging TCD technique (Adams et al 1998) and thresholds for imaging TCD (TCDi) technique as published by Bulas (Bulas et al 2005).

** 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 Jan 2013.

*** As the eligibility criteria have been changed with this amendment, patients previously enrolled but not randomised may be reassessed for eligibility. Patients fulfilling all inclusion criteria and no exclusion criteria can be re-enrolled.

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 parent/both parents/legal guardian (according to local regulations) and assent or consent from the child/adolescent (where required by local regulations) before any study specific procedures are performed. Patient is considered enrolled in the study after she/he has signed the informed consent form. If a patient was previously enrolled into the present study, but not randomised, a new informed consent document should be signed by the parent/both parents/legal guardian (according to local regulations) and assent or consent from the child/adolescent (where required by local regulations) before any study specific procedures are performed. The patient must receive a new unique enrolment number.
2. Assign 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
3. Determine patient eligibility. See Section 3.1 and 3.2. Patient who does not meet the eligibility criteria is considered as screening failure
4. Assign eligible patient unique randomisation code. Patient will be randomised once or twice, both in Part A and Part B and will receive 2 unique randomisation codes

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

Part A will be performed in open label fashion i.e. the patient as well as members of the study team, at investigational centres or third party vendors conducting the study or handling data, AstraZeneca R&D Supply Chain (including packaging and distribution vendors on their behalf) and bio analysis personnel analysing the PK samples will all have access to the randomisation schedule. Part B will be double blind i.e. no member of the study team at

AstraZeneca, the Steering Committee (SC), personnel at investigational centres or any contract Research Organization (CRO) handling data will have access to the randomisation scheme during the conduct of the study, with the exception of the Supply Chain Study Management department, CRO unblinded team and the Patient Safety department at AstraZeneca.

Randomisation codes will be assigned strictly sequentially as patients become eligible for randomisation for both Part A and/or Part B.

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 medication. 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 Investigator should inform the [redacted] Study Physician immediately, and a discussion should occur between the [redacted] Study Physician and the Investigator regarding whether to continue or discontinue the patient from treatment. Patients who are withdrawn from the study due to error in randomisation in Part A will be replaced.

The [redacted] Study Physician may consult with the AstraZeneca Physician for further discussion if necessary.

The ICON Study Physician must ensure all decisions are appropriately documented. In situations where an agreement cannot be reached, the patient should have his/her study therapy stopped.

3.5 Methods for assigning treatment groups

The randomisation codes will be computer generated by AstraZeneca R&D using the AZ Global Randomisation system (GRand). Randomisation codes will be generated in blocks to ensure approximate balance between dose schemes (1:1) in Part A and between the ticagrelor and placebo arms (2:1) in Part B. Randomisation codes will be assigned sequentially as patients become eligible for randomisation.

3.6 Methods for ensuring blinding

The treatment allocation in part B will be double blind. Ticagrelor and matching ticagrelor placebo granules will be provided (see Section 7), identical in appearance and packaging. Each kit will be labelled with a unique kit ID number that will be used to assign the treatment to the patient but will not indicate treatment allocation to the Investigator.

3.7 Methods for unblinding

Individual treatment codes, indicating the treatment randomisation for each randomised patient in part B, will be available to the Investigator(s) or pharmacists from the call center.

The treatment code should not be broken except in medical emergencies when the appropriate management of the subject requires knowledge of the treatment randomisation. The Investigator documents and reports the action to AstraZeneca, without revealing the treatment given to subject to the AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational product 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 subject have been made and documented.

3.8 Restrictions

Patients may not participate in another clinical study that involves an investigational product (active or placebo) 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 should be discontinued from study medication in the following situations:

3.9.1 Criteria for interruption or discontinuation of investigational product (active and placebo)

- Severe illness
- Major or minor surgery or invasive procedures
- Clinically significant thrombocytopenia which mandates an interruption of study drug due to patient safety in the assessment of the Investigator. Repeat laboratory

studies and standard of care (SOC) should be followed until resolution of laboratory abnormality

- Need of treatment with prohibited concomitant medications, see Section 7.7

Elective procedures or surgery should be deferred until after completion of the study. For necessary minor surgery or other invasive procedures, study drug may be interrupted temporarily at the discretion of the Investigator; however, such cases should be discussed with the [redacted] Study Physician as soon as the Investigator is aware.

3.9.2 Permanent discontinuation from investigational product (active and placebo)

- The patient (or parent/caregiver/legal guardian) is at any time free to discontinue treatment or advise the patient to discontinue treatment, without prejudice to further treatment
- Any major bleeding
- Risk to patients as judged by the Investigator
- If PRU is <95 despite an individual dose reduction having already been made, the patient will be discontinued from further study drug for safety reasons
- AE judged by the Investigator to be related to the investigational product, for which he/she feels continued participation would put the patient at undue risk. Examples of this could be:
  - Resting heart rate <40 bpm or any symptomatic bradycardia lasting for more than 60 seconds
  - Ventricular pauses longer than 3 seconds occurring more than twice during a 60 second period
  - Atrioventricular block II/III suspected to be caused by ticagrelor
  - Development of a bundle branch block
- Abnormal TCD indicating need for transfusion therapy
- Development of proliferative retinopathy
- Inability to manage pain without chronic NSAIDs
- Severe non-compliance to study protocol
- Pregnancy

3.9.3 Procedures for investigational product (active and placebo) in case of bleeding:

In case of a major bleeding event (see definitions in Section 6.3.8), investigational product (active and placebo) must be stopped immediately. The investigational product (active and placebo) administration need not be stopped in case of non-major bleeding. All bleeding events should be treated and followed up according to local clinical practice. Major bleeding events should be managed as medically indicated, with general support and transfusions as

indicated. It should be noted that platelet transfusion has not been studied with ticagrelor; new platelets may be inhibited by ticagrelor as long as it is circulating in the blood (see Section 6.3.8 for bleeding definitions).

There is no antidote to ticagrelor and treatment of bleeding should therefore be symptomatic and handled according to the clinical routines at the investigational site.

Bleeding events should be recorded as AEs, see Section 6.3.

3.9.4 Procedures for discontinuation of a patient from investigational product

At any time, patients are free to discontinue investigational product (active and placebo). If the patient is discontinued from investigational product after the second randomisation, the scheduled visits, data collection and procedures (except for blood sampling of PK and PD) should continue according to the study protocol, until patient completes Part B.

At any time, patients are free to withdraw from the study (i.e., investigational product and assessments - see Section 3.10), without prejudice to further treatment. Such patients (or parent/legal guardian) will always be asked about the reason(s) and the presence of any AEs. Patient will be asked to complete a follow-up visit. Alternatively, if patient does not agree to the option, a modified follow up through e.g, regular telephone contacts or a contact at study closure should be arranged, if agreed to by the patient and in compliance with local data privacy laws/practices. AEs will be followed up (See Section 6.3); electronic devices for Patient Reported Outcomes (ePRO) and all study drugs should be returned by the patient.

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

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 (investigational product (active and placebo) 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 AE. 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 who prematurely discontinue before completion of Visit 3 will be replaced. 36 evaluable patients with data from the two single doses are needed.

3.11 Discontinuation of the study

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

- Major bleeding that is drug-related in >1 patient
- If any of the heart rate/electrocardiogram (ECG) criteria below are fulfilled in >2 patients and judged to be related to the investigational product (active)
  - Resting heart rate <40 bpm or any symptomatic bradycardia lasting for more than 60 seconds
  - Ventricular pauses longer than 3 seconds occurring more than twice during a 60 second period
  - Atrioventricular block II/III suspected to be caused by ticagrelor
  - Development of bundle branch block

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

Assessment	Part A			Part B					
	Enrolment	Dose 1	Dose 2	Repeated treatment phase				End of treatment	Follow-up
Visit	**1[m]**	**2[m]**	**3**	**4[l]**	**5[r]**	**6**	**7[r]**	**8**	**9[l]**
Week		**0**	**1**	**2**	**3**	**4**	**5**	**6**	**10**
Day (Visit window)	**-30 - -14**	**0**	**7 (+3)**	**14 (+7)**	**21 (+3)**	**28 (+3)**	**35 (+3)**	**42 (+3)**	**72-77** 30-35 days following last dose for Visit 8 **(or Visit 4)[d]**
Signed Informed Assent/Consent	X								
Randomisation		X		X					
Inclusion/exclusion criteria	X	X[a]							
Relevant Medical and Surgical history, SCD characteristics and history	X								
Demographics	X								
Vital signs (BP, pulse)	X	X	X	X	X[r]	X	X[r]	X	X
Physical examination	X								X
Weight, height[e]	X	X	X					X	
Transcranial Doppler exam[o]	X								
Ophthalmological (Eye) exam[o]	X								
12-lead ECG[p]	X[p]			X					
Daily pain assessment[g]	X	X	X	X	X	X	X	X	
FLACC assessment[q]	X			X					
Daily recording of analgesic use[g]	X	X	X	X	X	X	X	X	
Days absent from school/work[g]	X	X	X	X	X	X	X	X	
Administration of IP at clinic[i]		X	X	X				X	
Treatment dispensed/returned[s]			X	X[j]	X	X	X	X[j]	
Compliance/ Drug accountability		X	X	X	X	X	X	X	

Table 1 Study Plan detailing the procedures

Assessment	Part A			Part B					
	Enrolment	Dose 1	Dose 2	Repeated treatment phase				End of treatment	Follow-up
Visit	**1[m]**	**2[m]**	**3**	**4[l]**	**5[r]**	**6**	**7[r]**	**8**	**9[l]**
Week		**0**	**1**	**2**	**3**	**4**	**5**	**6**	**10**
Day (Visit window)	**-30 - -14**	**0**	**7 (+3)**	**14 (+7)**	**21 (+3)**	**28 (+3)**	**35 (+3)**	**42 (+3)**	**72-77** 30-35 days following last dose for Visit 8 **(or Visit 4)[d]**
Acceptability/Palatability[h]		X							
Concomitant medication	X	X	X	X	X	X	X	X	X
Adverse event review (AEs and SAEs)	X[f]	X	X	X	X	X	X	X	X
Blood samples for haematology and clinical chemistry (incl uric acid)	X[n]			X[k]				X	
Blood samples for coagulation (INR and PTT)	X[n]								
VerifyNow™ PRU[c]		X	X	X					
Pregnancy test (dipstick)[b]	X	X		X[b]				X	
Collection of VOC in CRF		X	X	X	X	X	X	X	X
Collection of transfusion data in CRF		X	X	X	X	X	X	X	X
Collection of bleeding events in CRF		X	X	X	X	X	X	X	X
Urinalysis	X[n]			X				X	
Blood sampling for pharmacokinetics[c]		X	X	X					

Abbreviations: AE = adverse event; BP = blood pressure; CRF = Case Report Form; ECG = electrocardiogram; eCRF = electronic Case Report Form; FLACC = Face, Legs, Activity, Cry, Consolability form; INR = International Normalised Ratio; PK = pharmacokinetics; PRU = $P2Y_{12}$ reaction units; PTT = Partial Thromboplastin Time; SAE = serious adverse event; SCD = Sickle Cell Disease; VOC = vaso-occlusive crisis

a Results from local laboratory must have been received before first dose to check eligibility criteria.
b In patient after menarche. Pregnancy testing at Visit 4 is only applicable for patients NOT performing Part B.
c Actual time of PK and PRU sampling should be recorded in the eCRF. See Table 2 and Table 3 for PK sampling time points.
d May occur following earlier visits than Visit 9.
e Height only at enrolment.
f Only SAE assessed at this time.

g Electronic diary recording by patient ≥4 years (when needed with parent/guardian help).
h Questions assessed by nurse in children <6 years, Hedonic Faces Scale (HFS) for children ≥6 years
i Actual time of dosing should be recorded in the eCRF.
j The time of drug administration in the morning and evening before Visit 4 and 8 will be registered in a patient diary.
k Blood sample for haematology and clinical chemistry (including uric acid) at Visit 4 will be collected 2h post-dose together with PK and PRU.
l If patient only participates in Part A, the follow-up Visit 9 should be performed after Visit 4 according to schedule.
m Visit 2 should be at least 14 days apart from Visit 1.
n Laboratory testing performed prior to Visit 1 as part of usual clinical care does not need to be repeated as long as the values were obtained within 30 days prior to Visit 2.
o The most recent examination must be performed within 12 months before Visit 1. If this is not the case, the examination must be done before proceeding in the study.
p 12-lead ECG must be performed within 6 months before Visit 1. If this is not the case, the examination must be done before proceeding in the study.
q FLACC for patients aged from 2 to <4 years only to be collected between Visit 1 and Visit 2, and between Visit 4 and Visit 5.
r Visit 5 and Visit 7 may be performed as telephone contacts, based on the opinion of the Investigator. Vital signs (BP and pulse) will only be measured if the patient visits the site.
s If Visit 5 and/or Visit 7 are performed as telephone contacts, doubles kits of study treatment will be dispended on Visit 4 and/or Visit 6 to cover the whole period.

During visits when investigational product is administered at clinic perform the following protocol procedures prior to administration of study drug (if applicable to the visit):

Review of AEs and concomitant medications, vital signs, weight, ECG, urine sampling (including pregnancy test if applicable), and pre-dose blood sampling (safety, PK, PD).

Table 2 Blood sampling in patients with a weight of >21 kg

Assessment	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
Coagulation (INR and PTT)	X								
Haematology and clinical chemistry (incl uric acid)	X			2h post-dose				X	
VerifyNow™ PRU		Pre-dose, 2, 6h post-dose	Pre-dose, 2, 6h post-dose	Pre-dose, 2h post-dose					
Blood sampling for pharmacokinetics		1, 2, 4, 6h post-dose	1, 2, 4, 6h post-dose	Pre-dose, 1, 2h post-dose					

Abbreviations: INR = International Normalised Ratio; PK = pharmacokinetics; PRU = $P2Y_{12}$ reaction units; PTT = Partial Thromboplastin Time
The 1, 2, 4, and 6 hour samples can be collected ±15 minutes from actual post-dose time point.
If applicable, PRU and PK sampling should be arranged at the same time to avoid repeated venipuncture.
A peripheral catheter can be used for blood sampling.

Table 3 Blood sampling in patients with a weight of 16-21 kg

Assessment	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
Coagulation (INR and PTT)	X								
Haematology and clinical chemistry (incl uric acid)	X			2h post-dose				X	
VerifyNow™ PRU		Pre-dose, 2h post-dose	Pre-dose, 2h post-dose	Pre-dose, 2h post-dose					
Blood sampling for pharmacokinetics		1, 2, 4, 6h post-dose	1, 2, 4, 6h post-dose	Pre-dose, 1, 2h post-dose					

Abbreviations: INR = International Normalised Ratio; PK = pharmacokinetics; PRU = $P2Y_{12}$ reaction units; PTT = Partial Thromboplastin Time
The 1, 2 and 4 and 6 hour samples can be collected ±15 minutes from actual post-dose time point.
If applicable, PRU and PK sampling should be arranged at the same time to avoid repeated venipuncture.
A peripheral catheter can be used for blood sampling.

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. It is planned for a minimum of 36 patients and a maximum of 50 patients (including the patients already randomised to date) to be randomised in the study, in order to ensure 36 evaluable patients completing two single doses in Part A. A patient is considered as evaluable if he/she has provided data up to and including Visit 3. Of these 36 evaluable patients, at least 12 patients must be 2 to 11 years of age and 12 patients must be 12 to 18 years. In addition, a minimum of 12 evaluable patients must complete Part B (through Visit 8).

A complete medical, surgical and medication history will be recorded for each patient at enrolment. All relevant medical conditions that have occurred within the past or conditions that are ongoing are to be recorded in the eCRF. The medication history must identify any known drug allergies, and use of chronic medications. Safety laboratory samples should be sent to the local laboratory for analysis.

If the patient is 16 years old or younger, a TCD must have been done within the past 1 year. If this is not the case, a TCD exam needs to be done before proceeding in the study.

If the patient is six years or older, an eye exam must have been done within the past 1 year. If this is not the case, the patient will need to be examined by an ophthalmologist before proceeding in the study.

At least a 14-day interval is needed between Visit 1 and Visit 2 to allow for the recording of the baseline data on patient diary (see Section 5.1.2) and to separate the blood sampling in time considering total blood sampling volume recommendations in children.

4.2 Treatment period

Descriptions of the procedures for this period are included in the Study Plan with exceptions of the following specific requirements for the treatment period:

The study consists of two parts, Part A: an open label part and Part B: a double blind part.

Part A:

Visit 2, 3 & 4: Randomisation will take place 14 to 30 days after enrolment. Patients will be randomised 1:1 to receive one of two dosing schedules, with each dose separated by 7 days. Platelet aggregation will be measured using the VerifyNow™ P2Y12 assay and reported as PRU. PRU will determine continued dosing. Patients are not allowed to eat 2 hours before and 1 hour after dosing at these visits. Palatability assessment will be performed (Visit 2). A study nurse will assess palatability directly after administration of dose (for more information see Section 5.3). The patients will be allowed to leave the clinic after all sampling has been completed. Following the 2 single doses, all patients will receive open-label one-week treatment with ticagrelor twice daily to determine tolerability prior to randomisation into

Part B. Dose to be administered twice daily within a 9-12 hours interval (starting in the evening the same day as Visit 3). For assessments performed during the visits see Table 1. For dosing see Figure 2, and Appendix E in case of potential change to dosing schedule. Patients only participating in Part A will complete Visit 4, see below, which will be their last visit on treatment and after Visit 4 perform Visit 9 (30-35 days following last dose for Visit 4).

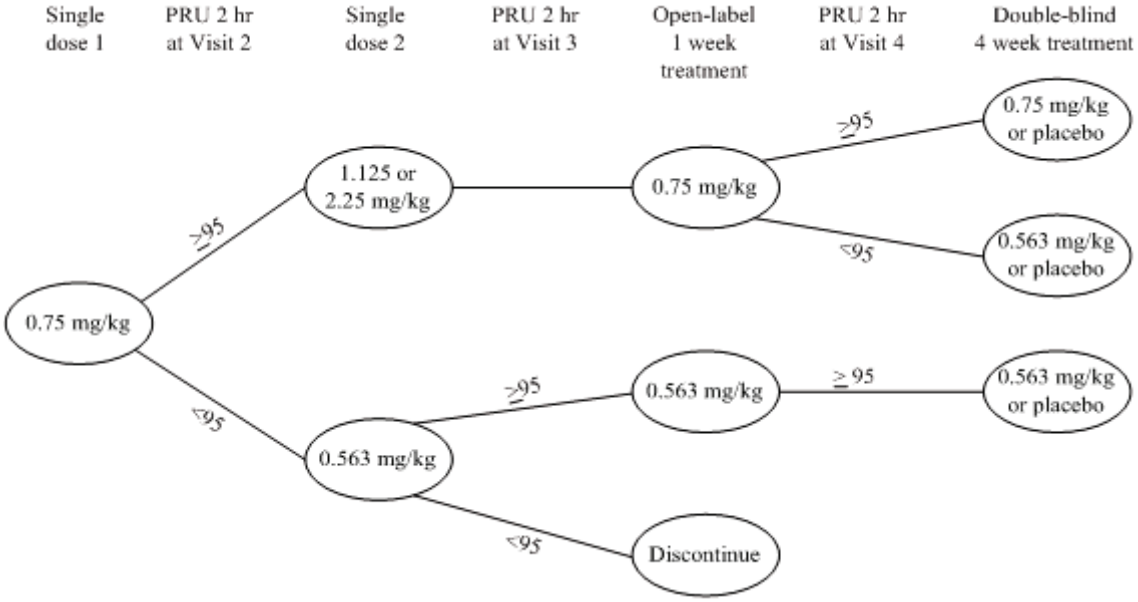
Part B:

Visit 4, 5, 6, 7 & 8: Visit 4 will be performed in all patients, including those not continuing to Part B. Participation in Part B is optional. The patient will register actual date and time of drug administration the morning and evening before Visit 4 in a Dosing Diary. He/she will be instructed to not take their dose at home in the morning of Visit 4. Study drug will be administered at the clinic and actual time of dosing should be recorded in the eCRF at Visit 4. For patients not participating in Part B, visit 4 will be the last visit on treatment. For patients continuing into Part B, patients will be randomised (2:1 ratio) to ticagrelor twice daily or placebo for a 4-week treatment phase and will return to the clinic on a weekly basis for study related procedures. Visit 5 and Visit 7 may optionally be performed as telephone contacts, based on the opinion of the Investigator (See Table 1, Visit 4-8). For dosing see Figure 2, and Appendix E in case of potential change to dosing schedule.

Patients will be followed for the occurrence of VOC events and for other disease manifestations such as daily pain, analgesic use, and complications of SCD throughout the study. Daily pain (ages ≥4 years only) and analgesic use will be reported by the patient (or if needed with the help of parent/guardian) using an electronic diary (for more information see Section 5.3). Specification of whether analgesics have been opiod or non-opiod will be done at follow-up site visit. Days of absence from school or work (ages ≥6 years only) will be collected weekly using the same electronic device.

For safety reasons the dosing schedule will be modified for individual patients based on their PRU at Visit 2, 3 and 4 (see Figure 2). The dose modifications may occur at Visit 2, 3 and 4.

Figure 2 Dosing schedule



4.3 Follow-up period

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

5. STUDY ASSESSMENTS

The Rave Web Based Data Capture (WBDC) system will be used for data collection and query handling. The Investigator will ensure that data are recorded on the eCRF as specified in the 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 electronic diary. These events will be identified using standard questioning of the patient at each visit, by information collected in the electronic dairy or by information that the Investigator may receive as part of standard medical practice.

For each event, the Investigator will complete necessary information in the eCRF. The Investigator should use the following definitions in assessing potential VOC.

5.1.1 Vaso-occlusive crisis (VOC)

VOC is defined as a painful sickle cell crisis requiring medical intervention including any of the following (1) hospitalization (2) emergency department, short-stay unit or clinic visit (3) medically supervised outpatient treatment with escalated doses of drugs for management of painful crisis (may include oral or parenteral opioids or non-steroidal anti-inflammatory drugs). At each visit, patients or guardians will be questioned regarding any painful sickle cell crises occurring since the last study visit.

5.1.2 Pain

Pain is commonly reported in clinical trials by having patients provide a rating of their own pain. Different measures of numerical rating scales have demonstrated good psychometric properties but are not fit for purpose for the youngest age groups due to their limited understanding of number concepts. Therefore, pain-rating scales with a series of faces depicting different levels of pain have been developed. The Faces Pain Scale - Revised (FSP-R) was validated by Hicks et al 2001 in 3 studies and has been judged as a well-established pain assessment tool in patients 4 to 16 years of age (Cohen et al 2008) and will be administered to all patients in this study age ≥4 years. When needed, a parent/guardian can help the child with the assessment.

The Faces Pain Scale will be collected daily at bedtime using an electronic device. The scale consists of six faces and scoring ranges between 0-10 (with an increase in numeric value by 2 i.e. (0, 2, 4, 6, 8, 10)), where 0 is no pain. 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. Please see Appendix G.

For patients aged from 2 to <4 years, a Face, Legs, Activity, Cry, Consolability (FLACC) form will be used for recording daily pain, between Visit 1 and 2 and between Visit 4 and 5. The FLACC form will be completed daily at bedtime by the primary caregiver, with the assessment of the time when the child is under the caregiver's care. If possible, the reporter should be the same caregiver during the reporting period. Please see Appendix G.

5.1.3 Other efficacy variables

Daily variables will be collected using a daily electronic diary both in Part A and Part B:

- Days of analgesic use (ages ≥4 years only)
- Days of absence from school or work (ages ≥6 years only), excluding days of absence due to study visits

For more details see Section 5.3.

5.2 Safety assessments

5.2.1 Laboratory safety assessments

Blood and urine samples for determination of clinical chemistry, haematology, coagulation, and urinalysis will be taken at the times indicated in the Study Plan (see Table 1).

At Visit 1, laboratory testing performed prior to enrolment as part of usual care does not need to be repeated as long as the values are obtained no more than 30 days prior to Visit 2.

Additional safety samples may be collected 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.

The clinical chemistry, haematology and urinalysis will be performed at the same local laboratory at or near to the Investigator site during the whole study. 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 6 and Table 7.

Urinalysis is to be performed at the investigational site by dipstick. A urine pregnancy test (U-HCG) will be taken at Visit 1, Visit 2 and repeated at Visit 4 (for patients only completing Part A) or Visit 8 (for patients completing Part B) in females of childbearing 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 4 Laboratory Safety Variables

Haematology/Haemostasis (whole blood)	**Clinical Chemistry (serum)**
B-Haemoglobin (Hb)	S-Creatinine
B-Haematocrit	S-Bilirubin, total
B-Leukocyte count	S-Alkaline phosphatise (ALP)
B-Leukocyte differential count (absolute count)	S-Aspartate transaminase (AST)
B-Platelet count	S-Alanine transaminase (ALT)
	S-Uric acid
Urinalysis (dipstick)	S-Blood Urea Nitrogen (BUN)
U-Hb/Erythrocytes/Blood	S-Na
U-Protein/Albumin	S-Cl
U-Glucose	S-K
U-Specific gravity	S-Glucose
	S-CO_2
Coagulation	
International Normalised Ratio (INR)	

Partial Thromboplastin Time (PTT)

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 subject shows an Aspartate transaminase (AST) **or** Alanine transaminase (ALT) ≥3x Upper Limit of Normal (ULN) **or** total bilirubin ≥2x ULN 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 and at the follow-up visit (Visit 9) 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 Vital signs

Vital signs consist of sitting pulse, sitting blood pressure (BP), weight and height.

BP and pulse will be measured at every on-site visit. Weight will be measured at Visit 1(enrolment), 2, 3 and 8 (follow-up). Height will only be measured at enrolment.

5.2.4 Electrocardiogram

12-lead ECG will be performed at Visit 1 (or within 6 months prior to enrolment) and at Visit 4. The following ECG parameters will be collected: heart rate and rhythm, PR interval, QRS duration, RR interval, QT interval, QTc interval (unspecified), and any abnormalities.

5.3 Other assessments

5.3.1 Patient reported outcomes

Patient reported outcomes (PROs) are an umbrella term referring to all outcomes and symptoms that are directly reported by the patient. In addition to the PROs for efficacy described in Section 5.1.2, the following PROs will be administered: Palatability Assessment, Use of analgesic, and Days of absence from school/work.

Many Investigators cite palatability as an important factor in determining medication adherence and completion of drug therapy in children. It is reasonable to assume that a better tasting drug is easier to administer to infants and young children (Matsui 2007). The palatability of the study drug will be assessed at Visit 2.

5.3.1.1 Palatability assessment by age group

The Facial Hedonic Scale (FHS) is a well-established method for assessing paediatric patients' responses to drug palatability (Davies and Tuleu 2008). The literature indicates that

the facial hedonic scale can be used for patients down to 3 years of age. The FHS consists of five faces with descriptions from 'Dislike very much' to 'Like very much'. For infants and very young children, a study nurse observing the child's behaviour when having received the study medication can perform an assessment of palatability.

Palatability will be assessed at Visit 2. Patients ≥6 years old will be asked to evaluate palatability immediately after dosing using the Hedonic Faces Scale. For patients under 6 years of age a nurse's assessment of the patient's behaviour, including willingness to swallow, will be performed directly after the patient has received the investigational product. For more information please see Appendix G.

Table 5 Palatability assessment

Method	Age group
Facial Hedonic Scale completed by patient	≥6 years to <18 years
Willingness to swallow, patient's behaviour indicative of a negative response to the taste of the investigational product	2 years to <6 years

5.3.1.2 Use of analgesic

Patients will be asked about their use of analgesics. When needed a parent/guardian can help the child with the assessment. The question 'Have you taken any medication because of your pain today' will be administered daily in the electronic device. Response options will be dichotomous, i.e. 'Yes' or 'No'. The question should be answered daily at bedtime. Specification of whether analgesics have been opiod or non-opiod will be done at follow-up site visit.

5.3.1.3 Absence from school/work

For patients aged ≥6 years, absence from school/work will be recorded. 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 due to study visits will not be recorded.

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 2. 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 drug concentration in plasma will be analysed by [redacted] on behalf of AstraZeneca, using an LC/MS after protein precipitation. The lower limit of quantification of ticagrelor and its active metabolite in plasma is 1.00 ng/mL and 2.50 ng/mL, respectively. 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 (ie. 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

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 pharmacokinetic 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.

Any residual back-up PK samples may be used for future exploratory biomarker research (in this case, residual back-up PK samples will be shipped to AZ Biobank; see details in the Laboratory Manual).

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 P2Y12 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. PRU <95 is associated with increased risk of bleeding based on data from patients with ACS.

Blood samples for determination of PRU in whole blood will be taken at the times presented in

Table 2. The actual date and time will be collected in the eCRF. VerifyNow™ P2Y12 assay will be used.

5.5.2 Collection of samples

Samples will be collected and labeled as detailed in the VerifyNow User's Manual. In addition, to reduce the blood volume required for the PD and PK samples, the following procedures will be utilized.

- For VerifyNow samples obtained through a peripheral indwelling cannula: Discard saline remaining in the cannula and 1 mL of blood. Draw 1.2 mL for PK sample (discard this blood if there is no PK sample at this time point). Draw 2 mL into the VerifyNow partial fill tube.
- For VerifyNow samples obtained through a central indwelling line: Discard saline or flush solution and 3.8 mL of blood. Draw 1.2 mL for PK sample (discard this blood if there is no PK sample at this time point). Draw 2 mL into the VerifyNow partial fill tube.
- For samples obtained through direct phlebotomy: Use a 21 gauge or larger needle or butterfly device and ensure an atraumatic venipuncture. Draw and discard 1 mL of blood. Draw 1.2 mL for PK sample (discard this blood if there is no PK sample at this time point). Draw 2 mL into the VerifyNow partial fill tube.

5.6 Pharmacogenetics (Not Applicable)

5.7 Biomarker analysis (Not Applicable)

5.8 Volume of blood

The total volume of blood that will be drawn from each patient is shown in Table 6 and Table 7.

Table 6 Volume of blood to be drawn from patients with a weight >21 kg

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 8	Total volume Visit 8 (mL)	Total (mL)
Haematology	1.2	1	1.2	0	0	0	0	1	1.2	1	1.2	
Clinical Chemistry	1.1	1	1.1	0	0	0	0	1	1.1	1	1.1	
Coagulation	1.2	1	1.2	0	0	0	0	0	0	0	0	
Pharmacokinetic	1.2	0	0	2	2.4	2	2.4	1	1.2	0	0	
PRU*	4.0	0	0	1	4.0	1	4.0	0	0	0	0	
Pharmacokinetic + PRU**	4.2	0	0	2	8.4	2	8.4	2	8.4	0	0	
Total			3.5		14.8		14.8		11.9		2.3	**47.3**

* PRU sampling via a central catheter may require up to an additional 3 mL at each PRU sampling timepoint.
** Timepoint with both PRU + PK required volume is 4.2 mL total for both.

Table 7 Volume of blood to be drawn from patient with a weight of 16-21 kg

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 8	Total volume Visit 8 (mL)	Total (mL)
Haematology	1.2	1	1.2	0	0	0	0	1	1.2	1	1.2	
Clinical Chemistry	1.1	1	1.1	0	0	0	0	1	1.1	1	1.1	
Coagulation	1.2	1	1.2	0	0	0	0	0	0	0	0	
Pharmacokinetic	1.2	0	0	3	3.6	3	3.6	1	1.2	0	0	
PRU*	4.0	0	0	1	4.0	1	4.0	0	0	0	0	
Pharmacokinetic + PRU**	4.2	0	0	1	4.2	1	4.2	2	8.4	0	0	
Total			3.5		11.8		11.8		11.9		2.3	**41.3**

* PRU sampling via a central catheter may require up to an additional 3 mL at each PRU sampling timepoint.
** Timepoint with both PRU + PK required volume is 4.2 mL total for both.
Reference Ethical considerations paediatric 2008

The maximum blood withdrawal during any 4 week period is 41.5 mL for patients weighing >21 kg and 35.5 mL for patients weighing 16-21 kg.

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

The Principal Investigator (PI) is responsible for ensuring that all staff involved in the study is 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, ECG). 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 SAE is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

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

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

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

AEs will be collected from first randomisation (Visit 2) throughout the treatment period and including the follow-up period up to Visit 9.

SAEs will be recorded from the time of informed consent and throughout the study.

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. AstraZeneca retains the right to request additional information for any subject 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 (time to be collected only at Visit 2 to end of Visit 3)
- Maximum intensity
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product (yes or no)
- Action taken with regard to investigational product
- AE caused subject's withdrawal from study (yes or no)
- Outcome

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

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

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

6.3.4 Causality collection

The Investigator will assess causal relationship between Investigational Product 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 CSP.

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/the child had any health problems since the previous visit/you were last asked?', or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

6.3.6 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 investigational product.

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 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 subject shows an AST or ALT ≥3xULN or total bilirubin ≥2xULN may need to be reported as SAEs. Please refer to Appendix D for further instruction in cases of combined increase of aminotransferase and total bilirubin.

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 assessment 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 one category, the bleed will be assigned to the most severe category. The bleeding definitions are (Mitchell et al 2011):

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 CNS 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)

VOC will be recorded as AEs. For definition of VOC please see Section 5.1.1.

6.4 Reporting of serious adverse events

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

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

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

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform [redacted] representatives of any follow-up information on a previously reported SAE within one 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 [redacted] and/or AstraZeneca representative.

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

The [redacted] representative will advise the Investigator/study site personnel how to proceed.

The reference document for definition of expectedness/listedness is the Investigator's Brochure for the AstraZeneca 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 AstraZeneca study drug occurs in the course of the study, then the Investigator or other site personnel inform appropriate [redacted] representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

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

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

6.6 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to [redacted]

6.6.1 Maternal exposure

Women of childbearing potential are not allowed to be included in this study unless they use a highly effective method of contraception which results in a low failure rate (i.e. less than 1% per year), and must refrain from becoming pregnant from 1 month following the last dose. Should a pregnancy still occur, the investigational product should be discontinued immediately and the pregnancy reported to designated ICON representative **within 1 day**.

6.6.2 Paternal exposure

There are no restrictions against fathering a child when treated with ticagrelor.

6.7 Management of Investigational Product related toxicities

Please see Section 3.9 and 3.11.

6.8 Study governance and oversight

6.8.1 Steering Committee (SC)

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

of the clinical study. A member of the SC will be designated as the Coordinating Investigator and will be responsible for review and signature of the CSR.

The SC will also be responsible for the overall design, including the development of any protocol amendments, supervision, interpretation and reporting (presentations at international congresses and publications in peer reviewed journals) of the study. The SC will make recommendations to AstraZeneca with regard to early stopping or modifications of the study based on accumulated study data (data from the double blind phase will be reviewed without unblinding). The SC will be comprised of 2 to 3 Investigators in the study and non-voting members of the Sponsor, and will operate under a separate charter.

The SC charter will be prepared to detail precise roles and responsibilities and procedures to ensure integrity of the study in the review of accumulating data.

In addition AstraZeneca representatives in consultation with the AZ Patient Safety Department closely monitor the safety of all AstraZeneca clinical studies on an on-going basis. 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	Granules for oral suspension 45 mg	Almac Pharma Services
Matching placebo for Ticagrelor	Granules for oral suspension	Almac Pharma Services

Ticagrelor granules for suspension and its matching placebo will be provided in brown glass bottles containing 1 g of granules.

7.2 Dose and treatment regimens

Part A:

Open-label single doses (Visit 2 and 3):

All patients will receive 0.75 mg/kg as their initial dose, followed 7 days later by 1.125 mg/kg or 2.25 mg/kg. Single doses will be administered at the clinic by site staff. Patients are not allowed to eat 2 hours before and 1 hour after dosing at Visit 2 and 3.

Repeated dosing (Visit 3-4):

Patients will self-administer 0.75 mg/kg of open label ticagrelor for 1 week. Dose to be administered twice daily within a 9-12 hours interval. The first dose will be administered in the evening the same day as Visit 3.

Doses may be adjusted following assessment by AstraZeneca and the Steering Committee of open label Part A results in the first 6-12 patients. Dose adjustment decisions will be based upon a review of PK, PD and adverse events (see Section 8.6).

Part B:

Repeated dosing (Visit 4-8):

Randomisation to twice daily treatment with ticagrelor or placebo will occur at Visit 4. Patients will self-administer 0.75 mg/kg of ticagrelor dose or placebo for 4 weeks. Dose will be administered twice daily within a 9-12 hours interval. The first dose will be administered in the evening the same day as Visit 4.

Doses may be adjusted following assessment by AstraZeneca and the Steering Committee of open label Part A results in the first 6-12 patients. Dose adjustment decisions will be based upon a review of PK, PD and adverse events (see Section 8.6).

Before each dosing occasion the granules will be constituted with 10 mLof purified water to form a homogenous suspension suitable for oral dosing. Dosing will be weight based and a suitable volume of suspension should be withdrawn from the bottle using a syringe suitable for oral dosing. For more information regarding volume to be administered please see dose tables, appendix F. The dose tables are based on predefined weight brackets in order to ensure dose accuracy and that the correct treatment strength is given to patient. All patients will receive a handling instruction together with study drug at each visit starting at Visit 3. The Investigator will enter the individual volume to be given in the handling instruction before the patient leaves the clinic.

For safety reasons the dosing schedule will be modified for individual patients based on their PRU at Visit 2, 3 and Visit 4, see Figure 2. The dose modifications may occur at Visit 2, 3 and 4.

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.

7.4 Storage

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

7.5 Compliance

The single doses (Visit 2 and 3) will be administered by the study personnel to the patients in Part A.

In the repeated dosing part, the patient will bring the investigational product (active or placebo) to their home, with instructions for mixing the appropriate weight-based dose. The patients will receive a Dosing Diary to record intake of investigational products (active or placebo).

The administration of all investigational products (active or placebo) should be recorded in the appropriate sections of the eCRF. Time of dose intake (both in the morning and evening) should be recorded on the day before Visit 4 and 8.

Compliance will also be checked by measurement of PRU at Visit 4 and Visit 8 (if applicable).

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.

Study site personnel or the [redacted] 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 (eg. clopidogrel, prasugrel, ticlopidine), dipyridamole and cilostazol is not allowed in the study.

Treatment with oral or parenteral anticoagulants, and daily aspirin is not allowed in the study except for prophylactic doses of heparins, eg, flushing of catheters (see exclusion criteria in Section 3.2). NSAIDs may not be administered more frequently than 3 days per week.

CYP3A4 inhibitors

Concomitant use of inhibitors of CYP3A4 (eg, 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 (eg, 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 investigational product and with any change in investigational product.

7.7.1 Blood transfusion

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

7.7.2 Other concomitant treatment

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.

7.8 Post Study Access to Study Treatment (Not applicable)

8. STATISTICAL ANALYSES BY [redacted]

8.1 Statistical considerations

A Statistical Analysis Plan containing further details will be prepared before first enrolled subject.

8.2 Sample size estimate

No formal sample size calculation has been performed. The sample size was selected to provide adequate PK/PD data to support the modelling-based dose selection and at the same exposing a minimum number of patients.

8.3 Definitions of analysis sets

8.3.1 Efficacy analysis set

All patients randomised in Part B will be included in the efficacy analysis set. Patients will be analysed according to their randomised study medication.

8.3.2 Safety analysis set

All patients who received at least one single dose of ticagrelor or at least one dose of randomised investigational product, ticagrelor or placebo, will be included in the safety population.

8.3.3 PK analysis set

The pharmacokinetic analysis set is a subset of the safety analysis set, including all patients having at least one 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 one PRU measured.

8.4 Outcome measures for analyses (Not applicable)

8.5 Methods for statistical analyses

The relationship between ticagrelor dose, plasma concentration and PRU will be characterized using a population PK/PD approach (i.e non-linear mixed effect modelling). This analysis will be based on all available PK and PRU data from which complete dosing and sampling history is collected. The PK/PD analyses will be performed sequentially, where first the PK of ticagrelor and its active metabolite will be characterized and followed by characterizing of the PK/PD relationship. Prior PK/PD knowledge from ticagrelor in adult ACS patients will serve as basis during analyses. A detailed analysis plan will be written prior to data base lock.

No statistical comparisons are planned for the primary objective. PK, PD and safety measures will be summarized descriptively using respective analysis set. Palatability measures will also be summarized descriptively for all patients for whom the assessment is performed.

A statistical analysis comparing ticagrelor and placebo will be performed for each of the following variables using the efficacy analysis set for Part B of the study:

- Percentage of days with pain (ages ≥4 years only)
- Percentage of days of opioid analgesic use
- Percentage of days of analgesic use (ages ≥4 years only)
- Percentage of days hospitalized for VOC or other complications of SCD
- Percentage days of absence from school or work (ages ≥6 years only)

A t-test will be performed for each of these variables at 5% significance level, provided that the efficacy analysis set contains at least 30 patients, otherwise only descriptive statistics will be used. The p-value and a 95% confidence interval for the difference between ticagrelor and placebo will be reported. There will be no adjustment for multiple comparisons. If it is inappropriate to assume a normal distribution, a Wilcoxon rank sum test may be performed. In case more than one adult equivalent dose is studied in Part B, the analysis will be repeated both for all ticagrelor doses versus placebo and for the dose the majority of patients received versus placebo.

Number of VOC, number of VOC requiring hospitalization and intensity of pain will be summarized descriptively by treatment group in Part B.

Efficacy variables collected in Part A, i.e. percentage of days with pain, percentage of days of opioid analgesic use, percentage of days of analgesic use, percentage of days of absence from school or work and intensity of pain will be summarized descriptively using the safety analysis set.

Exploratory variables, days with pain and intensity of pain (ages <4 years only), will be presented descriptively using the safety analysis set.

8.6 Interim analysis and potential further dose adjustments

An interim analysis was conducted per protocol after 12 patients had completed dosing in part A. The mean PRU reduction 2 hours post-dose at Visit 4 was <20%, and plasma ticagrelor concentrations were lower than expected. This triggered a protocol amendment to increase the weight-adjusted dosing in order to achieve a higher level of platelet inhibition.

Doses may be further adjusted following assessment by AstraZeneca and the Steering Committee of Part A results in the first 6-12 patients randomised under this amendment. Dose adjustment decisions will be based upon a review of PK, PD and adverse events and will apply only to patients randomised subsequent to the dose change decision.

For more details on potential dose adjustment see Appendix E.

9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA

9.1 Training of study site personnel

Before the first patient is entered into the study, AstraZeneca or its representatives will review and discuss the requirements of the CSP and related documents with the investigational staff and also train them in any study specific procedures and the WBDC 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).

Site training will be recorded on the site-training log.

9.2 Monitoring of the study

During the study, AstraZeneca or its representatives 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 subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent/assent 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 /destroyed accordingly, and the action is documented, and reported to the patient

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

9.2.1 Source data

Please see the 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 CSP and the CSA, the terms of CSP shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the CSA shall prevail.

Agreements between AstraZeneca or [redacted] 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 subject undergoing the study'.

The study is expected to start in Q3 2014 and to end by Q1 2017.

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, or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with ticagrelor.

9.4 Data management by AstraZeneca or delegate

Data management will be performed by [redacted].

The data collected through third party sources will be obtained and reconciled against study data.

AE 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 AstraZeneca Drug Dictionary. All coding will be performed by [redacted]

Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trail.

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

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

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 biological samples will be transferred from laboratory(ies) internal or external to AstraZeneca.

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 AstraZeneca policy on Bioethics and Human Biological Samples.

10.2 Subject data protection

The Informed Consent Form (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(s) of the assent/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 AstraZeneca 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.

AstraZeneca should approve any modifications to the assent/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 national regulatory authority approves the final study protocol, including the final version of the assent/ICF, or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca or its representatives will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca or its representatives 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. AstraZeneca or its representatives will provide this information to the PI so that he/she can meet these reporting requirements.

10.4 Informed consent

The PI (s) at each centre will:

- Ensure each patient, parent or legal guardian is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study (before any study procedures are performed) as per local requirements. The assent/ICF form needs to be adjusted as per local requirements
- Ensure each patient, parent or legal guardian is notified that they are free to discontinue from the study at any time
- Ensure that each patient, parent or legal guardian is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each patient, parent or legal guardian provides signed and dated assent/informed consent before conducting any procedure specifically for the study. Local regulations are to be followed in determining the assent/consent requirements for children of different age groups
- Ensure the original, signed assent/ICF(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed assent/ICF is given to the patient, parent or legal guardian
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the informed consent form that is approved by an 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 AstraZeneca.

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

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

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each PIs. For distribution to EC see Section 10.3.

If a protocol amendment requires a change to a centre's ICF, AstraZeneca and the centre's EC 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 Ethics Committee.

10.6 Audits and inspections

Authorised representatives of AstraZeneca, 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 AstraZeneca immediately if contacted by a regulatory agency about an inspection at the centre.

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Clinical Study Protocol Appendix B	
Drug Substance	Ticagrelor
Study Code	D5136C00007
Edition Number	1
Date	5 March, 2014

Appendix B
Additional Safety Information

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

Life threatening

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

Hospitalisation

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

Important medical event or medical intervention

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

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse.

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?
- Dechallenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.
- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

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

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

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

- Is this a recognised feature of overdose of the drug?
- Is there a known mechanism?

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Clinical Study Protocol Appendix C	
Drug Substance	Ticagrelor
Study Code	D5136C00007
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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.

AstraZeneca

Clinical Study Protocol Appendix D	
Drug Substance	Ticagrelor
Study Code	D5136C00007
Edition Number	1
Date	5 March, 2014

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

TABLE OF CONTENTS PAGE

1. INTRODUCTION

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

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

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

2. DEFINITIONS

Potential Hy's Law (PHL)

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

Hy's Law (HL)

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

3. IDENTIFICATION OF POTENTIAL HY'S LAW CASES

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

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

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

- Notify the AstraZeneca representative
- 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 CRF

4. FOLLOW-UP

4.1 Potential Hy's Law Criteria not met

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

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

4.2 Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

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

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

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

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

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

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

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

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

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF
- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the AZ standard processes

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

- Report an SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

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

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review

6. REFERENCES

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

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

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Clinical Study Protocol Appendix E

Drug Substance	Ticagrelor
Study Code	D5136C00007
Edition Number	3
Date	22 December, 2015

Appendix E
PK/PD monitoring dose adjustments

An interim analysis was conducted per protocol after 12 patients had completed dosing in part A. The mean PRU reduction 2 hours post-dose at Visit 4 was <20%, and plasma ticagrelor concentrations were lower than expected. This triggered a protocol amendment to increase the weight-adjusted dosing in order to achieve a higher level of platelet inhibition.

Doses may be further adjusted following assessment by AstraZeneca and the Steering Committee of results in the first 6-12 patients randomised under this amendment. Dose adjustment decisions will be based upon a review of PK, PD and adverse events and will apply only to patients randomised subsequent to the dose change decision.

Alternative Dosing Schedule 1:

The dose for Visit 2, Part A and Part B may be reduced from 0.75 mg/kg to 0.563 mg/kg and the highest dose administered on Visit 3 may be reduced from 2.25 mg/kg to 1.69 mg/kg.

Refer to Figure 1: Alternative dosing schedule 1, reduced doses in Appendix E

Alternative Dosing Schedule 2:

If two or more patients exceed the paediatric exposure limit (Cmax 2000 ng/mL) after receiving 2.25 mg/kg as single dose on visit 3, this dose will be reduced from 2.25 mg/kg to 1.69 mg/kg.

Refer to Figure 2: Alternative dosing schedule 2, reduced top dose in Appendix E

Alternative Dosing Schedule 3:

The dose at visit 2 and during repeated dosing in Part A and Part B may be increased from 0.75 mg/kg to 1.125 mg/kg, and the single doses at visit 3 may be increased to 1.69 mg/kg and 2.25 mg/kg

Refer to Figure 3: Alternative dosing schedule 3, increased doses in Appendix E

Table 1 Adult equivalents of doses in the alternative dosing schedules

Weight-based Dose (mg/kg)	Adult equivalent dose (mg)
0.375	30
0.563	45
0.75	60
1.125	90
1.69	135
2.25	180

Figure 1 in this Appendix will replace Figure 2 in the main body of the Clinical Study Protocol if the **doses are reduced**, see Section 4.2

Figure 1 Alternative dosing schedule 1, reduced doses

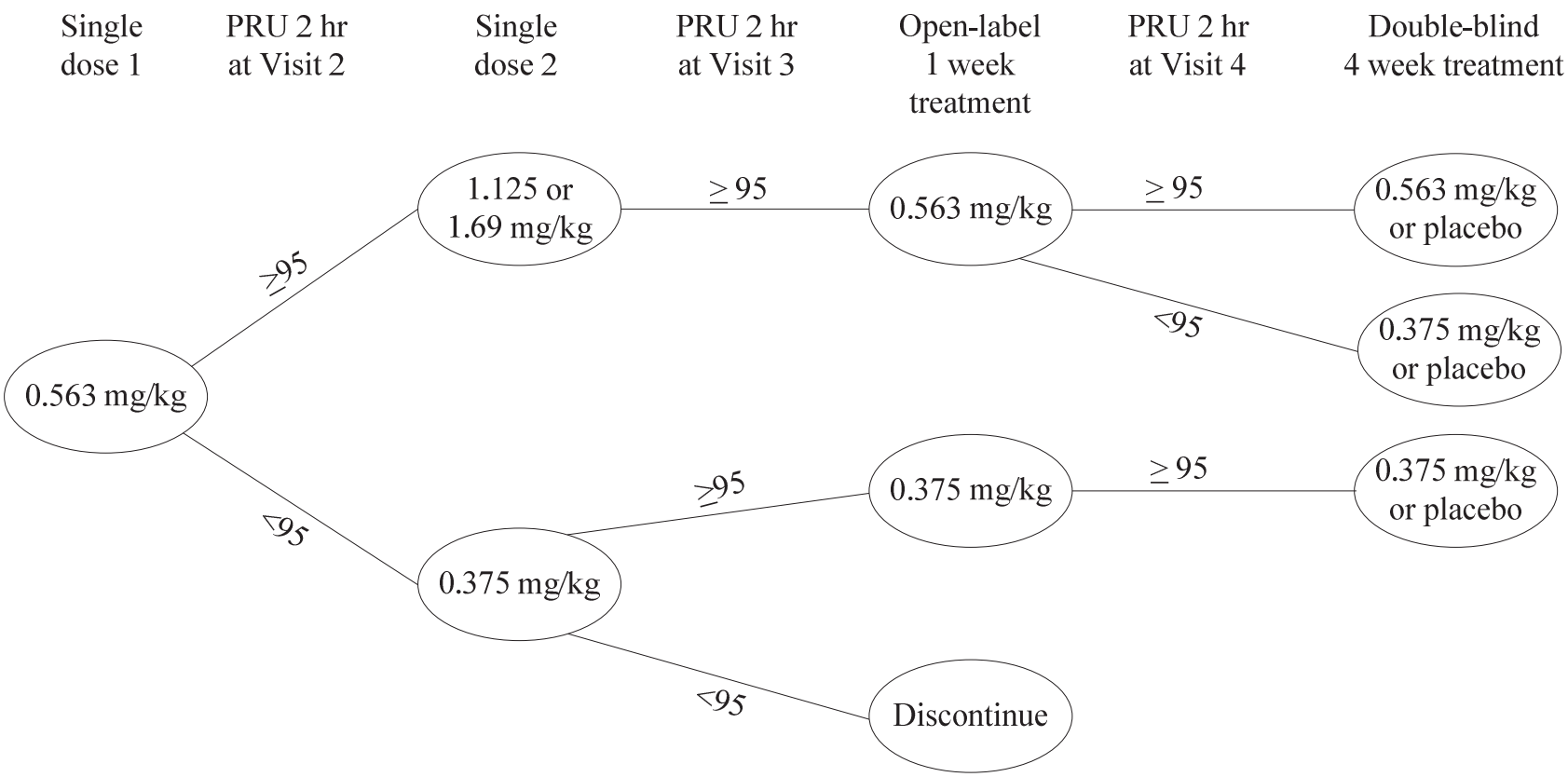


Figure 2 in this Appendix will replace Figure 2 in the main body of the Clinical Study Protocol if the **top dose is reduced**, see Section 4.2.

Figure 2 Alternative dosing schedule 2, reduced top dose:

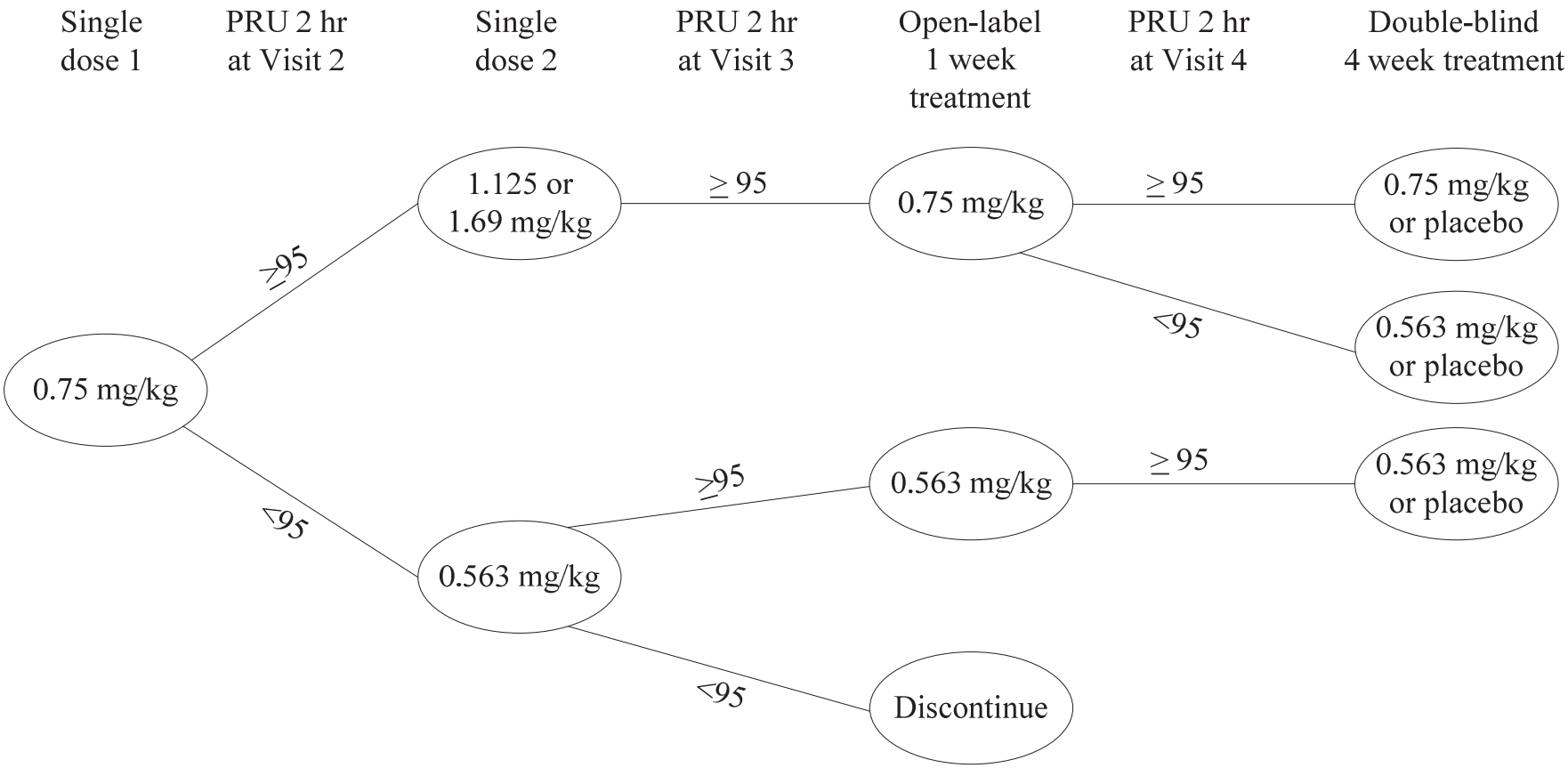
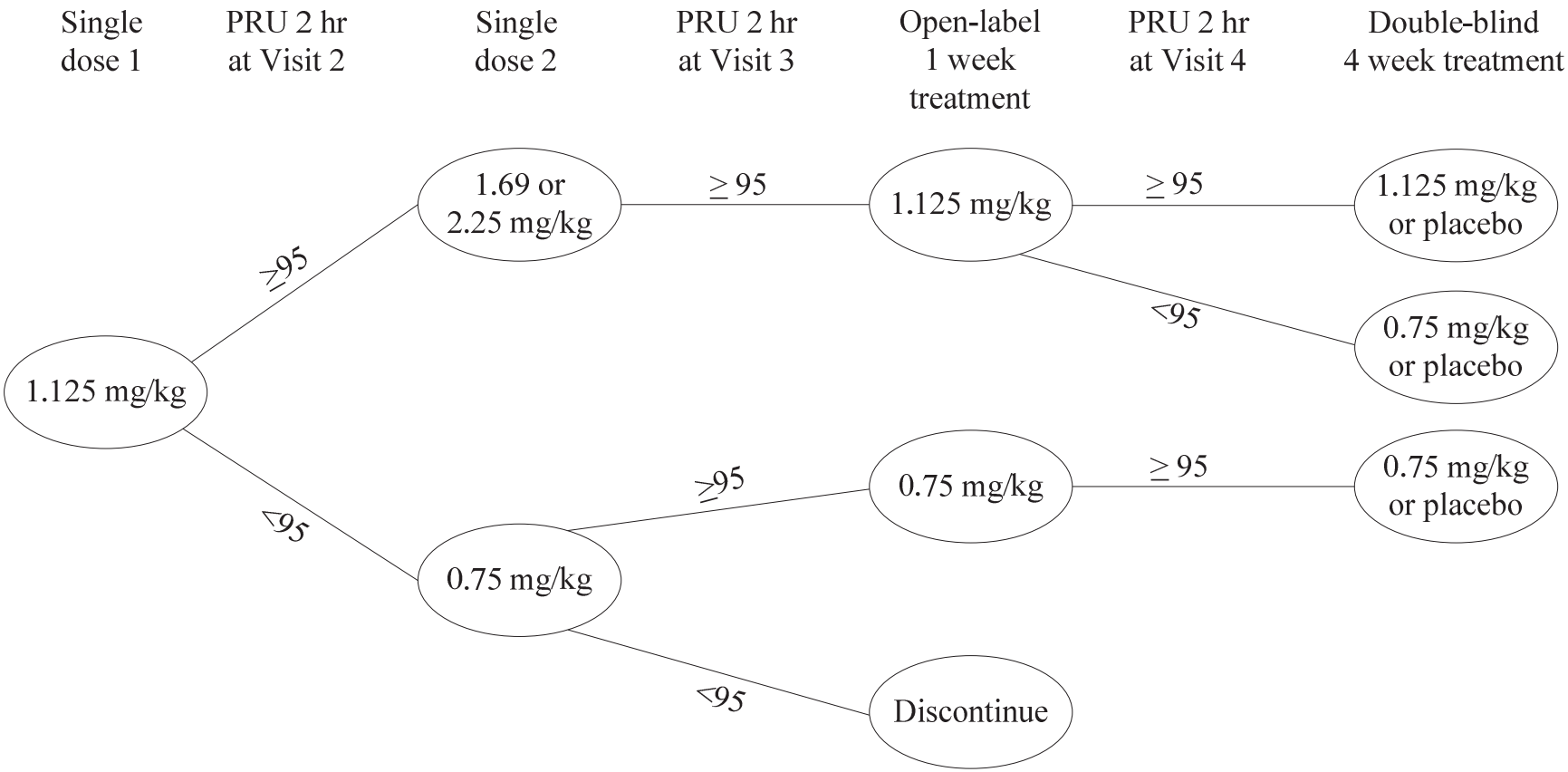


Figure 3 in this Appendix will replace Figure 2 in the main body of the Clinical Study Protocol if the **doses are increased**, see Section 4.2.

Figure 3 Alternative dosing schedule 3, increased doses:



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Clinical Study Protocol Appendix F

Drug Substance	Ticagrelor
Study Code	D5136C00007
Edition Number	3
Date	22 December, 2015

Appendix F
Dose tables with predefined weight brackets

Before each dosing occasion the granules will be constituted with a 10 mL volume of purified water to form a homogenous suspension suitable for oral dosing. Dosing will be weight based and a suitable volume of suspension should be withdrawn from the bottle using a syringe suitable for oral dosing. The dose volume to be given to the patient is defined in Table 1-6. The dose tables are based on predefined weight brackets in order to ensure dose accuracy (only whole mL to be given, except for the 0.375 mg/kg dose) and that the correct treatment dose strength is given to patient. All patients will receive a handling instruction together with study drug at each visit starting at Visit 3. The investigator will enter the individual volume to be given in the handling instruction before the patient leaves the clinic. For more information, please see Section 7.2 in the Clinical Study Protocol.

Table 1 0.375 mg/kg

Weight (kg)	Bottle strength (mg)	Dose volume (mL)	Actual dose (mg) *
16-27	45	1.3	6
28-41	45	3	13.5
42-55	45	4	18
56-69	45	5	22.5
≥70	45	7	31.5

Table 2 0.563 mg/kg

Weight (kg)	Bottle strength (mg)	Dose volume (mL)	Actual dose (mg) *
16-27	45	2	9
28-41	45	4	18
42-55	45	6	27
56-69	45	8	36
≥70	45	10	45

Table 3 0.75 mg/kg

Weight (kg)	Bottle strength (mg)	Dose volume (mL)	Actual dose (mg) *
16-27	45	3	13.5
28-41	45	6	27
42-55	45	8	36
56-69	45	10	45
≥70	45	13	58.5

Table 4 1.125 mg/kg

Weight (kg)	Bottle strength (mg)	Dose volume (mL)	Actual dose (mg) *
16-27	45	4	18
28-41	45	9	40.5
42-55	45	12	54
56-69	45	16	72
≥70	45	20	90**

Table 5 1.69 mg/kg

Weight (kg)	Bottle strength (mg)	Dose volume (mL)	Actual dose (mg) *
16-27	45	6	27
28-41	45	13	58.5
42-55	45	18	81
56-69	45	23	103.5
≥70	45	30	135

Table 6 2.25 mg/kg

Weight (kg)	Bottle strength (mg)	Dose volume (mL)	Actual dose (mg) *
16-27	45	8	36
28-41	45	17	76.5
42-55	45	24	108
56-69	45	31	139.5
≥70	45	40	180**

* Actual doses were calculated using the mean weight in the weight bands ((Upper weight-Lower weight)/2+Lower weight) except for the highest and lowest weight bands, where 80kg and the 16kg was used respectively.
** The highest dose in this study is 180 mg for single doses, and 90 mg for repeated doses.

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Clinical Study Protocol Appendix G

Drug Substance	Ticagrelor
Study Code	D5136C00007
Edition Number	2
Date	5 March, 2014

Appendix G
Patient Reported Outcomes

Study Medication Palatability Assessment
Observer Assessment for Patients Under 6 Years of Age

Instructions to Study Staff

Immediately after administration of Brilinta at Visit 2, capture the patients' reaction of the taste of the medication. Use this CRF for all patients taking the study drug who are under 6 years of age.

1. Choose the response that best matches a description of what you observe of the patients' willingness to swallow the study medication.

Willingness to Swallow

☐ Swallowed without problem

☐ Some resistance but did swallow

☐ Spit out some / all of medication

☐ Vomited up medication

2. Was any behavior observed when the study medication was given to this patient that would be indicative of a negative response to the palatability of the study medication?

☐ YES ☐ NO

If answered YES, please answer the following questions:

2a. Did the patient turn their head to reject intake of the medication?

☐ YES ☐ NO

2b. Did the patient twist their face or mouth in an expression of displeasure?

☐ YES ☐ NO

2c. Did the patient display any other negative behavior?

☐ YES ☐ NO

If YES, please describe: _____

_____

Patient ID: _____

Assessment Date: _____

Assessment Time: _____

Initials of person administering the assessment: _____

Study Medication Palatability Assessment

Instructions to Study Staff

Immediately after administration of Brilinta on visit 2, capture the patients' assessment of the taste of the medication. Use this question for all patients taking the study drug who are 6 years of age or older.

Read to patient

I have a question about the medication you have just taken. I would like you to tell me how you feel about the taste of the medicine you have just swallowed. You can give your answer by making a mark ("X") on the box below the faces to show how much you like or dislike the taste of the medicine. You can choose from 'Dislike very much' to Like very much' [**If child cannot read, point at one face at a time and read the descriptive text below**].

☐	☐	☐	☐	☐
Dislike very much	Dislike a little	Not sure	Like a little	Like very much

Patient ID: _____

Assessment Date: _____

Assessment Time: _____

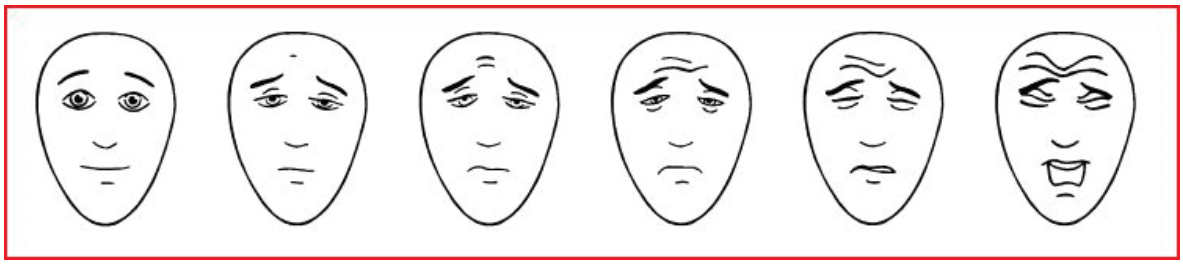
Initials of person administering the assessment: _____

Faces Pain Scale - Revised

NB - this will be administered via an electronic device

Instructions

These faces show how much something can hurt. The face to the left shows no pain. The faces show more and more pain up to the right face - it shows very much pain. Please choose the face that shows how much pain you have had today.



☐ 0 ☐ 2 ☐ 4 ☐ 6 ☐ 8 ☐ 10

Patient ID:_____

Assessment Date: _____

Assessment Time:_____

Initials of person administering the assessment:_____

SICKLE CELL PAIN DIARY (children aged 2-3)

<u>Instruction for Caregiver (e.g. parent) on completion</u>

_____ (child's name) is taking part in a study of children with sickle cell disease. The study is collecting information about pain, so that we can learn how to help children with sickle cell disease feel better. Please complete the sickle pain diary ***every evening*** *from _____ (date) until your next clinic visit _____ (date).*

1. ***Enter assessment date for each day of assessment.***

2. ***Answer the question:*** **<u>Has your child had any sickle cell pain during the last 24 hours?</u>**
   If your child has had any sickle cell pain during the last 24 hours, please describe how your child behaved while under your care due to the pain. For each category (face, legs, activity, crying, and consolability), please mark an X in the one box that best describes your answer.

Please remember the ***same caregiver*** *(e.g. parent) is to complete the diary every evening.*

Please contact Your Study Doctor or Study Nurse if you have doubts how to complete diary.

Please remember to return the completed sickle cell pain diary on the next visit to the clinical site.

SICKLE CELL PAIN Diary – patients ages 2 through <4

Patient ID/E-code : _____ Assessment Date : _____

Instructions

Please answer this question every night when participating in the study.

Has your child had any sickle cell pain during the last 24 hours?

☐ **No** ☐ **Yes**

If Yes, please continue to the next page

English for USA

Please describe how your child behaved because of the pain. For each category (face, legs, activity, cry and consolability), please mark an X in the box that best describes your answer.

FACE	No particular expression or smile ☐ 0	Occasional grimace or frown, withdrawn, disinterested ☐ 1	Frequent to constant frown, clenched jaw, quivering chin ☐ 2
LEGS	Normal position or relaxed ☐ 0	Uneasy, restless, tense ☐ 1	Kicking, or legs drawn up ☐ 2
ACTIVITY	Lying quietly, normal position, moves easily ☐ 0	Squirming, shifting back and forth, tense ☐ 1	Arched, rigid, or jerking ☐ 2
CRY	No cry (awake or asleep) ☐ 0	Moans or whimpers, occasional complaint ☐ 1	Crying steadily, screams or sobs, frequent complaints ☐ 2
CONSOLABILITY	Content, relaxed ☐ 0	Reassured by occasional touching, hugging, or being talked to, distractable ☐ 1	Difficult to console or comfort ☐ 2

English for USA

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Clinical Study Protocol Appendix H

Drug Substance	Ticagrelor
Study Code	D5136C00007
Edition Number	2
Date	05 March 2015

Appendix H
Child-Pugh Classification

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) or Prothrombin time (INR)	< 4 < 1.7	4 - 6 1.7 - 2.3	> 6 > 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.

Clinical Study Protocol Amendment	
Amendment Number	1
Drug Substance	Ticagrelor
Study Code	D5136C00007
Date	23 April 2014
Protocol Dated	05 Mars 2014

Multicenter, open-label, randomised, pharmacokinetic (PK) and pharmacodynamic (PD) dose-ranging Phase II study of ticagrelor followed by a double-blind, randomised, parallel-group, placebo-controlled 4 weeks extension phase in paediatric patients with sickle cell disease

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden.

Centres affected by the Amendment:

This amendment affects all centres in the study.

The protocol for the study is to be amended as follows:

Section of protocol affected:

Synopsis, 3.1 Inclusion criteria, 3.2 Exclusion criteria

Previous text:

Inclusion criterion 2. Experienced at least one vaso-occlusive crisis requiring medical intervention during the past 12 months

Exclusion criterion 1. Previous history of transient ischemic attack (TIA) or cerebrovascular accident (CVA) (ischemic or haemorrhagic), severe head trauma, intracranial haemorrhage, intracranial neoplasm, arteriovenous malformation, aneurysm, or proliferative retinopathy

Exclusion criterion 12. **Males and** females (if after menarche) who are not willing to use a medically accepted method of contraception that is considered reliable in the judgement of the investigator during the study

Revised text:

Inclusion criterion 2. Experienced at least **2** vaso-occlusive crisis requiring medical intervention during the past 12 months

Exclusion criterion 1. Previous history of transient ischemic attack (TIA) or **clinically overt** cerebrovascular accident (CVA) (ischemic or haemorrhagic), severe head trauma, intracranial haemorrhage, intracranial neoplasm, arteriovenous malformation, aneurysm, or proliferative retinopathy

Exclusion criterion 12. Females (if after menarche) who are not willing to use a medically accepted method of contraception that is considered reliable in the judgement of the investigator during the study

Section of protocol affected:

Synopsis, 1.2.3 Primary and secondary outcome measures, 2.2 Secondary Objective, 4. Study plan and timing of procedures, 4.2 Treatment period, 5.1.2 Pain

Previous text:

Secondary Objective:	**Outcome Measure:**
To determine the PK properties of ticagrelor in paediatric patients with SCD and to assess impact of weight, age and other demographic on the ticagrelor pharmacokinetics	Ticagrelor concentrations. Population PK parameters (Oral Clearance (CL/F) and AUC)
Investigation of efficacy of ticagrelor vs. placebo in paediatric patients with SCD in reducing:	Number of VOC Number of VOC requiring hospitalization or emergency department visits Days hospitalized for VOC or other complications of SCD Days with pain Intensity of pain Days of analgesic use Days of opioid analgesic use Days of absence from school or work (ages ≥6 years only

5.1.2 Pain

The Faces Pain Scale – Revised (FSP-R) was validated by Hicks et al 2001 in 3 studies and has been judged as a well-established pain assessment tool in patients 4 to 16 years of age (Cohen et al 2008). Due to the limited number of participants the FPS-R will be used for all patients in the study.

Revised text:

Secondary Objective:	**Outcome Measure:**
To determine the PK properties of ticagrelor in paediatric patients with SCD and to assess impact of weight, age and other demographic on the ticagrelor pharmacokinetics	Ticagrelor concentrations. Population PK parameters (Oral Clearance (CL/F) and AUC)
Investigation of efficacy of ticagrelor vs. placebo in paediatric patients with SCD in reducing:	Number of VOC Number of VOC requiring hospitalization or emergency department visits Days hospitalized for VOC or other complications of SCD Days with pain **(ages ≥4 years only)** Intensity of pain **(ages ≥4 years only)** Days of analgesic use Days of opioid analgesic use Days of absence from school or work (ages ≥6 years only**)**

5.1.2 Pain

The Faces Pain Scale - Revised (FSP-R) was validated by Hicks et al 2001 in 3 studies and has been judged as a well-established pain assessment tool in patients 4 to 16 years of age (Cohen et al 2008) and will be administered to all patients in this study age ≥4 years.

Section of protocol affected:

3.9.2 Permanent discontinuation from investigational product (active and placebo),
3.11 Discontinuation of the study, 6.3.3 Variables

Previous text:

3.9.2 Permanent discontinuation from investigational product (active and placebo)

- The patient (or parent/caregiver/legal guardian) is at any time free to discontinue treatment or advise the patient to discontinue treatment, without prejudice to further treatment
- Risk to patients as judged by the investigator
- If PRU is <95 on any two dosing occasions following dosing of 0.0625 mg/kg, the patient will be discontinued from further study drug for safety reasons
- AE judged by the investigator to be related to the investigational product, for which he/she feels continued participation would put the patient at undue risk. Examples of this could be:
  - Major bleeding requiring medical intervention

  - Resting heart rate <40 bpm or any symptomatic bradycardia lasting for more than 60 seconds
  - Ventricular pauses longer than 3 seconds occurring more than twice during a 60 second period
  - Atrioventricular block II/III suspected to be caused by ticagrelor
  - Development of a bundle branch block
- Abnormal transcranial Doppler indicating need for transfusion therapy
- Development of proliferative retinopathy
- Inability to manage pain without chronic NSAIDs
- Severe non-compliance to study protocol
- Pregnancy

3.11 Discontinuation of the study

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

- Major bleeding that is drug-related
- If any of the heart rate/ECG criteria below are fulfilled in >2 patients and judged to be related to the investigational product (active)
  - Resting heart rate <40 bpm or any symptomatic bradycardia lasting for more than 60 seconds
  - Ventricular pauses longer than 3 seconds occurring more than twice during a 60 second period
  - Atrioventricular block II/III suspected to be caused by ticagrelor
  - Development of bundle branch block

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 (time to be collected only at Visit 2-end of Visit 3)
- Maximum intensity
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product (yes or no)
- Action taken with regard to investigational product

- **Any prescription or non prescription drug therapy started as result of the AE**
- AE caused subject's withdrawal from study (yes or no)
- Outcome

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

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

Revised text:

3.9.2 Permanent discontinuation from investigational product (active and placebo)

- The patient (or parent/caregiver/legal guardian) is at any time free to discontinue treatment or advise the patient to discontinue treatment, without prejudice to further treatment
- **Any major bleeding**
- Risk to patients as judged by the investigator
- If PRU is <95 on any two dosing occasions following dosing of 0.0625 mg/kg, the patient will be discontinued from further study drug for safety reasons

- AE judged by the investigator to be related to the investigational product, for which he/she feels continued participation would put the patient at undue risk. Examples of this could be:
  - Resting heart rate <40 bpm or any symptomatic bradycardia lasting for more than 60 seconds
  - Ventricular pauses longer than 3 seconds occurring more than twice during a 60 second period
  - Atrioventricular block II/III suspected to be caused by ticagrelor
  - Development of a bundle branch block
- Abnormal transcranial Doppler indicating need for transfusion therapy
- Development of proliferative retinopathy
- Inability to manage pain without chronic NSAIDs
- Severe non-compliance to study protocol
- Pregnancy

3.11 Discontinuation of the study

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

- **Major bleeding that is drug-related in > 1 patient**
- If any of the heart rate/ECG criteria below are fulfilled in >2 patients and judged to be related to the investigational product (active)
  - Resting heart rate <40 bpm or any symptomatic bradycardia lasting for more than 60 seconds
  - Ventricular pauses longer than 3 seconds occurring more than twice during a 60 second period
  - Atrioventricular block II/III suspected to be caused by ticagrelor
- Development of bundle branch block

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 (time to be collected only at Visit 2-end of Visit 3)
- Maximum intensity
- Whether the AE is serious or not

- Investigator causality rating against the Investigational Product (yes or no)
- Action taken with regard to investigational product
- AE caused subject's withdrawal from study (yes or no)
- Outcome

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

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

The definitions for intensity rating are:

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

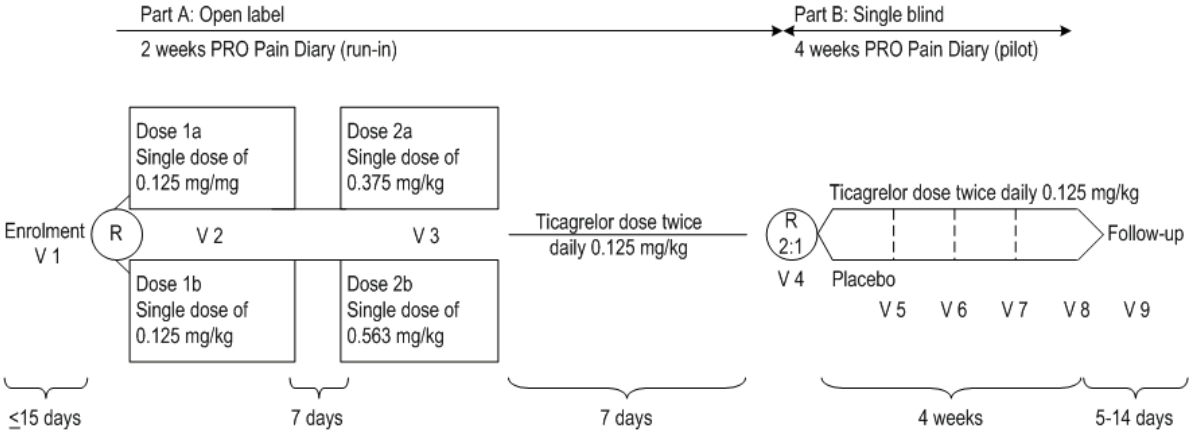
Section of protocol affected:

Title of the CSP, Synopsis, 1.2.2 Study design, 1.4 Study design, 3.3 Patient enrolment and randomisation, 3.6 Methods for ensuring blinding, 3.7 Methods for unblinding, 4.2 Treatment period, Figure 2, 6.8.1 Steering Committee, All figures in Appendix E

Previous text:

Multicenter, open-label, randomised, pharmacokinetic (PK) and pharmacodynamic (PD) dose-ranging Phase II study of ticagrelor followed by a single-blind, randomised, parallel-group, placebo-controlled 4 weeks extension phase in paediatric patients with sickle cell disease

Figure 1 Study flow chart before interim analysis



3.3 Patient enrolment and randomisation

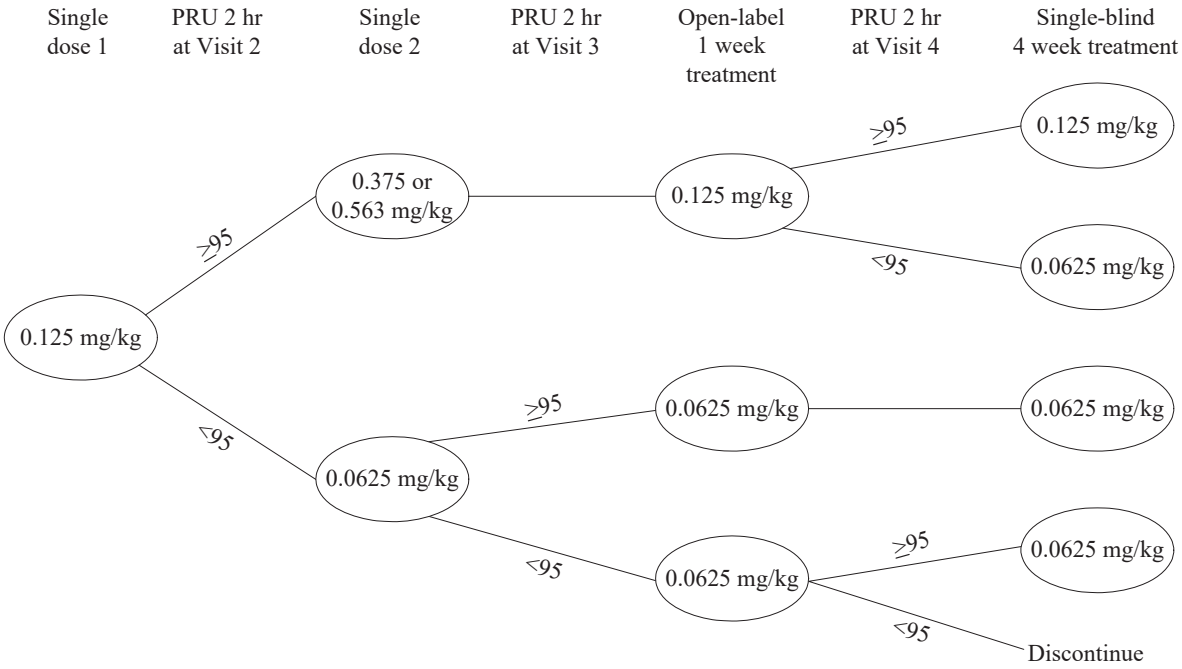
Part B will be single blind i.e. only the patient will be unaware of study therapy.

3.6 Methods for ensuring blinding

All packaging and labelling will be created in such a way as to ensure blinding for the patient in Part B.

3.7 Methods for unblinding (Not Applicable)

Figure 2 Dosing schedule before interim analysis



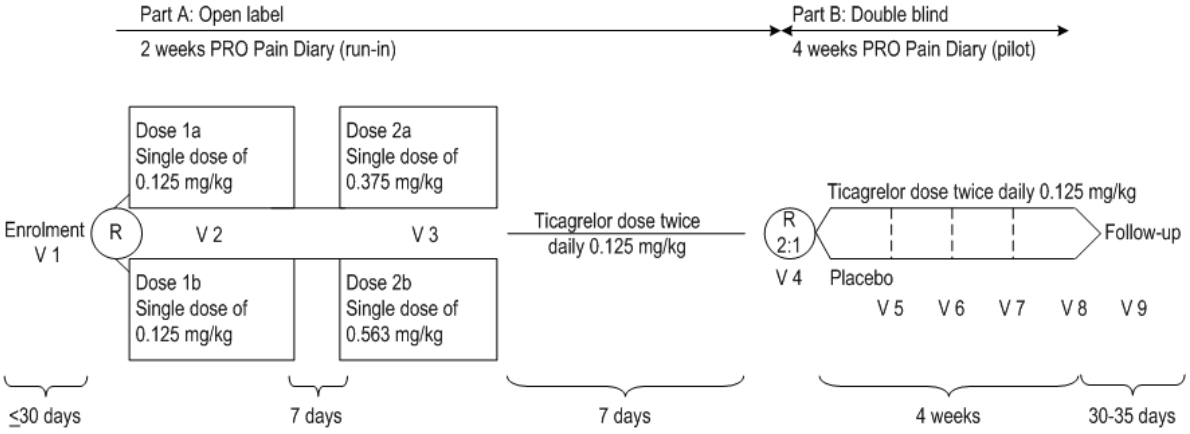
6.8.1 Steering committee

The SC will make recommendations to AstraZeneca with regard to early stopping or modifications of the study based on accumulated study data. The SC will be comprised of 2-3 investigators in the study and non-voting members of the Sponsor, and will operate under a separate charter.

Revised text:

Multicenter, open-label, randomised, pharmacokinetic (PK) and pharmacodynamic (PD) dose-ranging Phase II study of ticagrelor followed by a **double-blind**, randomised, parallel-group, placebo-controlled 4 weeks extension phase in paediatric patients with sickle cell disease

Figure 1 Study flow chart before interim analysis



3.3 Patient enrolment and randomisation

Part B will be double blind i.e. no member of the study team at AstraZeneca, the Steering Committee, personnel at investigational centres or any CRO handling data will have access to the randomisation scheme during the conduct of the study, with the exception of the Supply Chain Study Management department, CRO unblinded team and the Patient Safety department at AstraZeneca.

3.6 Methods for ensuring blinding

The treatment allocation in part B will be double blind. Ticagrelor and matching ticagrelor placebo granules will be provided (see Section 7), identical in appearance and packaging. Each kit will be labelled with a unique kit ID number that will be used to assign the treatment to the patient but will not indicate treatment allocation to the investigator.

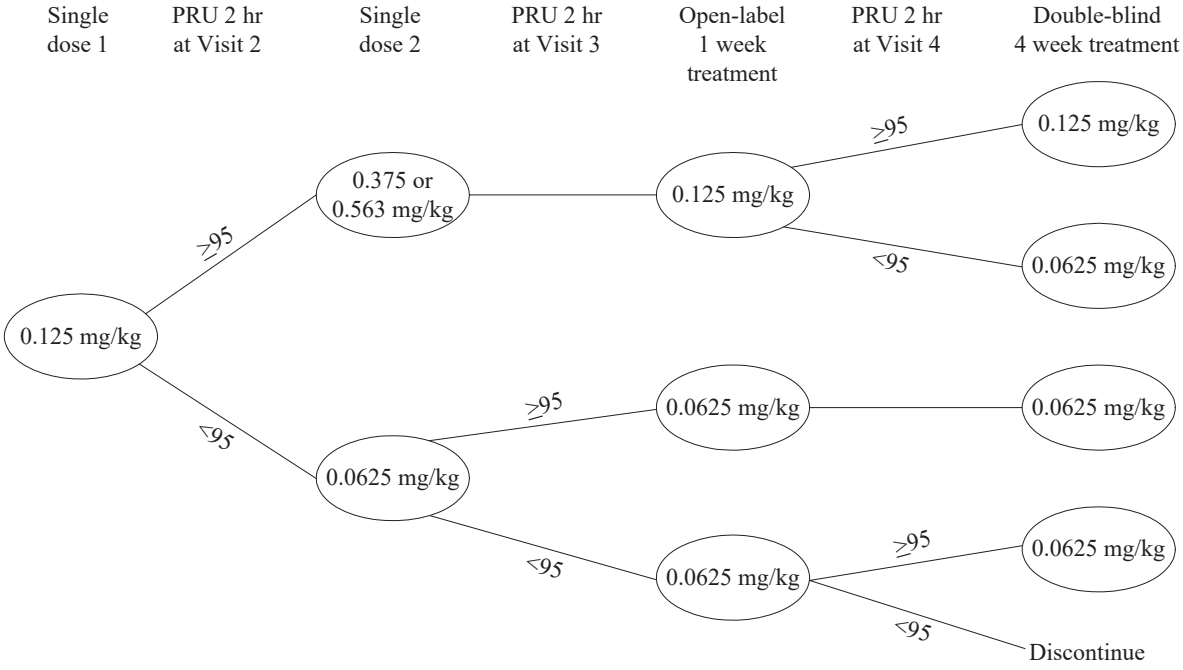
3.7 Methods for unblinding

Individual treatment codes, indicating the treatment randomisation for each randomised patient in part B, will be available to the Investigator(s) or pharmacists from the call center.

The treatment code should not be broken except in medical emergencies when the appropriate management of the subject requires knowledge of the treatment randomisation. The Investigator documents and reports the action to AstraZeneca, without revealing the treatment given to subject to the AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational product 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 subject have been made and documented.

Figure 2 Dosing schedule before interim analysis



6.8.1 Steering committee

The SC will make recommendations to AstraZeneca with regard to early stopping or modifications of the study based on accumulated study data **(data from the double blind phase will be reviewed without unblinding)**. The SC will be comprised of 2-3 investigators in the study and non-voting members of the Sponsor, and will operate under a separate charter.

Section of protocol affected:

Synopsis, 4 Study plan and timing of procedures, 5.8 Volume of blood, 7.2 Dose and treatment regimens, 7.5 Compliance

Previous text:

Duration of treatment

The total expected study duration for an individual patient is approximately 2 months.

Table 1 Study Plan detailing the procedures

	Part A			Part B					
Assessment	**Enrolment**	**Dose 1**	**Dose 2**	**Repeated treatment phase**				**End of treatment**	**Follow-up**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Visit window:	Days -15 to 0 for Visit 1	±0 day for Visit 2	+ 7 days	+7 days	+ 7 days	+ 7 days	+ 7 days	+ 7 days	5-14 days following last dose for Visit 8[d]
Week	**-2**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	
Day	**-15**	**0**	**7**	**14**	**21**	**28**	**35**	**42**	**47-56**
Signed Informed Assent/Consent	X								
Randomisation		X		X					
Inclusion/exclusion criteria	X	X[a]							
Relevant Medical and Surgical history, SCD characteristics and history	X								
Demographics	X								
Vital signs (BP, pulse)	X	X	X	X	X	X	X	X	X
Physical examination	X								X
Weight, height[e]	X	X	X					X	
12-lead ECG (within past 6 months)	X								
12-lead ECG				X					
Daily pain assessment[g]	X	X	X	X	X	X	X	X	
Daily recording of analgesic use[g]	X	X	X	X	X	X	X	X	
Days absent from school/work[g]	X	X	X	X	X	X	X	X	
Administration of IP at clinic[i]		X	X	X				X	
Treatment dispensed/returned			X	X[j]	X	X	X	X[j]	
Compliance/ Drug accountability		X	X	X	X	X	X	X	
Acceptability/Palatability[h]		X							
Concomitant medication	X	X	X	X	X	X	X	X	X
Adverse event review (AEs and SAEs)	X[f]	X	X	X	X	X	X	X	X
Blood samples for haematology and clinical chemistry (incl uric acid)	X							X	
Blood samples for coagulation (INR and PTT)	X								
VerifyNow™ PRU[c]		X	X	X				X	

Table 1 Study Plan detailing the procedures

	Part A			Part B					
Assessment	**Enrolment**	**Dose 1**	**Dose 2**	**Repeated treatment phase**				**End of treatment**	**Follow-up**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Visit window:	Days -15 to 0 for Visit 1	±0 day for Visit 2	+ 7 days	+7 days	+ 7 days	+ 7 days	+ 7 days	+ 7 days	5-14 days following last dose for Visit 8[d]
Week	**-2**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	
Day	**-15**	**0**	**7**	**14**	**21**	**28**	**35**	**42**	**47-56**
Pregnancy test (dipstick)[b]	X		X					X	
Collection of VOC in CRF		X	X	X	X	X	X	X	X
Collection of transfusion data in CRF		X	X	X	X	X	X	X	X
Collection of bleeding events in CRF		X	X	X	X	X	X	X	X
Urinalysis	X							X	
Blood sampling for pharmacokinetics[c]		X	X	X				X	

a Results from local laboratory must have been received before first dose to check eligibility criteria.
b In patient after menarche.
c Actual time of PK and PRU sampling should be recorded in the eCRF.
d May occur following earlier visits than Visit 9.
e Height only at enrolment.
f Only SAE assessed at this time.
g Electronic diary recording by patient (when needed with parent/guardian help)
h Questions assessed by nurse in children <6 years, Hedonic Faces Scale (HFS) for children ≥6 years
i Actual time of dosing should be recorded in the eCRF.
j The time of drug administration the morning and evening before Visit 4 and 8 will be registered in a patient diary.

Table 2 Blood sampling in patients with a weight of >21 kg

Assessment	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
Coagulation (INR and PTT)	X								
Haematology and clinical chemistry (incl uric acid)	X							X	
VerifyNow™ PRU		Pre-dose, 2, 8h	Pre-dose, 2, 8h	2h				Pre-dose, 2h	
Blood sampling for pharmacokinetics		1, 2, 4, 8 h	1, 2, 4, 8 h	2h				Pre-dose, 1, 2, 4h	

The 1, 2, 4, and 8 hour samples can be collected ±15 minutes from actual post-dose time point.
A peripheral catheter can be used for blood sampling.

Table 3 Blood sampling in patients with a weight of 16-21 kg

Assessment	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
Coagulation (INR and PTT)	X								
Haematology and clinical chemistry (incl uric acid)	X							X	
VerifyNow™ PRU		Pre-dose, 2h	Pre-dose, 2h	2h				Pre-dose, 2h	
Blood sampling for pharmacokinetics		1, 2, 4, 8 h	1, 2, 4, 8 h	2h				Pre-dose, 2h	

The 1, 2 and 4 and 8 hour samples can be collected ±15 minutes from actual post-dose time point.
A peripheral catheter can be used for blood sampling.

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. It is planned for a minimum of 36 patients and a maximum of 50 patients to be randomised in the study, in order to ensure 36 evaluable patients completing two single doses in Part A. A patient is considered as evaluable if he/she has completed the study up to and including Visit 3.

A complete medical, surgical and medication history will be recorded for each patient at enrolment. All relevant medical conditions that have occurred within the past or conditions that are ongoing are to be recorded in the eCRF. The medication history must identify any known drug allergies, and use of chronic medications. Safety laboratory samples should be sent to the local laboratory for analysis.

Table 6 Volume of blood to be drawn from patients with a weight >21 kg

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 8	Total volume Visit 8 (mL)	Total (mL)
Haematology	1.2	1	1.2	0	0	0	0	0	0	1	1.2	
Clinical Chemistry	1.1	1	1.1	0	0	0	0	0	0	1	1.1	
Coagulation	1.2	1	1.2	0	0	0	0	0	0	0	0	
Pharmacokinetic	1.2	0	0	4	4.8	4	4.8	1	1.2	4	4.8	
PRU	4.0	0	0	3	12.0	3	12	1	4	2	8	
Total			3.5		16.8		16.8		5.2		15.1	**57.4**

Table 7 Volume of blood to be drawn from patient with a weight of 16-21 kg

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 8	Total volume Visit 8 (mL)	Total (mL)
Haematology	1.2	1	1.2	0	0	0	0	0	0	1	1.2	
Clinical Chemistry	1.1	1	1.1	0	0	0	0	0	0	1	1.1	
Coagulation	1.2	1	1.2	0	0	0	0	0	0	0	0	
Pharmacokinetic	1.2	0	0	4	4.8	4	4.8	1	1.2	2	1.4	
PRU	4.0	0	0	2	8	2	8	1	4	2	8	
Total			3.5		12.8		12.8		5.2		11.7	**46**

Reference Ethical considerations paediatric 2008 in CSP

7.2 Dose and treatment regimens

Repeated dosing (Visit 3-4):

Patients will self administer 0.125 mg/kg of open label ticagrelor for 1 week. Dose to be administered twice daily within a 9-12 hours interval. The first dose will be administered in the morning the day after Visit 3.

7.5 Compliance

In the repeated dosing part, the patient will bring the investigational product (active or placebo) to their home, with instructions for mixing the appropriate weight-based dose.

Revised text:

Duration of treatment

The total expected study duration for an individual patient is approximately **3 months (including 30 days follow-up after last dose)**.

Table 1 Study Plan detailing the procedures

	Part A			Part B					
Assessment	**Enrolment**	**Dose 1**	**Dose 2**	**Repeated treatment phase**				**End of treatment**	**Follow-up**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Visit window:	Days **-30** to 0 for Visit 1	±0 day for Visit 2	+ 7 days	+7 days	+ 7 days	+ 7 days	+ 7 days	+ 7 days	**30-35** days following last dose for Visit 8[d]
Week		**0**	**1**	**2**	**3**	**4**	**5**	**6**	**10**
Day		**0**	**7**	**14**	**21**	**28**	**35**	**42**	**72-77**
Signed Informed Assent/Consent	X								
Randomisation		X		X					
Inclusion/exclusion criteria	X	X[a]							
Relevant Medical and Surgical history, SCD characteristics and history	X								
Demographics	X								
Vital signs (BP, pulse)	X	X	X	X	X	X	X	X	X
Physical examination	X								X
Weight, height[e]	X	X	X					X	
Transcranial Doppler exam (within past 1 year)	**X**								
Ophthalmological (Eye) exam (within past 1 year)	**X**								
12-lead ECG (within past 6 months)	X								
12-lead ECG				X					
Daily pain assessment[g]	X	X	X	X	X	X	X	X	
Daily recording of analgesic use[g]	X	X	X	X	X	X	X	X	
Days absent from school/work[g]	X	X	X	X	X	X	X	X	
Administration of IP at clinic[i]		X	X	X				X	
Treatment dispensed/returned			X	X[j]	X	X	X	X[j]	
Compliance/ Drug accountability		X	X	X	X	X	X	X	
Acceptability/Palatability[h]		X							
Concomitant medication	X	X	X	X	X	X	X	X	X
Adverse event review (AEs and SAEs)	X[f]	X	X	X	X	X	X	X	X
Blood samples for haematology and clinical chemistry (incl uric acid)	X			**X**				X	

Table 1 Study Plan detailing the procedures

	Part A			Part B					
Assessment	**Enrolment**	**Dose 1**	**Dose 2**	**Repeated treatment phase**				**End of treatment**	**Follow-up**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Visit window:	Days **-30** to 0 for Visit 1	±0 day for Visit 2	+ 7 days	+7 days	+ 7 days	+ 7 days	+ 7 days	+ 7 days	**30-35** days following last dose for Visit 8[d]
Week		**0**	**1**	**2**	**3**	**4**	**5**	**6**	**10**
Day		**0**	**7**	**14**	**21**	**28**	**35**	**42**	**72-77**
Blood samples for coagulation (INR and PTT)	X								
VerifyNow™ PRU[c]		X	X	X				X	
Pregnancy test (dipstick)[b]	X		X					X	
Collection of VOC in CRF		X	X	X	X	X	X	X	X
Collection of transfusion data in CRF		X	X	X	X	X	X	X	X
Collection of bleeding events in CRF		X	X	X	X	X	X	X	X
Urinalysis	X			**X**				X	
Blood sampling for pharmacokinetics[c]		X	X	X				X	

a Results from local laboratory must have been received before first dose to check eligibility criteria.
b In patient after menarche.
c Actual time of PK and PRU sampling should be recorded in the eCRF.
d May occur following earlier visits than Visit 9.
e Height only at enrolment.
f Only SAE assessed at this time.
g Electronic diary recording by patient (when needed with parent/guardian help, **daily pain assessment only for ages ≥4 years)**
h Questions assessed by nurse in children <6 years, Hedonic Faces Scale (HFS) for children ≥6 years
i Actual time of dosing should be recorded in the eCRF.
j The time of drug administration the morning and evening before Visit 4 and 8 will be registered in a patient diary.

During visits when investigational product is administered at clinic perform the following protocol procedures prior to administration of study drug (if applicable to the visit):

Review of AEs and concomitant medications, vital signs weight, ECG, urine sampling (including pregnancy test if applicable), and pre-dose blood sampling (safety, PK, PD)

Table 2 Blood sampling in patients with a weight of >21 kg

Assessment	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
Coagulation (INR and PTT)	X								
Haematology and clinical chemistry (incl uric acid)	X			**Pre-dose**				X	
VerifyNow™ PRU		Pre-dose, 2, 8h	Pre-dose, 2, 8h	2h				Pre-dose, 2h	
Blood sampling for pharmacokinetics		1, 2, 4, 8 h	1, 2, 4, 8 h	2h				Pre-dose, 1, 2, 4h	

The 1, 2, 4, and 8 hour samples can be collected ±15 minutes from actual post-dose time point.
A peripheral catheter can be used for blood sampling.

Table 3 Blood sampling in patients with a weight of 16-21 kg

Assessment	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
Coagulation (INR and PTT)	X								
Haematology and clinical chemistry (incl uric acid)	X			**Pre-dose**				X	
VerifyNow™ PRU		Pre-dose, 2h	Pre-dose, 2h	2h				Pre-dose, 2h	
Blood sampling for pharmacokinetics		1, 2, 4, 8 h	1, 2, 4, 8 h	2h				Pre-dose, 2h	

The 1, 2 and 4 and 8 hour samples can be collected ±15 minutes from actual post-dose time point.
A peripheral catheter can be used for blood sampling.

4.1 Enrolment/screening period

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

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. It is planned for a minimum of 36 patients and a maximum of 50 patients to be randomised in the study, in order to ensure 36 evaluable patients completing two single doses in Part A. A patient is considered as evaluable if he/she has completed the study up to and including Visit 3.

A complete medical, surgical and medication history will be recorded for each patient at enrolment. All relevant medical conditions that have occurred within the past or conditions that are ongoing are to be recorded in the eCRF. The medication history must identify any known drug allergies, and use of chronic medications. Safety laboratory samples should be sent to the local laboratory for analysis.

If the patient is 16 years old or younger, a transcranial Doppler examination (TCD) must have been done within the past 1 year. If this is not the case, a TCD exam needs to be done before proceeding in the study.

If the patient is six years or older, an eye exam must have been done within the past 1 year. If this is not the case, the patient will need to be examined by an ophthalmologist before proceeding in the study.

Table 6 Volume of blood to be drawn from patients with a weight >21 kg

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 8	Total volume Visit 8 (mL)	Total (mL)
Haematology	1.2	1	1.2	0	0	0	0	**1**	**1.2**	1	1.2	
Clinical Chemistry	1.1	1	1.1	0	0	0	0	**1**	**1.1**	1	1.1	
Coagulation	1.2	1	1.2	0	0	0	0	0	0	0	0	
Pharmacokinetic	1.2	0	0	4	4.8	4	4.8	1	1.2	4	4.8	
PRU	4.0	0	0	3	12.0	3	12	1	4	2	8	
Total			3.5		16.8		16.8		**7.5**		15.1	**59.7**

Table 7 Volume of blood to be drawn from patient with a weight of 16-21 kg

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 8	Total volume Visit 8 (mL)	Total (mL)
Haematology	1.2	1	1.2	0	0	0	0	**1**	**1.2**	1	1.2	
Clinical Chemistry	1.1	1	1.1	0	0	0	0	**1**	**1.1**	1	1.1	
Coagulation	1.2	1	1.2	0	0	0	0	0	0	0	0	
Pharmacokinetic	1.2	0	0	4	4.8	4	4.8	1	1.2	2	1.4	
PRU	4.0	0	0	2	8	2	8	1	4	2	8	
Total			3.5		12.8		12.8		**7.5**		11.7	**48.3**

Reference Ethical considerations paediatric 2008 in CSP

7.3 Dose and treatment regimens

Repeated dosing (Visit 3-4):

Patients will self administer 0.125 mg/kg of open label ticagrelor for 1 week. Dose to be administered twice daily within a 9-12 hours interval. **The first dose will be administered in the evening the same day as Visit 3**.

7.5 Compliance

In the repeated dosing part, the patient will bring the investigational product (active or placebo) to their home, with instructions for mixing the appropriate weight-based dose. **The patients will receive a Dosing Diary to record intake of investigational products (active or placebo).**

Reason for Amendment:

The purpose of this amendment is to address changes done in the CSP related to the FDA's identified potential hold issues and non-hold comments for IND 120,366, dated April 11, 2014.

An additional hematology and chemistry assessment has been included in the CSP at Visit 4, i.e., the beginning of Part B. See Table 1, revised version.

The stopping rules in Section 3.11 have been revised as recommended.

The CSP Section 3.9.2 has been amended. Patients will be discontinued from investigational product if any major bleeding should occur, not at the discretion of the investigator.

The time of the study follow-up visit (Visit 9) has been changed, and is 30-35 days after last dose. See Table 1, revised version.

Severity of AEs will be collected by maximum intensity, see Section 6.3.3. The intensity ratings are mild, moderate and severe.

Definitions: 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).

The Faces Pain Scale - Revised (FSP-R) will be administered to patients aged ≥4 years instead of all patients.

The CSP has been amended in Section 3.1, inclusion criterion 2 now reads: "Experienced at least 2 vaso-occlusive crisis requiring medical intervention during the past 12 months"

The study has been amended to a double-blind design.

In addition clarifications on exclusion criterion 1, order of study procedures during study visits and recording of study drug intake in dosing diary have been made.

First dose after each visit in the repeated dosing phase will be administered in the evening to simplify for the patients.

Exclusion criterion 12; Males has been deleted and one variable collected for AE has been deleted due to error in writing.

The time of the study enrolment visit (Visit 1) has been changed, and is ≤30 days before visit 2. See Table 1. Transcranial Doppler exams and ophthalmological exams have now been added as study procedures, for any patients who have not had the exams within the specified time periods, the new maximum time between visit 1 and 2 allows for these exams to be scheduled if needed.

Persons who initiated the Amendment:

FDA and AZ study team.

Clinical Study Protocol Amendment	
Amendment Number	2
Drug Substance	Ticagrelor
Study Code	D5136C00007
Date	05 March 2015
Protocol Dated	05 March 2014

Multicenter, open-label, randomised, pharmacokinetic (PK) and pharmacodynamic (PD) dose-ranging Phase II study of ticagrelor followed by a double-blind, randomised, parallel-group, placebo-controlled 4 weeks extension phase in paediatric patients with sickle cell disease

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden.

Centres affected by the Amendment:

This amendment affects all centres in the study.

The protocol for the study is to be amended as follows:

Section of protocol affected:

3.1 Inclusion criteria, 3.2 Exclusion criteria, 3.8 Restrictions, 3.9.1 Criteria for interruption or discontinuation of investigational product (active and placebo), 6.6.1 Women of childbearing potential

Previous text:

Inclusion criterion 3. If ≤16 years, must have had transcranial Doppler within the past year prior to **enrolment**

Inclusion criterion 4. If ≥6 years old, must have had an ophthalmological examination within the past year prior to **enrolment**

Inclusion criterion 5. If treated with an anti-sickling agent such as hydroxyurea, dose must be stable for 3 months before enrolment.

Exclusion criterion 2. **Abnormal or conditional transcranial Doppler (velocity in middle or anterior cerebral, or internal carotid artery ≥170 centimeter per second) within the past year prior to enrolment**

Exclusion criterion 3. **History of, or are** undergoing treatment with, chronic RBC transfusion therapy

Exclusion criterion 4. **Receiving chronic treatment (>3 days per week) with** non-steroidal anti-inflammatory drugs (NSAIDs)

Exclusion criterion 6. Moderate or severe hepatic impairment, or renal failure requiring dialysis

Exclusion criterion 7. Increased risk of bleeding complications according to investigator

Exclusion criterion 12. Females (if after menarche) who are not willing to use a **medically accepted method of contraception that is considered reliable in the judgment of the investigator during the study**

3.8 Restrictions

Females of child-bearing potential are not allowed to be included in this study unless they use **an approved pregnancy prevention method** and must refrain from becoming pregnant from 1 month following the last dose. There are no restrictions against fathering a child when treated with ticagrelor. For further details, please see Section 6.6.

3.9.1 Criteria for interruption or discontinuation of investigational product (active and placebo)

- **Thrombocytopenia (platelet count <80,000/uL).** Repeat laboratory studies and standard of care (SOC) should be followed until resolution of laboratory abnormality

6.6.1 Maternal exposure

Women of childbearing potential are not allowed to be included in this study unless they use **an approved pregnancy prevention method** and must refrain from becoming pregnant from 1 month following the last dose. Should a pregnancy still occur, the investigational product should be discontinued immediately and the pregnancy reported to designated [redacted] representative within 1 day.

Revised text:

Inclusion criterion 3. If ≤16 years, must have had transcranial Doppler (TCD) within the past year prior to **Visit 1. If this is not the case, a TCD examination must be done before proceeding in the study**.

Inclusion criterion 4. If ≥6 years old, must have had an ophthalmological examination within the past year prior to **Visit 1. If this is not the case, the patient must be examined by an ophthalmologist before proceeding in the study**.

Inclusion criterion 5. If treated with an anti-sickling agent such as hydroxyurea, **the weight-adjusted** dose must be stable for 3 months before enrolment

Exclusion criterion 2. **Findings on TCD: Current or previous values for time averaged mean of the maximum velocity (TAMMV) that are Conditional or Abnormal*. Conditional TAMMV values are ≥153 cm/sec using imaging TCD (TCDi) technique (corresponding to ≥170 cm/sec by the non-imaging technique). Both the middle cerebral artery and the internal carotid artery should be considered. Abnormal TAMMV values are ≥180 cm/sec using TCDi (corresponding to ≥200 cm/sec by the non-imaging technique) and are an indication for chronic transfusions because of a high stroke risk. Any other criteria that would locally be considered as TCD indications for chronic transfusion would also exclude the patient.**
*** According to STOP study thresholds for non-imaging TCD technique (Adams et al.1998) and thresholds for imaging TCD (TCDi) technique as published by Bulas et al. (2005).**

Exclusion criterion 3. **Undergoing** treatment with chronic RBC transfusion therapy

Exclusion criterion 4. **Use of** non-steroidal anti-inflammatory drugs (NSAIDs) **>3 days per week**

Exclusion criterion 6. Moderate or severe hepatic impairment, **defined as Child-Pugh Class B or C (see Appendix H)** or renal failure requiring dialysis

Exclusion criterion 7. **Active pathological bleeding or** increased risk of bleeding complications according to Investigator

Exclusion criterion 12. Females (if after menarche) who are not willing to use a **highly effective method of contraception which results in a low failure rate (i.e. less than 1% per year)**

3.8 Restrictions

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.

3.9.1 Criteria for interruption or discontinuation of investigational product (active and placebo)

- **Clinically significant thrombocytopenia which mandates an interruption of study drug due to patient safety in the assessment of the investigator.** Repeat laboratory studies and standard of care (SOC) should be followed until resolution of laboratory abnormality

6.6.1 Maternal exposure

Women of childbearing potential are not allowed to be included in this study unless they use **a highly effective method of contraception which results in a low failure rate (i.e. less than 1% per year)**, and must refrain from becoming pregnant from 1 month following the last dose. Should a pregnancy still occur, the investigational product should be discontinued immediately and the pregnancy reported to designated [redacted] representative within 1 day.

Section of protocol affected:

Synopsis, 1.2.3 Primary and secondary outcome measures, 1.4 Study design, 2.2 Secondary Objectives, 2.4 Exploratory Objectives (newly added section), 8.5 Methods for statistical analyses

Previous text:

Synopsis

Study site(s) and number of subjects planned

This study is planned to be conducted in approximately 4 countries (United States (US), United Kingdom (UK), South Africa and Canada) and approximately 8 to 20 sites, with a minimum of 36 patients and a maximum of 50 patients to be randomised in the study, depending on how many patients are required in order to have 36 evaluable patients.

Secondary Objective:	**Outcome Measure:**
To determine the PK properties of ticagrelor in paediatric patients with SCD and to assess impact of weight, age and other demographic on the ticagrelor pharmacokinetics	Ticagrelor concentrations. Population PK parameters (Oral Clearance (CL/F) and AUC)

1.2.3 Primary and secondary outcome measures

The primary study endpoint is the evaluation of the PK and PD properties of ticagrelor in children after each of 3 dose strengths given as single doses (0.125 mg/kg, 0.375 mg/kg or 0.563 mg/kg) and after attainment of steady-state following twice-daily administration of 0.125 mg/kg. PK will be determined using standard methodologies. The PD measure employed will be the VerifyNow P2Y12 assay (Jeong et al 2012) that is a well-validated and commercially

available point-of-care assay to assess inhibition of the P2Y12 platelet receptor.

1.4 Study design

This study is planned to be conducted in approximately 4 countries (United States [US], United Kingdom [UK], South Africa and Canada) and approximately 8 to 20 sites, with a minimum of 36 patients and a maximum of 50 patients to be randomised in the study, depending on how many patients are required in order to have 36 evaluable patients.

2.2 Secondary objectives

Secondary Objective:	**Outcome Measure:**
To determine the PK properties of ticagrelor in paediatric patients with SCD and to assess impact of weight, age and other demographic on the ticagrelor pharmacokinetics	Ticagrelor concentrations. Population PK parameters (Oral Clearance [CL/F] and AUC)

8.5 Methods for statistical analyses

The relationship between ticagrelor dose, plasma concentration and PRU will be characterized using a population PK/PD approach (i.e. non-linear mixed effect modeling). This analysis will be based on all available PK and PRU data from which complete dosing and sampling history is collected. The PK/PD analyses will be performed sequentially, where first the PK of ticagrelor will be characterized and followed by characterizing of the PK/PD relationship. Prior PK/PD knowledge from ticagrelor in adults ACS patients will serve as basis during analyses. A detailed analysis plan will be written prior to data base lock.

No statistical comparisons are planned for the primary objective. PK, PD and safety measures will be summarized descriptively using respective analysis set. Palatability measures will also be summarized descriptively for all patients for whom the assessment is performed.

A statistical analysis comparing ticagrelor and placebo will be performed for each of the following variables using the efficacy analysis set for Part B of the study:

- Percentage of days with pain
- Percentage of days of opioid analgesic use
- Percentage of days of analgesic use
- Percentage of days hospitalized for VOC or other complications of SCD
- Percentage days of absence from school or work

A t-test will be performed for each of these variables at 5% significance level. The p-value and a 95% confidence interval for the difference between ticagrelor and placebo will be reported. There will be no adjustment for multiple comparisons. If it is inappropriate to assume a normal distribution, a Wilcoxon rank sum test may be performed. In case more than one adult equivalent dose is studied in Part B, the analysis will be repeated both for all ticagrelor doses

versus placebo and for the dose the majority of patients received versus placebo. Number of VOC, number of VOC requiring hospitalization and intensity of pain will be summarized descriptively by treatment group in Part B.

Efficacy variables collected in Part A, ie percentage of days with pain, percentage of days of opioid analgesic use, percentage of days of analgesic use, percentage of days of absence from school or work and intensity of pain will be summarized descriptively using the safety analysis set.

Revised text

Synopsis

Study site(s) and number of subjects planned

This study is planned to be conducted in approximately 4 countries (United States (US), United Kingdom (UK), South Africa and Canada) and approximately 8 to 20 sites, with a minimum of 36 patients and a maximum of 50 patients to be randomised in the study, depending on how many patients are required in order to have 36 evaluable patients. **Of these 36 evaluable patients, at least 12 patients must be 2 to 11 years of age and 12 patients must be 12 to 18 years. In addition, a minimum of 12 evaluable patients must complete Part B (through Visit 8).**

Secondary Objective:	**Outcome Measure:**
To determine the PK properties of ticagrelor **and its active metabolite** in paediatric patients with SCD and to assess impact of weight, age and other demographic on the ticagrelor pharmacokinetics	Concentrations of ticagrelor **and its active metabolite**. Population PK parameters (Oral Clearance (CL/F) and AUC)

Exploratory Objective:	**Outcome Measure:**
Investigation of efficacy of ticagrelor vs. placebo in paediatric patients with SCD in reducing:	**Days with pain (ages <4 years only)** **Intensity of pain (ages <4 years only)**

1.2.3 Primary and secondary outcome measures

The primary study endpoint is the evaluation of the PK and PD properties of ticagrelor **and its active metabolite** in children after each of 3 dose strengths given as single doses (0.125 mg/kg, 0.375 mg/kg or 0.563 mg/kg) and after attainment of steady-state following twice-daily administration of 0.125 mg/kg. PK will be determined using standard methodologies. The PD measure employed will be the VerifyNow P2Y12 assay (Jeong et al 2012) that is a well-validated and commercially available point-of-care assay to assess inhibition of the P2Y12 platelet receptor.

The secondary PK objectives are to determine the PK properties of ticagrelor and its active metabolite and to access the impact of demographic characteristics on the PK of ticagrelor. Outcome measures including:

- **Concentrations of ticagrelor and its active metabolite.**
- **Population PK parameters (Oral Clearance (CL/F) and AUC)**

1.4 Study design

This study is planned to be conducted in approximately 4 countries (US, United Kingdom (UK), South Africa and Canada) and approximately 8 to 20 sites, with a minimum of 36 patients and a maximum of 50 patients to be randomised in the study, depending on how many patients are

required in order to have 36 evaluable patients. **Of these 36 evaluable patients, at least 12 patients must be 2 to 11 years of age and 12 patients must be 12 to 18 years. In addition, a minimum of 12 evaluable patients must complete Part B (through Visit 8).**

2.2 Secondary objectives

Secondary Objective:	**Outcome Measure:**
To determine the PK properties of ticagrelor **and its active metabolite** in paediatric patients with SCD and to assess impact of weight, age and other demographic on the ticagrelor pharmacokinetics	Concentrations of ticagrelor **and its active metabolite**. Population PK parameters (Oral Clearance (CL/F) and AUC)

2.4 Exploratory objectives

Exploratory Objective:	**Outcome Measure:**
Investigation of efficacy of ticagrelor vs. placebo in paediatric patients with SCD in reducing:	**Days with pain (ages <4 years only)** **Intensity of pain (ages <4 years only)**

8.5 Methods for statistical analyses

The relationship between ticagrelor dose, plasma concentration and PRU will be characterized using a population PK/PD approach (i.e. non-linear mixed effect modeling). This analysis will be based on all available PK and PRU data from which complete dosing and sampling history is collected. The PK/PD analyses will be performed sequentially, where first the PK of ticagrelor **and its active metabolite** will be characterized and followed by characterizing of the PK/PD relationship. Prior PK/PD knowledge from ticagrelor in adult ACS patients will serve as basis during analyses. A detailed analysis plan will be written prior to data base lock.

No statistical comparisons are planned for the primary objective. PK, PD and safety measures will be summarized descriptively using respective analysis set. Palatability measures will also be summarized descriptively for all patients for whom the assessment is performed.
A statistical analysis comparing ticagrelor and placebo will be performed for each of the following variables using the efficacy analysis set for Part B of the study:

- Percentage of days with pain **(ages ≥4 years only)**
- Percentage of days of opioid analgesic use
- Percentage of days of analgesic use **(ages ≥4 years only)**
- Percentage of days hospitalized for VOC or other complications of SCD
- Percentage days of absence from school or work **(ages ≥6 years only)**

A t-test will be performed for each of these variables at 5% significance level. The p-value and a 95% confidence interval for the difference between ticagrelor and placebo will be reported. There will be no adjustment for multiple comparisons. If it is inappropriate to assume a normal distribution, a Wilcoxon rank sum test may be performed. In case more than one adult equivalent dose is studied in Part B, the analysis will be repeated both for all ticagrelor doses

versus placebo and for the dose the majority of patients received versus placebo.

Number of VOC, number of VOC requiring hospitalization and intensity of pain will be summarized descriptively by treatment group in Part B.

Efficacy variables collected in Part A, i.e. percentage of days with pain, percentage of days of opioid analgesic use, percentage of days of analgesic use, percentage of days of absence from school or work and intensity of pain will be summarized descriptively using the safety analysis set.

Exploratory variables, days with pain and intensity of pain (ages <4 years only), will be presented descriptively using the safety analysis set.

Section of protocol affected:

4 Study plan and timing of procedures: Table 1, Table 2, Table 3, Table 6, Table 7,
4.1 Enrolment/screening period, 4.2 Treatment period

Previous text:

Table 1 Study Plan detailing the procedures

	Part A			Part B					
Assessment	**Enrolment**	**Dose 1**	**Dose 2**	**Repeated treatment phase**				**End of treatment**	**Follow-up**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Visit window:	Days -30 to 0 for Visit 1	±0 day for Visit 2	+ 7 days	+7 days	+ 7 days	+ 7 days	+ 7 days	+ 7 days	30-35 days following last dose for Visit 8[d]
Week		**0**	**1**	**2**	**3**	**4**	**5**	**6**	**10**
Day		**0**	**7**	**14**	**21**	**28**	**35**	**42**	**72-77**
Signed Informed Assent/Consent	X								
Randomisation		X		X					
Inclusion/exclusion criteria	X	X[a]							
Relevant Medical and Surgical history, SCD characteristics and history	X								
Demographics	X								
Vital signs (BP, pulse)	X	X	X	X	X	X	X	X	X
Physical examination	X								X
Weight, height[e]	X	X	X					X	
Transcranial Doppler exam (within past 1 year)	X								
Ophthalmological (Eye) exam (within past 1 year)	X								
12-lead ECG (within past 6 months)	X								
12-lead ECG				X					
Daily pain assessment[g]	X	X	X	X	X	X	X	X	
Daily recording of analgesic use[g]	X	X	X	X	X	X	X	X	
Days absent from school/work[g]	X	X	X	X	X	X	X	X	
Administration of IP at clinic[i]		X	X	X				X	
Treatment dispensed/returned			X	X[j]	X	X	X	X[j]	
Compliance/ Drug accountability		X	X	X	X	X	X	X	
Acceptability/Palatability[h]		X							
Concomitant medication	X	X	X	X	X	X	X	X	X
Adverse event review (AEs and SAEs)	X[f]	X	X	X	X	X	X	X	X

	Part A			Part B					
Assessment	**Enrolment**	**Dose 1**	**Dose 2**	**Repeated treatment phase**				**End of treatment**	**Follow-up**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Visit window:	Days -30 to 0 for Visit 1	±0 day for Visit 2	+ 7 days	+7 days	+ 7 days	+ 7 days	+ 7 days	+ 7 days	30-35 days following last dose for Visit 8[d]
Week		**0**	**1**	**2**	**3**	**4**	**5**	**6**	**10**
Day		**0**	**7**	**14**	**21**	**28**	**35**	**42**	**72-77**
Blood samples for haematology and clinical chemistry (incl uric acid)	X			X				X	
Blood samples for coagulation (INR and PTT)	X								
VerifyNow™ PRU[c]		X	X	X				X	
Pregnancy test (dipstick)[b]	X		X					X	
Collection of VOC in CRF		X	X	X	X	X	X	X	X
Collection of transfusion data in CRF		X	X	X	X	X	X	X	X
Collection of bleeding events in CRF		X	X	X	X	X	X	X	X
Urinalysis	X			X				X	
Blood sampling for pharmacokinetics[c]		X	X	X				X	

a Results from local laboratory must have been received before first dose to check eligibility criteria.
b In patient after menarche.
c Actual time of PK and PRU sampling should be recorded in the eCRF.
d May occur following earlier visits than Visit 9.
e Height only at enrolment.
f Only SAE assessed at this time.
g Electronic diary recording by patient (when needed with parent/guardian help**, daily pain assessment only for ages ≥4 years**)
h Questions assessed by nurse in children <6 years, Hedonic Faces Scale (HFS) for children ≥6 years
i Actual time of dosing should be recorded in the eCRF.
j The time of drug administration the morning and evening before Visit 4 and 8 will be registered in a patient diary.

Table 2 Blood sampling in patients with a weight of >21 kg

Assessment	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
Coagulation (INR and PTT)	X								
Haematology and clinical chemistry (incl uric acid)	X			Pre-dose				X	
VerifyNow™ PRU		Pre-dose, 2, **8h**	Pre-dose, 2, **8h**	2h				Pre-dose, 2h	
Blood sampling for pharmacokinetics		1, 2, 4, **8 h**	1, 2, 4, **8 h**	2h				Pre-dose, 1, 2, 4h	

The 1, 2, 4, **and 8** hour samples can be collected ±15 minutes from actual post-dose time point.
A peripheral catheter can be used for blood sampling.

Table 3 Blood sampling in patients with a weight of 16-21 kg

Assessment	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
Coagulation (INR and PTT)	X								
Haematology and clinical chemistry (incl uric acid)	X			Pre-dose				X	
VerifyNow™ PRU		Pre-dose, 2h	Pre-dose, 2h	2h				Pre-dose, 2h	
Blood sampling for pharmacokinetics		1, 2, 4, **8 h**	1, 2, 4, **8 h**	2h				Pre-dose, 2h	

The 1, 2 and 4 **and 8** hour samples can be collected ±15 minutes from actual post-dose time point.
A peripheral catheter can be used for blood sampling.

Table 1 Volume of blood to be drawn from patients with a weight >21 kg

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 8	Total volume Visit 8 (mL)	Total (mL)
Haematology	1.2	1	1.2	0	0	0	0	1	1.2	1	1.2	
Clinical Chemistry	1.1	1	1.1	0	0	0	0	1	1.1	1	1.1	
Coagulation	1.2	1	1.2	0	0	0	0	0	0	0	0	
Pharmacokinetic	1.2	0	0	4	4.8	4	4.8	1	1.2	4	4.8	
PRU	4.0	0	0	3	12.0	3	12	1	4	2	8	
Total			3.5		16.8		16.8		7.5		15.1	59.7

Table 2 Volume of blood to be drawn from patient with a weight of 16-21 kg

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 8	Total volume Visit 8 (mL)	Total (mL)
Haematology	1.2	1	1.2	0	0	0	0	1	1.2	1	1.2	
Clinical Chemistry	1.1	1	1.1	0	0	0	0	1	1.1	1	1.1	
Coagulation	1.2	1	1.2	0	0	0	0	0	0	0	0	
Pharmacokinetic	1.2	0	0	4	4.8	4	4.8	1	1.2	2	**1.4**	
PRU	4.0	0	0	2	8	2	8	1	4	2	8	
Total			3.5		12.8		12.8		7.5		**11.7**	**48.3**

Reference Ethical considerations paediatric 2008

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. It is planned for a minimum of 36 patients and a maximum of 50 patients to be randomised in the study, in order to ensure 36 evaluable patients completing two single doses in Part A. A patient is considered as evaluable if he/she has **completed the study** up to and including Visit 3.

A complete medical, surgical and medication history will be recorded for each patient at enrolment. All relevant medical conditions that have occurred within the past or conditions that are ongoing are to be recorded in the eCRF. The medication history must identify any known drug allergies, and use of chronic medications. Safety laboratory samples should be sent to the local laboratory for analysis.

If the patient is 16 years old or younger, a transcranial Doppler examination (TCD) must have been done within the past 1 year. If this is not the case, a TCD exam needs to be done before proceeding in the study.

If the patient is six years or older, an eye exam must have been done within the past 1 year. If this is not the case, the patient will need to be examined by an ophthalmologist before proceeding in the study.

4.2 Treatment period

Part A:

Visit 2 & 3: Patients will be randomised 1:1 to receive one of two dosing schedules, with each dose separated by 7 days. Platelet aggregation will be measured using the VerifyNow™ P2Y12 assay and reported as PRU. PRU will determine continued dosing. Patients are not allowed to eat 2 hours before and 1 hour after dosing at these visits. Palatability assessment will be performed (Visit 2). A study nurse will assess palatability directly after administration of dose (for more information see Section 5.3). The patients will be allowed to leave the clinic after all sampling has been completed. Following the 2 single doses, all patients will receive open-label one-week treatment with ticagrelor twice daily to determine tolerability prior to randomisation into Part B. Dose to be administered twice daily within a 9-12 hours interval (starting in the morning the day after Visit 3). For assessments performed during the visits see Table 1. For dosing before interim analysis see Figure 2 and for dosing after interim analysis see Appendix E.

Part B:

Visit 4, 5, 6, 7 & 8: The patient will register actual date and time of drug administration the morning and evening before Visit 4 in a Dosing Diary. He/she will be instructed to not take their dose at home in the morning of Visit 4. Study drug will be administered at the clinic and actual time of dosing should be recorded in the eCRF at Visit 4. Patients will be randomised (2:1 ratio) to

ticagrelor twice daily or placebo for a 4-week treatment phase and will return to the clinic on a weekly basis for study related procedures. (See Table 1, Visit 4-8). The patient will register actual date and time of drug administration the morning and evening before Visit 8 in a Dosing Diary. He/she will be instructed to not take their dose at home in the morning of Visit 8. Study drug will be administered at the clinic and actual time of dosing should be recorded in the eCRF at Visit 8. For dosing before interim analysis see Figure 2 and for dosing after interim analysis see Appendix E.

Revised Text:

Table 1 Study Plan detailing the procedures

	Part A			Part B					
Assessment	**Enrolment**	**Dose 1**	**Dose 2**	**Repeated treatment phase**				**End of treatment**	**Follow-up**
Visit	**1[m]**	**2[m]**	**3**	**4**	**5[r]**	**6**	**7[r]**	**8**	**9**
Visit window:	Days -30 to **-7** for Visit 1	±0 day for Visit 2	+ 7 days	+7 days	+ 7 days	+ 7 days	+ 7 days	+ 7 days	30-35 days following last dose for Visit 8[d]
Week		**0**	**1**	**2**	**3**	**4**	**5**	**6**	**10**
Day		**0**	**7**	**14**	**21**	**28**	**35**	**42**	**72-77**
Signed Informed Assent/Consent	X								
Randomisation		X		X					
Inclusion/exclusion criteria	X	X[a]							
Relevant Medical and Surgical history, SCD characteristics and history	X								
Demographics	X								
Vital signs (BP, pulse)	X	X	X	X	X[r]	X	X[r]	X	X
Physical examination	X								X
Weight, height[e]	X	X	X					X	
Transcranial Doppler exam[o]	X								
Ophthalmological (Eye) exam[o]	X								
12-lead ECG[p]	X								
12-lead ECG				X					
Daily pain assessment[g]	X	X	X	X	X	X	X	X	
FLACC assessment[q]	**X**			**X**					
Daily recording of analgesic use[g]	X	X	X	X	X	X	X	X	
Days absent from school/work[g]	X	X	X	X	X	X	X	X	
Administration of IP at clinic[i]		X	X	X				X	
Treatment dispensed/returned[s]			X	X[j]	X	X	X	X[j]	
Compliance/ Drug accountability		X	X	X	X	X	X	X	
Acceptability/Palatability[h]		X							
Concomitant medication	X	X	X	X	X	X	X	X	X
Adverse event review (AEs and SAEs)	X[f]	X	X	X	X	X	X	X	X

	Part A			Part B					
Assessment	**Enrolment**	**Dose 1**	**Dose 2**	**Repeated treatment phase**				**End of treatment**	**Follow-up**
Visit	**1[m]**	**2[m]**	**3**	**4**	**5[r]**	**6**	**7[r]**	**8**	**9**
Visit window:	Days -30 to **-7** for Visit 1	±0 day for Visit 2	+ 7 days	+7 days	+ 7 days	+ 7 days	+ 7 days	+ 7 days	30-35 days following last dose for Visit 8[d]
Week		**0**	**1**	**2**	**3**	**4**	**5**	**6**	**10**
Day		**0**	**7**	**14**	**21**	**28**	**35**	**42**	**72-77**
Blood samples for haematology and clinical chemistry (incl uric acid)	X[n]			X[k]				X	
Blood samples for coagulation (INR and PTT)	X[n]								
VerifyNow™ PRU[c]		X	X	X[l]				X	
Pregnancy test (dipstick)[b]	X		X					X	
Collection of VOC in CRF		X	X	X	X	X	X	X	X
Collection of transfusion data in CRF		X	X	X	X	X	X	X	X
Collection of bleeding events in CRF		X	X	X	X	X	X	X	X
Urinalysis	X[n]			X				X	
Blood sampling for pharmacokinetics[c]		X	X	X[l]				X	

Abbreviations: AE = adverse event; BP = blood pressure; CRF = Case Report Form; ECG = electrocardiogram; eCRF = electronic Case Report Form; FLACC = the Face, Legs, Activity, Cry, Consolability form; INR = International Normalized Ratio; PK = pharmacokinetics; PRU = $P2Y_{12}$ reaction units; PTT = Partial Thromboplastin Time; SAE = serious adverse event; SCD = Sickle Cell Disease; VOC = vaso-occlusive crisis

a Results from local laboratory must have been received before first dose to check eligibility criteria.
b In patient after menarche.
c Actual time of PK and PRU sampling should be recorded in the eCRF.
d May occur following earlier visits than Visit 9.
e Height only at enrolment.
f Only SAE assessed at this time.
g Electronic diary recording by patient **≥4 years** (when needed with parent/guardian help).
h Questions assessed by nurse in children <6 years, Hedonic Faces Scale (HFS) for children ≥6 years
i Actual time of dosing should be recorded in the eCRF.
j The time of drug administration in the morning and evening before Visit 4 and 8 will be registered in a patient diary.
k Blood sample for haematology and clinical chemistry (including uric acid) at Visit 4 will be collected 2h post-dose together with PK and PRU.
l PK and PRU sampling at Visit 4 will be performed at 2 hours post-dose ONLY.
m Visit 2 should be at least 7 days apart from Visit 1.
n Laboratory testing performed prior to Visit 1 as part of usual clinical care does not need to be repeated as long as the values were obtained within 30 days prior to Visit 2.

o The most recent examination must be performed within 12 months before Visit 1. If this is not the case, the examination must be done before proceeding in the study.

p 12-lead ECG must be performed within 6 months before Visit 1. If this is not the case, the examination must be done before proceeding in the study.

q FLACC for patients aged from 2 to <4 years only to be collected between Visit 1 and Visit 2, and between Visit 4 to Visit 5.

r Visit 5 and Visit 7 may be performed as telephone contacts, based on the opinion of the Investigator. Vital signs (BP and pulse) will only be measured if the patient visits the site.

s If Visit 5 and/or Visit 7 are performed as telephone contacts, doubles kits of study treatment will be dispended on Visit 4 and/or Visit 6 to cover the whole period.

Table 2 Blood sampling in patients with a weight of >21 kg

Assessment	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
Coagulation (INR and PTT)	X								
Haematology and clinical chemistry (incl uric acid)	X			**2h post-dose**				X	
VerifyNow™ PRU		Pre-dose, 2, **6h post-dose**	Pre-dose, 2, **6h post-dose**	2h **post-dose**				Pre-dose, 2h **post-dose**	
Blood sampling for pharmacokinetics		1, 2, 4, **6h post-dose**	1, 2, 4, **6h post-dose**	2h **post-dose**				Pre-dose, 1, 2, 4h **post-dose**	

Abbreviations: INR = International Normalized Ratio; PK = pharmacokinetics; PRU = $P2Y_{12}$ reaction units; PTT = Partial Thromboplastin Time
The 1, 2, 4, **and 6** hour samples can be collected ±15 minutes from actual post-dose time point.
If applicable, PRU and PK sampling should be arranged at the same time to avoid repeated venipuncture.
A peripheral catheter can be used for blood sampling.

Table 3 Blood sampling in patients with a weight of 16-21 kg

Assessment	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
Coagulation (INR and PTT)	X								
Haematology and clinical chemistry (incl uric acid)	X			**2h post-dose**				X	
VerifyNow™ PRU		Pre-dose, 2h **post-dose**	Pre-dose, 2h **post-dose**	2h **post-dose**				Pre-dose, 2h **post-dose**	
Blood sampling for pharmacokinetics		1, 2, 4, **6h post-dose**	1, 2, 4, **6h post-dose**	2h **post-dose**				Pre-dose, 2h **post-dose**	

Abbreviations: INR = International Normalized Ratio; PK = pharmacokinetics; PRU = $P2Y_{12}$ reaction units; PTT = Partial Thromboplastin Time
The 1, 2, 4 **and 6** hour samples can be collected ±15 minutes from actual post-dose time point.
If applicable, PRU and PK sampling should be arranged at the same time to avoid repeated venipuncture.
A peripheral catheter can be used for blood sampling.

Table 3 Volume of blood to be drawn from patients with a weight >21 kg

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 8	Total volume Visit 8 (mL)	Total (mL)
Haematology	1.2	1	1.2	0	0	0	0	1	1.2	1	1.2	
Clinical Chemistry	1.1	1	1.1	0	0	0	0	1	1.1	1	1.1	
Coagulation	1.2	1	1.2	0	0	0	0	0	0	0	0	
Pharmacokinetic	1.2	0	0	4	4.8	4	4.8	1	1.2	4	4.8	
PRU*	4.0	0	0	3	12.0	3	12	1	4	2	8	
Total			3.5		16.8		16.8		7.5		15.1	59.7

*** PRU sampling via a central catheter may require up to an additional 3 mL at each PRU sampling timepoint.**

Table 4 Volume of blood to be drawn from patient with a weight of 16-21 kg

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 8	Total volume Visit 8 (mL)	Total (mL)
Haematology	1.2	1	1.2	0	0	0	0	1	1.2	1	1.2	
Clinical Chemistry	1.1	1	1.1	0	0	0	0	1	1.1	1	1.1	
Coagulation	1.2	1	1.2	0	0	0	0	0	0	0	0	
Pharmacokinetic	1.2	0	0	4	4.8	4	4.8	1	1.2	2	**2.4**	
PRU*	4.0	0	0	2	8	2	8	1	4	2	8	
Total			3.5		12.8		12.8		7.5		**12.7**	**49.3**

*** PRU sampling via a central catheter may require up to an additional 3 mL at each PRU sampling timepoint.**

Reference Ethical considerations paediatric 2008

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. It is planned for a minimum of 36 patients and a maximum of 50 patients to be randomised in the study, in order to ensure 36 evaluable patients completing two single doses in Part A. A patient is considered as evaluable if he/she has **provided data** up to and including Visit 3. **Of these 36 evaluable patients, at least 12 patients must be 2 to 11 years of age and 12 patients must be 12 to 18 years. In addition, a minimum of 12 evaluable patients must complete Part B (through Visit 8).**

A complete medical, surgical and medication history will be recorded for each patient at enrolment. All relevant medical conditions that have occurred within the past or conditions that are ongoing are to be recorded in the eCRF. The medication history must identify any known drug allergies, and use of chronic medications. Safety laboratory samples should be sent to the local laboratory for analysis.

If the patient is 16 years old or younger, a TCD must have been done within the past 1 year. If this is not the case, a TCD exam needs to be done before proceeding in the study.

If the patient is six years or older, an eye exam must have been done within the past 1 year. If this is not the case, the patient will need to be examined by an ophthalmologist before proceeding in the study.

At least a 7-day interval is needed between Visit 1 and Visit 2 to allow for the recording of the baseline data on patient diary (see Section 5.1.2).

4.2 Treatment period

Part A:

Visit 2 & 3: **Randomisation will take place 7 to 30 days after enrolment.** Patients will be randomised 1:1 to receive one of two dosing schedules, with each dose separated by 7 days. Platelet aggregation will be measured using the VerifyNow™ P2Y12 assay and reported as PRU. PRU will determine continued dosing. Patients are not allowed to eat 2 hours before and 1 hour after dosing at these visits. Palatability assessment will be performed (Visit 2). A study nurse will assess palatability directly after administration of dose (for more information see Section 5.3). The patients will be allowed to leave the clinic after all sampling has been completed. Following the 2 single doses, all patients will receive open-label one-week treatment with ticagrelor twice daily to determine tolerability prior to randomisation into Part B. Dose to be administered twice daily within a 9-12 hours interval (starting in the **evening the same day as** Visit 3). For assessments performed during the visits see Table 1. For dosing before interim analysis see Figure 2 and for dosing after interim analysis see Appendix E.

Part B:

Visit 4, 5, 6, 7 & 8: The patient will register actual date and time of drug administration the morning and evening before Visit 4 in a Dosing Diary. He/she will be instructed to not take their dose at home in the morning of Visit 4. Study drug will be administered at the clinic and actual time of dosing should be recorded in the eCRF at Visit 4. Patients will be randomised (2:1 ratio) to ticagrelor twice daily or placebo for a 4-week treatment phase and will return to the clinic on a weekly basis for study related procedures. **Visit 5 and Visit 7 may optionally be performed as phone contacts, based on the opinion of the Investigator** (See Table 1, Visit 4-8). The patient will register actual date and time of drug administration the morning and evening before Visit 8 in a Dosing Diary. He/she will be instructed to not take their dose at home in the morning of Visit 8. Study drug will be administered at the clinic and actual time of dosing should be recorded in the eCRF at Visit 8. For dosing before interim analysis see Figure 2 and for dosing after interim analysis see Appendix E.

Section of protocol affected:

5.1.1 Vaso-occlusive crisis (VOC), 5.1.2 Pain, 5.1.3 Other efficacy variables, 5.2.1 Laboratory safety assessment, 5.2.3 Vital signs, 5.2.4 Electrocardiogram (newly added section), 5.5.2 Collection of samples, 7.7 Concomitant and other treatments, 7.7.1 Blood transfusion (newly added section), 7.7.2 Other concomitant treatment

Previous text:

5.1.1 Vaso-occlusive crisis (VOC)

VOC is defined as a painful sickle cell crisis requiring medical intervention including any of the following (1) hospitalization (2) emergency department or clinic visit (3) medically supervised outpatient treatment with escalated doses of drugs for management of painful crisis (may include oral or parenteral opioids or non-steroidal anti-inflammatory drugs). At each visit, patients or guardians will be questioned regarding any painful sickle cell crises occurring since the last study visit.

5.1.2 Pain

Pain is commonly reported in clinical trials by having patients provide a rating of their own pain. Different measures of numerical rating scales have demonstrated good psychometric properties but are not fit for purpose for the youngest age groups due to their limited understanding of number concepts. Therefore, pain-rating scales with a series of faces depicting different levels of pain have been developed. The Faces Pain Scale - Revised (FSP-R) was validated by Hicks et al 2001 in 3 studies and has been judged as a well-established pain assessment tool in patients 4 to 16 years of age (Cohen et al 2008) and will be administered to all patients in this study age ≥4 years. When needed a parent/guardian can help the child with the assessment.

The Faces Pain Scale will be collected daily at bedtime using an electronic device. The scale consists of six faces and scoring ranges between 0-10 (with an increase in numeric value by 2 i.e. (0,2,4,6,8,10)), where 0 is no pain. 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. Please see Appendix G.

5.1.3 Other efficacy variables

Daily variables will be collected using a daily electronic diary both in Part A and Part B:

- Days of analgesic use
- Days of absence from school or work (ages ≥6 years only)

For more details see Section 5.3.

5.2.1 Laboratory safety assessments

Blood and urine samples for determination of clinical chemistry, haematology, coagulation, and urinalysis will be taken at the times indicated in the Study Plan (see Table 1).

Additional safety samples may be collected 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.

5.2.3 Vital signs

BP and pulse will be measured at every visit. Weight will be measured at Visit 1(enrolment), 2, 3 and 8 (follow-up). Height will only be measured at enrolment.

5.5.2 Collection of samples

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

7.7 Concomitant and other treatments

Treatment with oral or parenteral anticoagulants, and daily aspirin or non-steroidal anti-inflammatory agents is not allowed in the study except for prophylactic doses of heparins, eg, flushing of catheters (see exclusion criteria in Section 3.2).

7.7.1 Other concomitant treatment

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.

Revised text:

5.1.1 Vaso-occlusive crisis (VOC)

VOC is defined as a painful sickle cell crisis requiring medical intervention including any of the following (1) hospitalization (2) emergency department**, short-stay unit** or clinic visit (3) medically supervised outpatient treatment with escalated doses of drugs for management of painful crisis (may include oral or parenteral opioids or non-steroidal anti-inflammatory drugs). At each visit, patients or guardians will be questioned regarding any painful sickle cell crises occurring since the last study visit.

5.1.2 Pain

Pain is commonly reported in clinical trials by having patients provide a rating of their own pain. Different measures of numerical rating scales have demonstrated good psychometric properties but are not fit for purpose for the youngest age groups due to their limited understanding of number concepts. Therefore, pain-rating scales with a series of faces depicting different levels of pain have been developed. The Faces Pain Scale - Revised (FSP-R) was validated by Hicks et al 2001 in 3 studies and has been judged as a well-established pain assessment tool in patients 4 to 16 years of age (Cohen et al 2008) and will be administered to all patients in this study age ≥4 years. When needed, a parent/guardian can help the child with the assessment.

The Faces Pain Scale will be collected daily at bedtime using an electronic device. The scale consists of six faces and scoring ranges between 0-10 (with an increase in numeric value by 2 i.e. (0, 2, 4, 6, 8, 10)), where 0 is no pain. 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. Please see Appendix G.

For patients aged from 2 to <4 years, a Face, Legs, Activity, Cry, Consolability (FLACC) form will be used for recording daily pain, between visit 1 and 2 and between visit 4 and 5. The FLACC form will be completed daily at bedtime by the primary caregiver, with the assessment of the time when the child is under the caregiver's care. If possible, the reporter should be the same caregiver during the reporting period. Please see Appendix G.

5.1.3 Other efficacy variables

Daily variables will be collected using a daily electronic diary both in Part A and Part B:

- Days of analgesic use **(ages ≥4 years only)**
- Days of absence from school or work (ages ≥6 years only), **excluding days of absence due to study visits**

For more details see Section 5.3.

5.2.1 Laboratory safety assessments

Blood and urine samples for determination of clinical chemistry, haematology, coagulation, and urinalysis will be taken at the times indicated in the Study Plan (see Table 1).

At Visit 1, laboratory testing performed prior to enrolment as part of usual care does not need to be repeated as long as the values are obtained no more than 30 days prior to Visit 2.

Additional safety samples may be collected 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.

5.2.3 Vital signs

BP and pulse will be measured at every **on-site** visit. Weight will be measured at Visit 1(enrolment), 2, 3 and 8 (follow-up). Height will only be measured at enrolment.

5.2.4 Electrocardiogram

12-lead ECG will be performed at Visit 1 (or within 6 months prior to enrolment) and at Visit 4. The following ECG parameters will be collected: heart rate and rhythm, PR interval, QRS duration, RR interval, QT interval, QTc interval (unspecified), and any abnormalities.

5.5.2 Collection of samples

Samples will be collected and labeled as detailed in the VerifyNow User's Manual. In addition, to reduce the blood volume required for the PD and PK samples, the following procedures will be utilized.

- **For VerifyNow samples obtained through a peripheral indwelling cannula: Discard saline remaining in the cannula and 1 mL of blood. Draw 1.2 mL for PK sample (discard this blood if there is no PK sample at this time point). Draw 2 mL into the VerifyNow partial fill tube.**

- **For VerifyNow samples obtained through a central indwelling line: Discard saline or flush solution and 3.8 mL of blood. Draw 1.2 mL for PK sample (discard this blood if there is no PK sample at this time point). Draw 2 mL into the VerifyNow partial fill tube.**

- **For samples obtained through direct phlebotomy: Use a 21 gauge or larger needle or butterfly device and ensure an atraumatic venipuncture. Draw and discard 1 mL of blood. Draw 1.2 mL for PK sample (discard this blood if there is no PK sample at this time point). Draw 2 mL into the VerifyNow partial fill tube.**

7.7 Concomitant and other treatments

Treatment with oral or parenteral anticoagulants, and daily aspirin is not allowed in the study except for prophylactic doses of heparins, eg, flushing of catheters (see exclusion criteria in Section 3.2). **NSAIDs may not be administered more frequently than 3 days per week.**

7.7.1 Blood transfusion

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

7.7.2 Other concomitant treatment

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.

Section of protocol affected:

11 List of References, Appendix F: Table 5, Appendix G FLACC form (newly added); Appendix H Child-Pugh Classification (newly added)

Previous text:

11 List of References

Ataga et al 2012
Ataga KI, Brittain JE, Desai P, May R, Jones S, Delaney J et al. Association of coagulation activation with clinical complications in sickle cell disease.
PLoS ONE 2012;7(1) doi:10.1371/journal.pone.0029786

Ballas 2007
Ballas SK. Current issues in sickle cell pain and its management.
Hematology Am Soc Hematol Educ Program 2007:97-105

Cabannes et al 1984
Cabannes R, Lonsdorfer J, Castaigne JP, Ondo A, Plassard A, Zohoun I et al. Clinical and biological double-blind-study of ticlopidine in preventive treatment of sickle-cell crises. Agents Actions 1984;Suppl 15:199-212

Appendix F

Table 5 0.563 mg/kg

Weight (kg)	Bottle strength (mg)	Dose volume (mL)	Actual dose (mg)
16-27	45	2	9
28-41	45	4	18
42-55	45	6	27
56-69	45	8	36
70-120	45	10	45

Revised text:

11 List of References

Adams et al 1998
Adams RJ, Mckie V, Hsu L et al. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. N Engl J Med 1998;339(1):5-11

Ataga et al 2012
Ataga KI, Brittain JE, Desai P, May R, Jones S, Delaney J et al. Association of coagulation activation with clinical complications in sickle cell disease.
PLoS ONE 2012;7(1) doi:10.1371/journal.pone.0029786

Ballas 2007
Ballas SK. Current issues in sickle cell pain and its management.
Hematology Am Soc Hematol Educ Program 2007:97-105

Bulas et al 2005
Bulas D. Screening children for sickle cell vasculopathy: guidelines for transcranial Doppler evaluation. Paediatric Radiology 2005;35:235-241

Cabannes et al 1984
Cabannes R, Lonsdorfer J, Castaigne JP, Ondo A, Plassard A, Zohoun I et al. Clinical and biological double-blind-study of ticlopidine in preventive treatment of sickle-cell crises. Agents Actions 1984;Suppl 15:199-212

Appendix F

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16-27	45	2	9
28-41	45	4	18
42-55	45	6	27
56-69	45	8	36
70-120	45	10	45*

*** The highest dose in this study is 45 mg, even if the patient weight is >120 kg.**

Appendix G

FLACC form

SICKLE CELL PAIN DIARY (children aged 2-3)

Instruction for Caregiver (e.g. parent) on completion

*_____ (child's name) is taking part in a study of children with sickle cell disease. The study is collecting information about pain, so that we can learn how to help children with sickle cell disease feel better. Please complete the sickle pain diary **every evening** from _____ (date) until your next clinic visit _____ (date).*

1. ***Enter assessment date for each day of assessment.***

2. ***Answer the question:*** **Has your child had any sickle cell pain during the last 24 hours?**
   If your child has had any sickle cell pain during the last 24 hours, please describe how your child behaved while under your care due to the pain. For each category (face, legs, activity, crying, and consolability), please mark an X in the one box that best describes your answer.

*Please remember the **same caregiver** (e.g. parent) is to complete the diary every evening.*

Please contact Your Study Doctor or Study Nurse if you have doubts how to complete diary.

Please remember to return the completed sickle cell pain diary on the next visit to the clinical site.

SICKLE CELL PAIN Diary – patients ages 2 through <4

Patient ID/E-code : _____ Assessment Date : _____

Instructions

Please answer this question every night when participating in the study.

Has your child had any sickle cell pain during the last 24 hours?

No **Yes**

If Yes, please continue to the next page

English for USA

Please describe how your child behaved because of the pain. For each category (face, legs, activity, cry and consolability), please mark an X in the box that best describes your answer.

FACE	No particular expression or smile ☐ 0	Occasional grimace or frown, withdrawn, disinterested ☐ 1	Frequent to constant frown, clenched jaw, quivering chin ☐ 2
LEGS	Normal position or relaxed ☐ 0	Uneasy, restless, tense ☐ 1	Kicking, or legs drawn up ☐ 2
ACTIVITY	Lying quietly, normal position, moves easily ☐ 0	Squirming, shifting back and forth, tense ☐ 1	Arched, rigid, or jerking ☐ 2
CRY	No cry (awake or asleep) ☐ 0	Moans or whimpers, occasional complaint ☐ 1	Crying steadily, screams or sobs, frequent complaints ☐ 2
CONSOLABILITY	Content, relaxed ☐ 0	Reassured by occasional touching, hugging, or being talked to, distractable ☐ 1	Difficult to console or comfort ☐ 2

English for USA

Appendix H

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 5 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) or Prothrombin time (INR)	< 4 < 1.7	4 - 6 1.7 - 2.3	> 6 > 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.

Reason for Amendment:

The purposes of this amendment are to:

Update the secondary objective to include the PK properties of the active metabolite of ticagrelor. Re-word some inclusion/exclusion criteria for clarification and consistency with other parts of the CSP.

- Patients aged ≤16 years must have a TCD exam before proceeding in the study if he/she hasn't had a TCD exam within the past year prior to Visit 1.
- Patients aged ≤6 years must be examined by an ophthalmologist before proceeding in the study if he/she hasn't had an ophthalmological examination within the past year prior to Visit 1.
- Weight-adjusted dose of hydroxyurea must be stable for 3 months to be eligible for enrolment.
- The TCD exclusion criterion was re-worded consistent with STOP study criteria and to include values for imaging TCD equipment.
- The exclusion concerning chronic transfusion was reworded to exclude only patients currently on a chronic transfusion program.
- Active pathological bleeding was added to exclusion criteria.
- Moderate or severe hepatic impairment which excludes a patient from the study is now defined specifically as Child-Pugh Class B or C.

Define a highly effective method of contraception as the one which results in a low failure rate (i.e. less than 1% per year) for consistency with UK regulatory definition. The methods meeting this definition are now specifically listed in section 3.8.

Highlight that at least a 7-day interval is needed between Visit 1 and Visit 2 to allow for baseline patient diary recording.

State that randomisation will take place 7 to 30 days after enrolment.

Change collection of haematology and clinical chemistry sample at visit 4 to 2 hours post-dose, to minimize number of separate venipunctures for the patient.

Shorten the PK and PRU sampling time for Visit 2 and Visit 3 as last measurement will occur at 6 hours post-dose; correct the volume of blood collection for patients with a weight of 16 to 21 kg; and clarify that an additional 3 mL of blood sample may be needed when using a central catheter for PRU sampling at each PRU sampling timepoint.

Clarify that days absent from school or work due to clinical study visits do not count as "days absent from school/work" on the eDiary.

Update the protocol to reflect the request of the Paediatric Committee (PDCO) that the 36 evaluable patients will include at least 12 patients aged 2 to 11 years and at least 12 patients aged 12 to 18 years; moreover, a minimum of 12 evaluable patients must complete Part B (through Visit 8).

Clarify that open-label one week treatment will start in the evening the same day as Visit 3.

Confirm that Visit 5 and Visit 7 may optionally be performed as telephone contacts rather than clinic visits if the investigator deems this acceptable.

Update the criteria for interruption or discontinuation of investigational product.

State that laboratory testing performed prior to enrolment as part of usual clinical care does not need to be repeated as long as the values were obtained no more than 30 days prior to Visit 2.

Add a new section (Section 5.2.4) to specify ECG parameters collected for the study.

State that NSAIDs drugs may not be administered more frequently than 3 days per week during the study.

Add a new section (Section 7.7.1) to clarify that any blood transfusion during the study will be recorded in the eCRF.

State the maximum dose of ticagrelor in this study is 45 mg, regardless of the weight of a patient.

Update the CSP to reflect the request from PDCO to add pain assessment for SCD pain for children aged 2 to < 4 years. FLACC form and instructions for completion of the form are added. This will be studied as exploratory objective with days of pain and intensity of pain as outcome measures.

Added description of how PD (VerifyNow P2Y12) samples are collected and handled.

Clarify that definition of VOC includes medical intervention at short-stay unit.

Add new reference articles.

Correct typographical errors and make general and administrative updates.

Persons who initiated the Amendment:

AstraZeneca Study Team initiated the amendment to clarify wording, decrease patient burden, and to incorporate requests from the Paediatric Committee of the European Medicines Agency and the MHRA.

Clinical Study Protocol Amendment	
Amendment Number	3
Drug Substance	Ticagrelor
Study Code	D5136C00007
Date	22 December 2015
Protocol Dated	05 March 2014

Multicenter, open-label, randomised, pharmacokinetic (PK) and pharmacodynamic (PD) dose-ranging Phase II study of ticagrelor followed by a double-blind, randomised, parallel-group, placebo-controlled 4 weeks extension phase in paediatric patients with sickle cell disease

Sponsor:

AstraZeneca AB, 151 85 Södertälje, Sweden.

Centres affected by the Amendment:

This amendment affects all centres in the study.

The protocol for the study is to be amended as follows:

Section of protocol affected:

Synopsis; 1.4 Study design; 4.1 Enrolment/screening period

Previous text:

This study is planned to be conducted in approximately 4 **countries (United States (US), United Kingdom (UK), South Africa and Canada) and approximately 8 to** 20 **sites,** with a minimum of 36 patients and a maximum of 50 patients to be randomised in the study, depending on how many patients are required in order to have 36 evaluable patients. Of these 36 evaluable patients, at least 12 patients must be 2 to 11 years of age and 12 patients must be 12 to 18 years. In addition, a minimum of 12 evaluable patients must complete Part B (through Visit 8).

Study period		Phase of development
Estimated date of first subject enrolled	Q3 2014	II
Estimated date of last subject completed	**Q2-Q3 2015**	

Revised text:

This study is planned to be conducted in approximately 6-10 countries in North America, Europe, Middle East and Africa at approximately 30 - 37 sites, with a minimum of 36 patients and a maximum of 50 patients **(including the patients already randomised to date)** to be randomised in the study, depending on how many patients are required in order to have 36 evaluable patients. Of these 36 evaluable patients, at least 12 patients must be 2 to 11 years of age and 12 patients must be 12 to 18 years. In addition, a minimum of 12 evaluable patients must complete Part B (through Visit 8).

Study period		Phase of development
Estimated date of first subject enrolled	Q3 2014	II
Estimated date of last subject completed	**Q1 2017**	

Section of protocol affected:

Synopsis

Previous text:

Part A: Patients will be randomised 1:1 to receive one of two dosing schedules. All patients will receive **0.125** mg/kg as their initial dose, followed 7 days later by **0.375** mg/kg or **0.563** mg/kg with determination of pharmacokinetic (PK) parameters and pharmacodynamic (PD) platelet inhibition following each dose. The PK and platelet aggregation data are intended to support modelling-based selection of a weight-based dose for Phase III. Platelet aggregation will be measured using the VerifyNow™ P2Y12 assay and reported as $P2Y_{12}$ reaction units (PRU).

Following the 2 single doses, all patients will receive open-label one-week treatment with ticagrelor **0.125** mg/kg twice daily to determine tolerability prior to randomisation into Part B.

Part B: In this part patients will be randomised (2:1 ratio) to ticagrelor **0.125** mg/kg twice daily or placebo for a 4-week treatment phase.

During the study, patients will be followed for the occurrence of vaso-occlusive crisis (VOC) and for other disease manifestations such as daily pain, analgesic use and complications of SCD.

For safety reasons the dosing schedule will be modified for individual patients as follows: If PRU at 2 hr following dosing of **0.125** mg/kg is <95, the subsequent maximum dose for this patient will be **0.0625** mg/kg throughout the study. If PRU <95 **on any two dosing occasions** following dosing of **0.0625** mg/kg, the patient will be discontinued from further study drug.

After 12 patients have completed dosing in Part A, a PK/PD evaluation (interim analysis) of the data will be conducted and the dose for the repeated dosing in both Part A and B for the remaining patients may be revised (aiming for a mean reduction in PRU 2 hour post-dose of 45%).

Revised text:

Part A: Patients will be randomised 1:1 to receive one of two dosing schedules. All patients will receive **0.75** mg/kg as their initial **single** dose, followed 7 days later by **1.125** mg/kg or **2.25** mg/kg with determination of pharmacokinetic (PK) parameters and pharmacodynamic (PD) platelet inhibition following each **single** dose. The PK and platelet aggregation data are intended to support modelling-based selection of a weight-based dose for Phase III. Platelet aggregation will be measured using the VerifyNow™ P2Y12 assay and reported as $P2Y_{12}$ reaction units (PRU).

Following the 2 single doses, all patients will receive open-label one-week treatment with ticagrelor **0.75** mg/kg twice daily to determine tolerability prior to randomisation into Part B.

Part B: **Part B will be optional for patients. The investigator should present Part B to each patient and the decision to participate in Part B should be made by the patient (or parents/legal guardian).** In this part patients will be randomised (2:1 ratio) to ticagrelor **0.75** mg/kg twice daily or placebo for a 4-week treatment phase. **In some countries, Part B will not be performed.**

During the study, patients will be followed for the occurrence of vaso-occlusive crisis (VOC) and for other disease manifestations such as daily pain, analgesic use and complications of SCD.

For safety reasons the dosing schedule will be modified for individual patients as follows: If PRU at 2 hr following dosing of **0.75** mg/kg is <95, the subsequent maximum dose for this patient will be **0.563** mg/kg throughout the study. If PRU <95 following dosing of **0.563** mg/kg, the patient will be discontinued from further study drug.

Since Part A of the study is open label, the PK and PD results will be monitored as the study proceeds and the doses may be further adjusted in both Part A and B based on emerging PK and PD results. Doses may be adjusted following assessment by AstraZeneca and the Steering Committee of open label Part A results in the first 6-12 patients randomised under this amendment. Dose adjustment decisions will be based upon a review of PK, PD and adverse events (see Section 8.6).

Section of protocol affected:

Synopsis

Previous text:

Target subject population

Patients eligible for this study include all children aged ≥2 to <18 years of age (age from birth to Visit 1) who are diagnosed with sickle cell disease [homozygous sickle cell (HbSS) or sickle beta-zero-thalassemia (HbS/β^0)] **and have experienced at least two VOC requiring medical intervention during the past 12 months.**

Duration of treatment

In Part A the treatment period consists of 2 single doses (separated by at least 7 days) followed by 7 days open label ticagrelor treatment twice daily. In Part B patients will be randomised to 4 weeks twice-daily treatment. There is no washout period between Part A and Part B. The total expected study duration for an individual patient is approximately 3 months (including 30 days follow-up after last dose).

Investigational product, dosage and mode of administration

Part A:

Ticagrelor **0.0625** mg/kg, **0.125** mg/kg, **0.375** mg/kg or **0.563** mg/kg given as oral single doses.

Ticagrelor **0.0625**, **0.125** mg/kg or potentially **0.25** mg/kg twice daily given orally.

Part B:

Ticagrelor **0.0625**, **0.125** mg/kg or potentially **0.25** mg/kg twice daily given orally and corresponding placebo.

Revised text:

Target subject population

Patients eligible for this study include all children aged ≥2 to <18 years of age (age from birth to Visit 1) who are diagnosed with sickle cell disease [homozygous sickle cell (HbSS) or sickle beta-zero-thalassemia (HbS/β^0)]**. ~~and have experienced at least two VOC requiring medical intervention during the past 12 months.~~**

Duration of treatment

In Part A the treatment period consists of 2 single doses (separated by at least 7 days) followed by 7 days open label ticagrelor treatment twice daily. In Part B patients will be randomised to 4 weeks twice daily treatment. There is no washout period between Part A and Part B. The total expected study duration for an individual patient **participating in both Part A and Part B** is approximately 3 months (including 30 days follow-up after last dose) **and**

approximately 2 months for an individual patient participating in only Part A (including 30 days follow-up after last dose).

Investigational product, dosage and mode of administration

Part A:

Ticagrelor **0.563 mg/kg, 0.75 mg/kg, 1.125 mg/kg, or 2.25 mg/kg** given as oral single doses.

Ticagrelor **0.563 mg/kg or 0.75 mg/kg** twice daily given orally.

These doses may be adjusted based upon evaluation of PK/PD data as described in Appendix E.

Part B:

Ticagrelor **0.563 mg/kg or 0.75 mg/kg** twice daily given orally and **matching** placebo.

These doses may be adjusted based upon evaluation of PK/PD data as described in Appendix E.

Section of protocol affected:

Synopsis, statistical methods

Previous text:

A t-test will be performed for each of these variables at 5% significance level. The p-value and a 95% confidence interval for the difference between ticagrelor and placebo will be reported. There will be no adjustment for multiple comparisons. If it is inappropriate to assume a normal distribution, a Wilcoxon rank sum test may be performed. Number of VOC requiring hospitalization and intensity of pain will be summarized descriptively.

Revised text:

A t-test will be performed for each of these variables at 5% significance level, **provided that the efficacy analysis set contains at least 30 patients, otherwise only descriptive statistics will be used.** The p-value and a 95% confidence interval for the difference between ticagrelor and placebo will be reported. There will be no adjustment for multiple comparisons. If it is inappropriate to assume a normal distribution, a Wilcoxon rank sum test may be performed. Number of VOC requiring hospitalization and intensity of pain will be summarized descriptively.

Section of protocol affected:

1.1.1 Disease under treatment

Previous text:

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.

Revised text:

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. **A low level of platelet inhibition with prasugrel for at least 9 months in children with SCD showed numerical reductions in rate of VOC's and pain crises, but differences were not statistically significant compared to placebo (Heeney et al 2015).**

Section of protocol affected:

1.2.2 Study design

Previous text:

The current study will randomise a minimum of 36 patients with SCD aged ≥2 years to <18 years. An open-label, randomised pharmacokinetic (PK) and pharmacodynamic (PD) evaluation of 2 single doses will be followed by one week of treatment with ticagrelor twice daily to determine tolerability. This will be followed by a 4-week randomised, double blind placebo-controlled treatment with twice-daily ticagrelor or placebo. There is no washout period between Part A and Part B. All patients will receive 2 single open-label doses of ticagrelor separated by at least 7 days, with determination of PK parameters and PD (inhibition of platelet activation) after each dose, to support modelling-based selection of a weight-based dose for the subsequent Phase III study. The current study is designed to provide PK and PD data on ticagrelor in children, and to provide initial experience with chronic daily dosing.

Revised text:

The current study will randomise a minimum of 36 patients with SCD aged ≥2 years to <18 years. An open-label, randomised pharmacokinetic (PK) and pharmacodynamic (PD) evaluation of 2 single doses will be followed by one week of treatment with ticagrelor twice daily to determine tolerability. This will be followed by an **optional** 4-week randomised,

double blind placebo-controlled treatment with twice-daily ticagrelor or placebo. There is no washout period between Part A and Part B. All patients will receive 2 single open-label doses of ticagrelor separated by at least 7 days, with determination of PK parameters and PD (inhibition of platelet activation) after each dose, to support modelling-based selection of a weight-based dose for the subsequent Phase III study. The current study is designed to provide PK and PD data on ticagrelor in children, and to provide initial experience with chronic daily dosing.

Section of protocol affected:

1.2.3 Primary and secondary outcome measures; 1.2.4 Dose and study duration

Previous text:

1.2.3 Primary and secondary outcome measures

The primary study endpoint is the evaluation of the PK and PD properties of ticagrelor and its active metabolite in children after **each of 3 dose strengths given** as single doses (**0.125** mg/kg, **0.375** mg/kg or **0.563** mg/kg) and after attainment of steady-state following twice-daily administration of **0.125** mg/kg. PK will be determined using standard methodologies. The PD measure employed will be the VerifyNow P2Y12 assay (Jeong et al 2012) that is a well-validated and commercially available point-of-care assay to assess inhibition of the $P2Y_{12}$ platelet receptor.

1.2.4 Dose and study duration

This is the first study in paediatric patients, and thus therapy will be initiated with a single low dose of ticagrelor with assessment of PK properties and PD effect. The initial dose will be a **0.125**mg/kg (weight-based dose equivalent to **10** mg in adults), **which is 11% of the approved dose for adults with ACS.** The second dose of ticagrelor will be **0.375** mg/kg or **0.563** mg/kg (weight-based dose equivalent to **30** or **45** mg in adults). **The chronic dose of 0.125 mg/kg to be administered during the repeated treatment phase of the study is a very low and thus conservative dose equivalent to 11% of the approved chronic dose for adults with ACS.**

For safety reasons the dosing schedule will be modified for individual patients as follows: If PRU at 2 hr following dosing of **0.125** mg/kg is <95, subsequent maximum dose for this patient will be **0.0625** mg/kg throughout the study. If PRU is <95 **on any two dosing occasions** following dosing of **0.0625** mg/kg, the patient will be discontinued from further study drug.

Dose selection in this study is informed by the substantial clinical pharmacology programme for ticagrelor in adults, which included 41 studies in approximately 1000 subjects examining the exposure-response relationship, safety, and drug interactions. The dose range of ticagrelor administered during these studies was 0.1 to 1260 mg, and 900 mg was established as the maximum tolerated dose (MTD) in healthy volunteers. The approved dose regimen in adults with ACS consists of a loading dose of 180 mg followed by 90 mg twice daily for up to one year.

The 4-week duration of the second part of the study is intended to provide preliminary data on tolerability of daily dosing in children, without imposing a large burden on the patients but providing a period of potential benefit.

For doses after interim analysis please see Appendix E.

Revised text:

1.2.3 Primary and secondary outcome measures

The primary study endpoint is the evaluation of the PK and PD properties of ticagrelor and its active metabolite in children after **administration** as single doses and after attainment of steady-state following twice-daily administration of ticagrelor. PK will be determined using standard methodologies. The PD measure employed will be the VerifyNow P2Y12 assay (Jeong et al 2012) that is a well-validated and commercially available point-of-care assay to assess inhibition of the $P2Y_{12}$ platelet receptor.

1.2.4 Dose and study duration

Assessment of the first 12 randomised patients indicates that higher doses are needed in order to accomplish the primary study objective of characterising the relationship between ticagrelor dose and inhibition of platelet aggregation to support dose selection for Phase III. This amendment provides for the following revised doses: The initial single dose will be a **0.75** mg/kg (weight-based dose equivalent to **60** mg in adults). The second **single** dose of ticagrelor will be **1.125** mg/kg or **2.25** mg/kg (weight-based dose equivalent to **90** or **180** mg in adults).

For safety reasons the dosing schedule will be modified for individual patients as follows: If PRU at 2 hr following dosing of **0.75** mg/kg is <95, subsequent maximum dose for this patient will be **0.563** mg/kg throughout the study. If PRU is <95 following dosing of **0.563** mg/kg, the patient will be discontinued from further study drug.

Dose selection in this study is informed by **the interim data from the 12 first patients in this study as well as** the substantial clinical pharmacology programme for ticagrelor in adults, which included 41 studies in approximately 1000 subjects examining the exposure-response relationship, safety, and drug interactions. The dose range of ticagrelor administered during these studies was 0.1 to 1260 mg, and 900 mg was established as the maximum tolerated dose (MTD) in healthy volunteers. The approved dose regimen in adults with ACS consists of a loading dose of 180 mg followed by 90 mg twice daily for up to one year. **In adult patients with prior myocardial infarction, a dose of 60 mg twice daily is approved by the US FDA and is under review in Europe and additional countries**.

The 4-week duration of the second part of the study is intended to provide preliminary data on tolerability of daily dosing in children, without imposing a large burden on the patients but providing a period of potential benefit.

For potential further dose adjustments after monitoring of PK and PD please see Appendix E.

Section of protocol affected:

1.3 Benefit/risk and ethical assessment

Previous text:

Two randomised studies of clopidogrel in paediatric patients have been performed in infants with cyanotic congenital heart disease palliated with a systemic-to-pulmonary artery shunt, with the objective of prevention of shunt thrombosis. The largest study, CLARINET, was a randomised, double-blind, study in 906 infants aged 92 days or younger randomised to receive clopidogrel 0.2 mg/kg/day versus placebo for a median duration of 5.8 months, in addition to standard of care (Wessel et al 2013). This dose provides a level of platelet inhibition similar to that provided by a 75 mg dose in an adult (30% to 50% inhibition after stimulation with 5 μM ADP). Aspirin was administered concomitantly to 88.7% of patients in the clopidogrel group and 87.0% of patients randomised to placebo. Serious bleeding occurred in 6.5% in the clopidogrel group and 7.3% in the placebo group. These data provide substantial reassurance that 30%-50% IPA produced by treatment with a $P2Y_{12}$ inhibitor is well tolerated even in a very young and vulnerable paediatric population.

The FDA Office of Surveillance and Epidemiology (OSE) recently evaluated post-market reports of AEs in paediatric patients (ages 0-17 years) treated with clopidogrel (FDA Office Surveillance end Epidemiology report, 2013). The report concludes that there was no new safety concerns identified with the use of clopidogrel in paediatric patients.

To date, there are no safety data regarding ticagrelor treatment in patients younger than 18 years. However, 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.

Revised text:

Two randomised studies of clopidogrel in paediatric patients have been performed in infants with cyanotic congenital heart disease palliated with a systemic-to-pulmonary artery shunt, with the objective of prevention of shunt thrombosis. The largest study, CLARINET, was a randomised, double-blind, study in 906 infants aged 92 days or younger randomised to receive clopidogrel 0.2 mg/kg/day versus placebo for a median duration of 5.8 months, in addition to standard of care (Wessel et al 2013). This dose provides a level of platelet inhibition similar to that provided by a 75 mg dose in an adult (30% to 50% inhibition after stimulation with 5 μM ADP). Aspirin was administered concomitantly to 88.7% of patients in the clopidogrel group and 87.0% of patients randomised to placebo. Serious bleeding occurred in 6.5% in the clopidogrel group and 7.3% in the placebo group. These data provide substantial reassurance that 30%-50% IPA produced by treatment with a $P2Y_{12}$ inhibitor is well tolerated even in a very young and vulnerable paediatric population. **The DOVE study was a randomised, placebo controlled study of the $P2Y_{12}$ inhibitor prasugrel in children with sickle cell disease evaluating doses of prasugrel providing a mean platelet inhibition of approximately 25%. This treatment was well tolerated with no significant differences in safety results compared to placebo, and numerical reduction in rate of pain crises**

although differences were not statistically significant compared to placebo (Heeney et al 2015)

The FDA Office of Surveillance and Epidemiology (OSE) recently evaluated post-market reports of AEs in paediatric patients (ages 0-17 years) treated with clopidogrel (FDA Office Surveillance end Epidemiology report, 2013). The report concludes that there was no new safety concerns identified with the use of clopidogrel in paediatric patients.

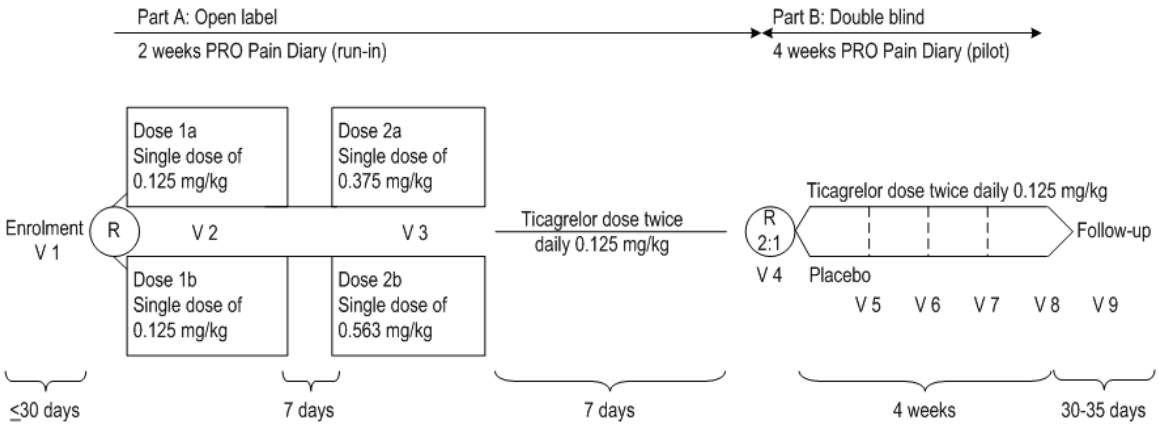
Prior to the current study, there are no safety data regarding ticagrelor treatment in patients younger than 18 years. However, more than **25,000** adult healthy subjects or patients have been exposed to ticagrelor in the completed Phase I, II, and III studies and the overall conclusion based on these studies is that ticagrelor has generally been well tolerated.

Section of protocol affected:

1.4 Study design

Previous text:

Figure 1 Study flow chart before <u>interim analysis</u>

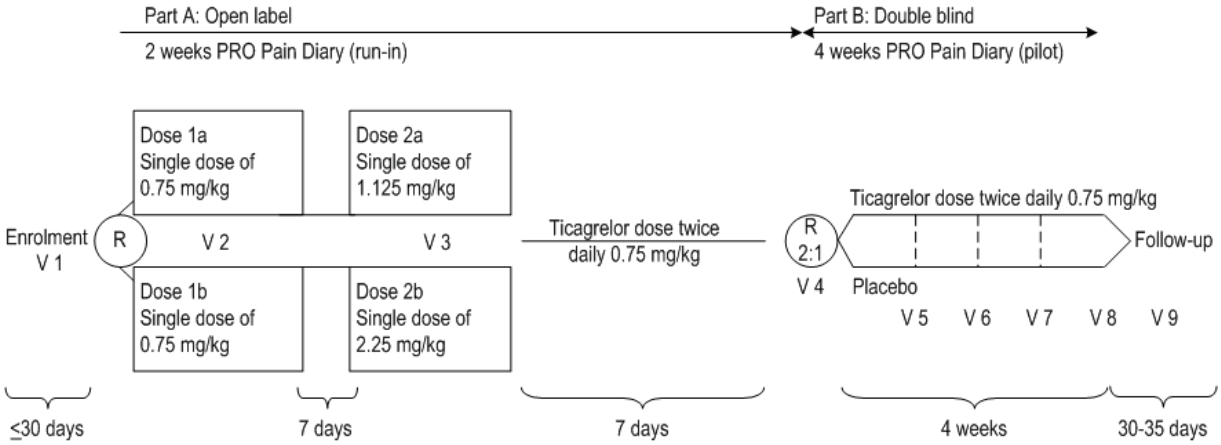


R = randomisation; PRO = patient reported outcome

For study flow chart after the interim analysis please see Appendix E.

Revised text:

Figure 1 Study flow chart



R = randomisation; PRO = patient reported outcome

~~**For study flow chart after the interim analysis please see Appendix E.**~~

Section of protocol affected:

3.1 Inclusion criteria

Previous text:

2. **Experienced at least 2 VOC requiring medical intervention during the past 12 months****

   ****VOC is defined as a painful sickle cell crisis requiring medical intervention including any of the following (1) hospitalization (2) emergency department or clinic visit (3) medically supervised outpatient treatment with escalated doses of drugs for management of painful crisis (may include oral or parenteral opioids or non-steroidal anti-inflammatory drugs).**

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

Revised text:

Inclusion criteria 2 concerning VOC in the prior 12 months has been removed.

4. If treated with an anti-sickling agent such as hydroxyurea, the weight-adjusted dose must be stable for **1** months before enrolment

Section of protocol affected:

3.2 Exclusion criteria

Previous text:

16. Previous enrolment in the present study

Revised text:

16. Previous randomisation in the present study***

***** As the eligibility criteria have been changed with this amendment, patients previously enrolled but not randomised may be reassessed for eligibility. Patients fulfilling all inclusion criteria and no exclusion criteria can be re-enrolled.**

Section of protocol affected:

3.3 Patient enrolment and randomisation

Previous text:

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 parent/both parents/legal guardian (according to local regulations) and assent or consent from the child/adolescent (where required by local regulations) before any study specific procedures are performed. Patient is considered enrolled in the study after she/he has signed the informed consent form
2. Assign 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
3. Determine patient eligibility. See Section 3.1 and 3.2. Patient who does not meet the eligibility criteria is considered as screening failure
4. Assign eligible patient unique randomisation code. Patient will be randomised twice, both in Part A and Part B and will receive 2 unique randomisation codes

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

Part A will be performed in open label fashion i.e. the patient as well as members of the study team, at investigational centres or third party vendors conducting the study or handling data, AstraZeneca R&D Supply Chain (including packaging and distribution vendors on their behalf) and bio analysis personnel analysing the PK samples will all have access to the randomisation schedule. Part B will be double blind i.e. no member of the study team at

AstraZeneca, the Steering Committee (SC), personnel at investigational centres or any contract Research Organization (CRO) handling data will have access to the randomisation scheme during the conduct of the study, with the exception of the Supply Chain Study Management department, CRO unblinded team and the Patient Safety department at AstraZeneca.

Randomisation codes will be assigned strictly sequentially as patients become eligible for randomisation for both Part A and Part B.

Revised text:

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 parent/both parents/legal guardian (according to local regulations) and assent or consent from the child/adolescent (where required by local regulations) before any study specific procedures are performed. Patient is considered enrolled in the study after she/he has signed the informed consent form**. If a patient was previously enrolled into the present study but not randomised, a new informed consent document should be signed by the parent/both parents/legal guardian (according to local legislation) and assent or consent from the child/adolescent (where required by local regulations) before any study specific procedures are performed. The patient must receive a new unique enrolment number.**

2. Assign 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

3. Determine patient eligibility. See Section 3.1 and 3.2. Patient who does not meet the eligibility criteria is considered as screening failure

4. Assign eligible patient unique randomisation code. Patient will be randomised **once or** twice, both in Part A and Part B and will receive 2 unique randomisation codes

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

Part A will be performed in open label fashion i.e. the patient as well as members of the study team, at investigational centres or third party vendors conducting the study or handling data, AstraZeneca R&D Supply Chain (including packaging and distribution vendors on their behalf) and bio analysis personnel analysing the PK samples will all have access to the randomisation schedule. Part B will be double blind i.e. no member of the study team at AstraZeneca, the Steering Committee (SC), personnel at investigational centres or any contract Research Organization (CRO) handling data will have access to the randomisation

scheme during the conduct of the study, with the exception of the Supply Chain Study Management department, CRO unblinded team and the Patient Safety department at AstraZeneca.

Randomisation codes will be assigned strictly sequentially as patients become eligible for randomisation for both Part A **and/or** Part B.

Section of protocol affected:

3.9.2 Permanent discontinuation from investigational product (active and placebo)

Previous text:

- If PRU is <95 **on any two dosing occasions following dosing of 0.0625** mg/kg, the patient will be discontinued from further study drug for safety reasons

Revised text:

- If PRU is <95 despite an individual dose reduction having already been made, the patient will be discontinued from further study drug for safety reasons.

Section of protocol affected:

4. STUDY PLAN AND TIMING OF PROCEDURES

Previous text:

Table 1 Study Plan detailing the procedures

		Part A		Part B					
Assessment	**Enrolment**	**Dose 1**	**Dose 2**	**Repeated treatment phase**				**End of treatment**	**Follow-up**
Visit	**1[m]**	**2[m]**	**3**	**4**	**5[r]**	**6**	**7[r]**	**8**	**9**
Visit window:	Days -30 to **-7** for Visit 1	±0 day for Visit 2	**+ 7 days**	+7 days	**+ 7 days**	**+ 7 days**	**+ 7 days**	**+ 7 days**	30-35 days following last dose for Visit 8[d]
Week		**0**	**1**	**2**	**3**	**4**	**5**	**6**	**10**
Day		**0**	**7**	**14**	**21**	**28**	**35**	**42**	**72-77**
Signed Informed Assent/Consent	X								
Randomisation		X		X					
Inclusion/exclusion criteria	X	X[a]							
Relevant Medical and Surgical history, SCD characteristics and history	X								
Demographics	X								
Vital signs (BP, pulse)	X	X	X	X	X[r]	X	X[r]	X	X
Physical examination	X								X
Weight, height[e]	X	X	X					X	
Transcranial Doppler exam[o]	X								
Ophthalmological (Eye) exam[o]	X								
12-lead ECG[p]	X[p]			X					
Daily pain assessment[g]	X	X	X	X	X	X	X	X	
FLACC assessment[q]	X			X					
Daily recording of analgesic use[g]	X	X	X	X	X	X	X	X	
Days absent from school/work[g]	X	X	X	X	X	X	X	X	
Administration of IP at clinic[i]		X	X	X				X	
Treatment dispensed/returned[s]			X	X[j]	X	X	X	X[j]	
Compliance/ Drug accountability		X	X	X	X	X	X	X	

Table 1 Study Plan detailing the procedures

Assessment	Enrolment	Part A Dose 1	Part A Dose 2	Part B Repeated treatment phase				Part B End of treatment	Part B Follow-up
Visit	**1[m]**	**2[m]**	**3**	**4**	**5[r]**	**6**	**7[r]**	**8**	**9**
Visit window:	Days -30 to **-7** for Visit 1	±0 day for Visit 2	**+ 7 days**	+7 days	**+ 7 days**	**+ 7 days**	**+ 7 days**	**+ 7 days**	30-35 days following last dose for Visit 8[d]
Week		**0**	**1**	**2**	**3**	**4**	**5**	**6**	**10**
Day		**0**	**7**	**14**	**21**	**28**	**35**	**42**	**72-77**
Acceptability/Palatability[h]		X							
Concomitant medication	X	X	X	X	X	X	X	X	X
Adverse event review (AEs and SAEs)	X[f]	X	X	X	X	X	X	X	X
Blood samples for haematology and clinical chemistry (incl uric acid)	X[n]			X[k]				X	
Blood samples for coagulation (INR and PTT)	X[n]								
VerifyNow™ PRU[c]		X	X	**X[l]**				**X**	
Pregnancy test (dipstick)[b]	X		**X**					**X**	
Collection of VOC in CRF		X	X	X	X	X	X	X	X
Collection of transfusion data in CRF		X	X	X	X	X	X	X	X
Collection of bleeding events in CRF		X	X	X	X	X	X	X	X
Urinalysis	X[n]			X				X	
Blood sampling for pharmacokinetics[c]		X	X	**X[l]**				**X**	

Abbreviations: AE = adverse event; BP = blood pressure; CRF = Case Report Form; ECG = electrocardiogram; eCRF = electronic Case Report Form; FLACC = Face, Legs, Activity, Cry, Consolability form; INR = International Normalised Ratio; PK = pharmacokinetics; PRU = $P2Y_{12}$ reaction units; PTT = Partial Thromboplastin Time; SAE = serious adverse event; SCD = Sickle Cell Disease; VOC = vaso-occlusive crisis

a Results from local laboratory must have been received before first dose to check eligibility criteria.
b In patient after menarche.
c Actual time of PK and PRU sampling should be recorded in the eCRF.
d May occur following earlier visits than Visit 9.
e Height only at enrolment.
f Only SAE assessed at this time.
g Electronic diary recording by patient ≥4 years (when needed with parent/guardian help).
h Questions assessed by nurse in children <6 years, Hedonic Faces Scale (HFS) for children ≥6 years
i Actual time of dosing should be recorded in the eCRF.

j The time of drug administration in the morning and evening before Visit 4 and 8 will be registered in a patient diary.
k Blood sample for haematology and clinical chemistry (including uric acid) at Visit 4 will be collected 2h post-dose together with PK and PRU.
l **PK and PRU sampling at Visit 4 will be performed at 2 hours post-dose ONLY.**
m Visit 2 should be at least **7** days apart from Visit 1.
n Laboratory testing performed prior to Visit 1 as part of usual clinical care does not need to be repeated as long as the values were obtained within 30 days prior to Visit 2.
o The most recent examination must be performed within 12 months before Visit 1. If this is not the case, the examination must be done before proceeding in the study.
p 12-lead ECG must be performed within 6 months before Visit 1. If this is not the case, the examination must be done before proceeding in the study.
q FLACC for patients aged from 2 to <4 years only to be collected between Visit 1 and Visit 2, and between Visit 4 and Visit 5.
r Visit 5 and Visit 7 may be performed as telephone contacts, based on the opinion of the Investigator. Vital signs (BP and pulse) will only be measured if the patient visits the site.
s If Visit 5 and/or Visit 7 are performed as telephone contacts, doubles kits of study treatment will be dispended on Visit 4 and/or Visit 6 to cover the whole period.

During visits when investigational product is administered at clinic perform the following protocol procedures prior to administration of study drug (if applicable to the visit):

Review of AEs and concomitant medications, vital signs, weight, ECG, urine sampling (including pregnancy test if applicable), and pre-dose blood sampling (safety, PK, PD).

Table 2 Blood sampling in patients with a weight of >21 kg

Assessment	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
Coagulation (INR and PTT)	X								
Haematology and clinical chemistry (incl uric acid)	X			2h post-dose				X	
VerifyNow™ PRU		Pre-dose, 2, 6h post-dose	Pre-dose, 2, 6h post-dose	2h post-dose				**Pre-dose, 2h post-dose**	
Blood sampling for pharmacokinetics		1, 2, 4, 6h post-dose	1, 2, 4, 6h post-dose	**2h post-dose**				**Pre-dose, 1, 2, 4h post-dose**	

Abbreviations: INR = International Normalised Ratio; PK = pharmacokinetics; PRU = $P2Y_{12}$ reaction units; PTT = Partial Thromboplastin Time
The 1, 2, 4, and 6 hour samples can be collected ±15 minutes from actual post-dose time point.
If applicable, PRU and PK sampling should be arranged at the same time to avoid repeated venipuncture.
A peripheral catheter can be used for blood sampling.

Table 3 Blood sampling in patients with a weight of 16-21 kg

Assessment	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
Coagulation (INR and PTT)	X								
Haematology and clinical chemistry (incl uric acid)	X			2h post-dose				X	
VerifyNow™ PRU		Pre-dose, 2h post-dose	Pre-dose, 2h post-dose	2h post-dose				**Pre-dose, 2h post-dose**	
Blood sampling for pharmacokinetics		1, 2, 4, 6h post-dose	1, 2, 4, 6h post-dose	**2h post-dose**				**Pre-dose, 2h post-dose**	

Abbreviations: INR = International Normalised Ratio; PK = pharmacokinetics; PRU = $P2Y_{12}$ reaction units; PTT = Partial Thromboplastin Time
The 1, 2 and 4 and 6 hour samples can be collected ±15 minutes from actual post-dose time point.
If applicable, PRU and PK sampling should be arranged at the same time to avoid repeated venipuncture.
A peripheral catheter can be used for blood sampling.

Revised text:

Table 1 Study Plan detailing the procedures

Assessment	Part A			Part B					
	Enrolment	Dose 1	Dose 2	Repeated treatment phase				End of treatment	Follow-up
Visit	**1[m]**	**2[m]**	**3**	**4[l]**	**5[r]**	**6**	**7[r]**	**8**	**9[l]**
Week		**0**	**1**	**2**	**3**	**4**	**5**	**6**	**10**
Day (Visit window)	**-30 - -14**	**0**	**7 (+3)**	**14 (+7)**	**21 (+3)**	**28 (+3)**	**35 (+3)**	**42 (+3)**	**72-77** 30-35 days following last dose for Visit 8 **(or Visit 4)[d]**
Signed Informed Assent/Consent	X								
Randomisation		X		X					
Inclusion/exclusion criteria	X	X[a]							
Relevant Medical and Surgical history, SCD characteristics and history	X								
Demographics	X								
Vital signs (BP, pulse)	X	X	X	X	X[r]	X	X[r]	X	X
Physical examination	X								X
Weight, height[e]	X	X	X					X	
Transcranial Doppler exam[o]	X								
Ophthalmological (Eye) exam[o]	X								
12-lead ECG[p]	X[p]			X					
Daily pain assessment[g]	X	X	X	X	X	X	X	X	
FLACC assessment[q]	X			X					
Daily recording of analgesic use[g]	X	X	X	X	X	X	X	X	
Days absent from school/work[g]	X	X	X	X	X	X	X	X	
Administration of IP at clinic[i]		X	X	X				X	
Treatment dispensed/returned[s]			X	X[j]	X	X	X	X[j]	
Compliance/ Drug accountability		X	X	X	X	X	X	X	
Acceptability/Palatability[h]		X							

Table 1 Study Plan detailing the procedures

Assessment	Part A			Part B					
	Enrolment	Dose 1	Dose 2	Repeated treatment phase				End of treatment	Follow-up
Visit	**1[m]**	**2[m]**	**3**	**4[l]**	**5[r]**	**6**	**7[r]**	**8**	**9[l]**
Week		**0**	**1**	**2**	**3**	**4**	**5**	**6**	**10**
Day (Visit window)	**-30 - -14**	**0**	**7 (+3)**	**14 (+7)**	**21 (+3)**	**28 (+3)**	**35 (+3)**	**42 (+3)**	**72-77** 30-35 days following last dose for Visit 8 **(or Visit 4)[d]**
Concomitant medication	X	X	X	X	X	X	X	X	X
Adverse event review (AEs and SAEs)	X[f]	X	X	X	X	X	X	X	X
Blood samples for haematology and clinical chemistry (incl uric acid)	X[n]			X[k]				X	
Blood samples for coagulation (INR and PTT)	X[n]								
VerifyNow™ PRU[c]		X	X	X					
Pregnancy test (dipstick)[b]	X	X		X[b]				X	
Collection of VOC in CRF		X	X	X	X	X	X	X	X
Collection of transfusion data in CRF		X	X	X	X	X	X	X	X
Collection of bleeding events in CRF		X	X	X	X	X	X	X	X
Urinalysis	X[n]			X				X	
Blood sampling for pharmacokinetics[c]		X	X	X					

Abbreviations: AE = adverse event; BP = blood pressure; CRF = Case Report Form; ECG = electrocardiogram; eCRF = electronic Case Report Form; FLACC = Face, Legs, Activity, Cry, Consolability form; INR = International Normalised Ratio; PK = pharmacokinetics; PRU = $P2Y_{12}$ reaction units; PTT = Partial Thromboplastin Time; SAE = serious adverse event; SCD = Sickle Cell Disease; VOC = vaso-occlusive crisis

a Results from local laboratory must have been received before first dose to check eligibility criteria.
b In patient after menarche. **Pregnancy testing at Visit 4 is only applicable for patients NOT performing Part B.**
c Actual time of PK and PRU sampling should be recorded in the eCRF. **See Table 2 and Table 3 for PK sampling time points.**
d May occur following earlier visits than Visit 9.
e Height only at enrolment.
f Only SAE assessed at this time.
g Electronic diary recording by patient ≥4 years (when needed with parent/guardian help).

h Questions assessed by nurse in children <6 years, Hedonic Faces Scale (HFS) for children ≥6 years
i Actual time of dosing should be recorded in the eCRF.
j The time of drug administration in the morning and evening before Visit 4 and 8 will be registered in a patient diary.
k Blood sample for haematology and clinical chemistry (including uric acid) at Visit 4 will be collected 2h post-dose together with PK and PRU.
l If patient only participates in Part A, the follow-up Visit 9 should be performed after Visit 4 according to schedule.
m Visit 2 should be at least **14** days apart from Visit 1.
n Laboratory testing performed prior to Visit 1 as part of usual clinical care does not need to be repeated as long as the values were obtained within 30 days prior to Visit 2.
o The most recent examination must be performed within 12 months before Visit 1. If this is not the case, the examination must be done before proceeding in the study.
p 12-lead ECG must be performed within 6 months before Visit 1. If this is not the case, the examination must be done before proceeding in the study.
q FLACC for patients aged from 2 to <4 years only to be collected between Visit 1 and Visit 2, and between Visit 4 and Visit 5.
r Visit 5 and Visit 7 may be performed as telephone contacts, based on the opinion of the Investigator. Vital signs (BP and pulse) will only be measured if the patient visits the site.
s If Visit 5 and/or Visit 7 are performed as telephone contacts, doubles kits of study treatment will be dispended on Visit 4 and/or Visit 6 to cover the whole period.

During visits when investigational product is administered at clinic perform the following protocol procedures prior to administration of study drug (if applicable to the visit):

Review of AEs and concomitant medications, vital signs, weight, ECG, urine sampling (including pregnancy test if applicable), and pre-dose blood sampling (safety, PK, PD).

Table 2 Blood sampling in patients with a weight of >21 kg

Assessment	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
Coagulation (INR and PTT)	X								
Haematology and clinical chemistry (incl uric acid)	X			2h post-dose				X	
VerifyNow™ PRU		Pre-dose, 2h, 6h post-dose	Pre-dose, 2, 6h post-dose	**Pre-dose,** 2h post-dose					
Blood sampling for pharmacokinetics		1, 2, 4, 6h post-dose	1, 2, 4, 6h post-dose	**Pre-dose, 1,** 2h **post-dose**					

Abbreviations: INR = International Normalised Ratio; PK = pharmacokinetics; PRU = $P2Y_{12}$ reaction units; PTT = Partial Thromboplastin Time
The 1, 2, 4, and 6 hour samples can be collected ±15 minutes from actual post-dose time point.
If applicable, PRU and PK sampling should be arranged at the same time to avoid repeated venipuncture.

A peripheral catheter can be used for blood sampling.

Table 3 Blood sampling in patients with a weight of 16-21 kg

Assessment	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
Coagulation (INR and PTT)	X								
Haematology and clinical chemistry (incl uric acid)	X			2h post-dose				X	
VerifyNow™ PRU		Pre-dose, 2h post-dose	Pre-dose, 2h post-dose	**Pre-dose,** 2h post-dose					
Blood sampling for pharmacokinetics		1, 2, 4, 6h post-dose	1, 2, 4, 6h post-dose	**Pre-dose, 1,** 2h post-dose					

Abbreviations: INR = International Normalised Ratio; PK = pharmacokinetics; PRU = $P2Y_{12}$ reaction units; PTT = Partial Thromboplastin Time
The 1, 2 and 4 and 6 hour samples can be collected ±15 minutes from actual post-dose time point.
If applicable, PRU and PK sampling should be arranged at the same time to avoid repeated venipuncture.
A peripheral catheter can be used for blood sampling.

Section of protocol affected:

4.1 Treatment period

Previous text:

At least a **7**-day interval is needed between Visit 1 and Visit 2 to allow for the recording of the baseline data on patient diary (see Section 5.1.2)

Revised text:

At least a **14**-day interval is needed between Visit 1 and Visit 2 to allow for the recording of the baseline data on patient diary (see section 5.1.2) **and to separate the blood sampling in time considering total blood sampling volume recommendations in children.**

Section of protocol affected:

4.2 Treatment period

Previous text:

Part A:

Visit 2 & 3: Randomisation will take place **7** to 30 days after enrolment. Patients will be randomised 1:1 to receive one of two dosing schedules, with each dose separated by 7 days. Platelet aggregation will be measured using the VerifyNow™ P2Y12 assay and reported as PRU. PRU will determine continued dosing. Patients are not allowed to eat 2 hours before and 1 hour after dosing at these visits. Palatability assessment will be performed (Visit 2). A study nurse will assess palatability directly after administration of dose (for more information see Section 5.3). The patients will be allowed to leave the clinic after all sampling has been completed. Following the 2 single doses, all patients will receive open-label one-week treatment with ticagrelor twice daily to determine tolerability prior to randomisation into Part B. Dose to be administered twice daily within a 9-12 hours interval (starting in the evening the same day as Visit 3). For assessments performed during the visits see Table 1. **For dosing before interim analysis see Figure 2 and for dosing after interim analysis see Appendix E.**

Part B:

Visit 4, 5, 6, 7 & 8: The patient will register actual date and time of drug administration the morning and evening before Visit 4 in a Dosing Diary. He/she will be instructed to not take their dose at home in the morning of Visit 4. Study drug will be administered at the clinic and actual time of dosing should be recorded in the eCRF at Visit 4. Patients will be randomised (2:1 ratio) to ticagrelor twice daily or placebo for a 4-week treatment phase and will return to the clinic on a weekly basis for study related procedures. Visit 5 and Visit 7 may optionally be performed as telephone contacts, based on the opinion of the Investigator (See Table 1, Visit 4-8). **The patient will register actual date and time of drug administration the morning and evening before Visit 8 in a Dosing Diary**. **He/she will be instructed to not take their dose at home in the morning of Visit 8. Study drug will be administered at the clinic and actual time of dosing should be recorded in the eCRF at Visit 8**. **For dosing before interim analysis see Figure 2 and for dosing after interim analysis see Appendix E.**

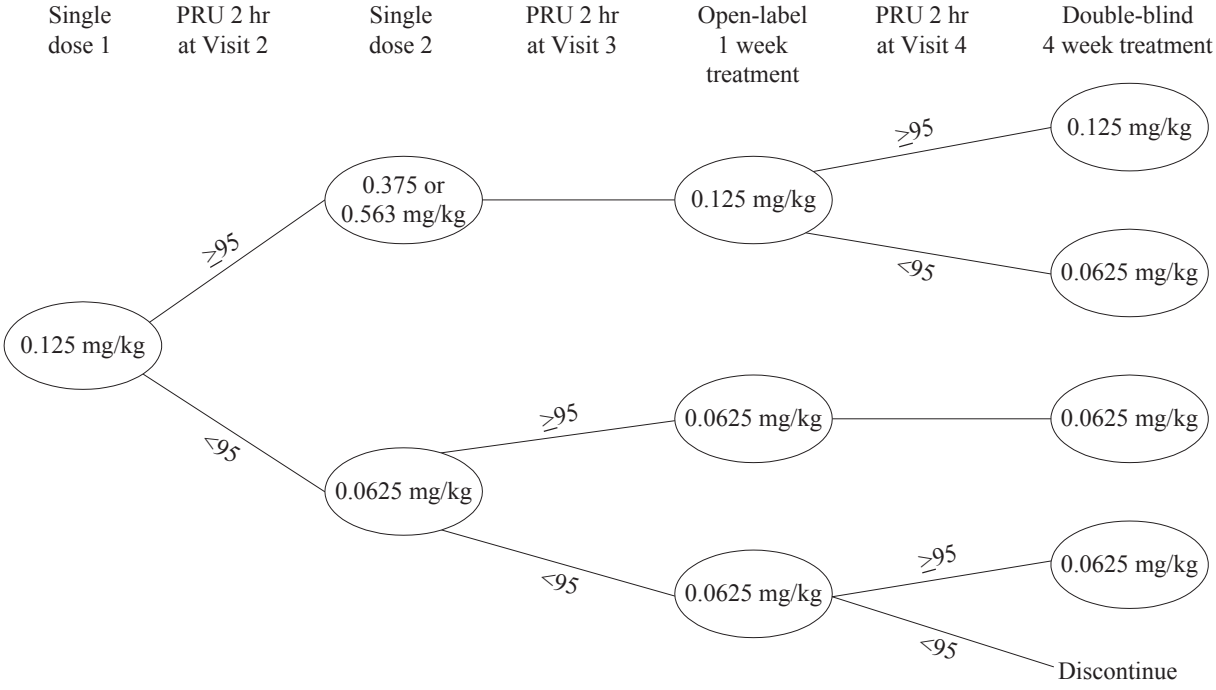
Patients will be followed for the occurrence of VOC events and for other disease manifestations such as daily pain, analgesic use, and complications of SCD throughout the study. Daily pain (ages ≥4 years only) and analgesic use will be reported by the patient (or if needed with the help of parent/guardian) using an electronic diary (for more information see Section 5.3). Specification of whether analgesics have been opiod or non-opiod will be done at follow-up site visit. Days of absence from school or work (ages ≥6 years only) will be collected weekly using the same electronic device.

For safety reasons the dosing schedule will be modified for individual patients based on their PRU at Visit 2, 3 and 4 (see Figure 2). The dose modifications may occur at Visit 2, 3 and 4.

After 12 patients have completed dosing in Part A, a PK/PD evaluation (interim analysis) of the data will be conducted and the dose for the repeated dosing in both Part A and B for the remaining patients may be adjusted (aiming for a mean reduction in PRU 2 hour post-dose of 45%) see Section 8.6.

Enrolment into the study will not be stopped during the interim analysis. For dosing of ticagrelor see Figure 2.

Figure 2 Dosing schedule before interim analysis



Revised text:

Part A:

Visit 2, 3 &4: Randomisation will take place **14** to 30 days after enrolment. Patients will be randomised 1:1 to receive one of two dosing schedules, with each dose separated by 7 days. Platelet aggregation will be measured using the VerifyNow™ P2Y12 assay and reported as PRU. PRU will determine continued dosing. Patients are not allowed to eat 2 hours before and 1 hour after dosing at these visits. Palatability assessment will be performed (Visit 2). A study nurse will assess palatability directly after administration of dose (for more information see Section 5.3). The patients will be allowed to leave the clinic after all sampling has been completed. Following the 2 single doses, all patients will receive open-label one-week treatment with ticagrelor twice daily to determine tolerability prior to randomisation into Part B. Dose to be administered twice daily within a 9-12 hours interval (starting in the evening the same day as Visit 3). For assessments performed during the visits see Table 1**.**
For dosing see Figure 2, and Appendix E in case of potential change to dosing schedule.

Patients only participating in Part A will complete Visit 4, see below, which will be their last visit on treatment and after Visit 4 perform Visit 9 (30-35 days following last dose for Visit 4).

Part B:

Visit 4, 5, 6, 7 & 8: Visit 4 will be performed in all patients, including those not continuing to Part B. Participation in Part B is optional. The patient will register actual date and time of drug administration the morning and evening before Visit 4 in a Dosing Diary. He/she will be instructed to not take their dose at home in the morning of Visit 4. Study drug will be administered at the clinic and actual time of dosing should be recorded in the eCRF at Visit 4. **For patients not participating in Part B, visit 4 will be the last visit on treatment. For patients continuing into Part B,** patients will be randomised (2:1 ratio) to ticagrelor twice daily or placebo for a 4-week treatment phase and will return to the clinic on a weekly basis for study related procedures. Visit 5 and Visit 7 may optionally be performed as telephone contacts, based on the opinion of the Investigator (See Table 1, Visit 4-8). ~~The patient will register actual date and time of drug administration the morning and evening before Visit 8 in a Dosing Diary~~. ~~He/she will be instructed to not take their dose at home in the morning of Visit 8. Study drug will be administered at the clinic and actual time of dosing should be recorded in the eCRF at Visit 8~~. **For dosing see Figure 2, and Appendix E in case of potential change to dosing schedule.** ~~For dosing before interim analysis see Figure 2 and for dosing after interim analysis see Appendix E.~~

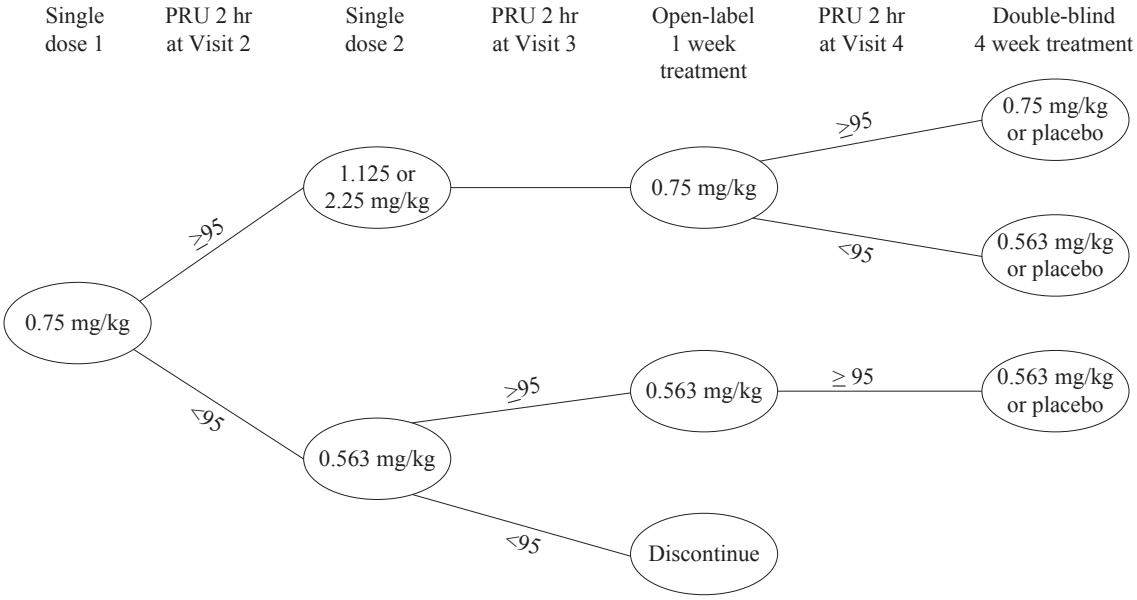
Patients will be followed for the occurrence of VOC events and for other disease manifestations such as daily pain, analgesic use, and complications of SCD throughout the study. Daily pain (ages ≥4 years only) and analgesic use will be reported by the patient (or if needed with the help of parent/guardian) using an electronic diary (for more information see Section 5.3) Specification of whether analgesics have been opiod or non-opiod will be done at follow-up site visit. Days of absence from school or work (ages ≥6 years only) will be collected weekly using the same electronic device.

For safety reasons the dosing schedule will be modified for individual patients based on their PRU at Visit 2, 3 and 4 (see Figure 2). The dose modifications may occur at Visit 2, 3 and 4.

~~After 12 patients have completed dosing in Part A, a PK/PD evaluation (interim analysis) of the data will be conducted and the dose for the repeated dosing in both Part A and B for the remaining patients may be adjusted (aiming for a mean reduction in PRU 2 hour post-dose of 45%) see Section 8.6.~~

~~Enrolment into the study will not be stopped during the interim analysis. For dosing of ticagrelor see Figure 2~~

Figure 2 Dosing schedule



Section of protocol affected:

5.2.1 Laboratory safety assessments

Previous text:

Urinalysis is to be performed at the investigational site by dipstick. A urine pregnancy test (U-HCG) will be taken at Visit 1 and repeated at **Visit 3 and Visit 8** in females of childbearing potential. If female patients achieve menarche during the study, a urine pregnancy test should be performed before any study procedures at the next visit.

Revised text:

Urinalysis is to be performed at the investigational site by dipstick. A urine pregnancy test (U-HCG) will be taken at Visit 1, **Visit 2** and repeated at **Visit 4 (for patients only completing Part A) or Visit 8 (for patients completing Part B)** in females of childbearing potential. If female patients achieve menarche during the study, a urine pregnancy test should be performed before any study procedures at the next visit.

Section of protocol affected:

5.8 Volume of blood

Previous text:

Table 6 Volume of blood to be drawn from patients with a weight >21 kg

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 8	Total volume Visit 8 (mL)	Total (mL)
Haematology	1.2	1	1.2	0	0	0	0	1	1.2	1	1.2	
Clinical Chemistry	1.1	1	1.1	0	0	0	0	1	1.1	1	1.1	
Coagulation	1.2	1	1.2	0	0	0	0	0	0	0	0	
Pharmacokinetic	1.2	0	0	4	4.8	4	4.8	**1**	**1.2**	**4**	**4.8**	
PRU*	4.0	0	0	3	12.0	3	12	**1**	4	2	8	
Total			3.5		**16.8**		**16.8**		**7.5**		**15.1**	**59.7**

* PRU sampling via a central catheter may require up to an additional 3 mL at each PRU sampling timepoint.

Table 7 Volume of blood to be drawn from patient with a weight of 16-21 kg

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 8	Total volume Visit 8 (mL)	Total (mL)
Haematology	1.2	1	1.2	0	0	0	0	1	1.2	1	1.2	
Clinical Chemistry	1.1	1	1.1	0	0	0	0	1	1.1	1	1.1	
Coagulation	1.2	1	1.2	0	0	0	0	0	0	0	0	
Pharmacokinetic	1.2	0	0	4	4.8	4	4.8	**1**	**1.2**	**2**	**2.4**	
PRU*	4.0	0	0	2	8	2	8	1	4	2	8	
Total			3.5		**12.8**		**12.8**		**7.5**		**12.7**	**49.3**

* PRU sampling via a central catheter may require up to an additional 3 mL at each PRU sampling timepoint.

Revised text:

Table 6 Volume of blood to be drawn from patients with a weight >21 kg

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 8	Total volume Visit 8 (mL)	Total (mL)
Haematology	1.2	1	1.2	0	0	0	0	1	1.2	1	1.2	
Clinical Chemistry	1.1	1	1.1	0	0	0	0	1	1.1	1	1.1	
Coagulation	1.2	1	1.2	0	0	0	0	0	0	0	0	
Pharmacokinetic	1.2	0	0	2	2.4	2	2.4	**1**	**1.2**	**0**	**0**	
PRU*	4.0	0	0	1	4.0	1	4.0	**0**	**0**	**0**	**0**	
Pharmacokinetic + PRU**	4.2	0	0	2	8.4	2	8.4	**2**	**8.4**	0	0	
Total			3.5		**14.8**		**14.8**		**11.9**		**2.3**	**47.3**

* PRU sampling via a central catheter may require up to an additional 3 mL at each PRU sampling timepoint.

**** Timepoint with both PRU + PK required volume is 4.2 mL total for both.**

Table 7 Volume of blood to be drawn from patient with a weight of 16-21 kg

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 8	Total volume Visit 8 (mL)	Total (mL)
Haematology	1.2	1	1.2	0	0	0	0	1	1.2	1	1.2	
Clinical Chemistry	1.1	1	1.1	0	0	0	0	1	1.1	1	1.1	
Coagulation	1.2	1	1.2	0	0	0	0	0	0	0	0	
Pharmacokinetic	1.2	0	0	3	3.6	3	3.6	**1**	**1.2**	**0**	**0**	
PRU*	4.0	0	0	1	4.0	1	4.0	**0**	**0**	**0**	**0**	
Pharmacokinetic + PRU**	4.2	0	0	1	4.2	1	4.2	**2**	8.4	0	**0**	
Total			3.5		**11.8**		**11.8**		**11.9**		**2.3**	**41.3**

* PRU sampling via a central catheter may require up to an additional 3 mL at each PRU sampling timepoint.

**** Timepoint with both PRU + PK required volume is 4.2 mL total for both.**

The maximum blood withdrawal during any 4 week period is 41.5 mL for patients weighing >21 kg and 35.5 mL for patients weighing 16-21 kg.

Section of protocol affected:

7.1 Identity of investigational product(s)

Previous text:

Investigational product	Dosage form and strength	Manufacturer
Ticagrelor	**Granules for oral suspension 10 mg**	**Almac Pharma Services**
Ticagrelor	Granules for oral suspension 45 mg	Almac Pharma Services
Matching placebo for Ticagrelor	Granules for oral suspension	Almac Pharma Services

Revised text:

Investigational product	Dosage form and strength	Manufacturer
~~**Ticagrelor**~~	~~**Granules for oral suspension 10 mg**~~	~~**Almac Pharma Services**~~
Ticagrelor	Granules for oral suspension 45 mg	Almac Pharma Services
Matching placebo for Ticagrelor	Granules for oral suspension	Almac Pharma Services

Section of protocol affected:

7.2 Dose and treatment regimens

Previous text:

Part A:

Open-label single doses (Visit 2 and 3):

All patients will receive **0.125** mg/kg as their initial dose, followed 7 days later by **0.375** mg/kg or **0.563** mg/kg. Single doses will be administered at the clinic by site staff. Patients are not allowed to eat 2 hours before and 1 hour after dosing at Visit 2 and 3.

Repeated dosing (Visit 3-4):

Patients will self-administer **0.125** mg/kg of open label ticagrelor for 1 week. Dose to be administered twice daily within a 9-12 hours interval. The first dose will be administered in the evening the same day as Visit 3.

Following an evaluation of the first 12 patients, the repeated treatment dose may be adjusted to 0.0625 mg/kg, 0.125 mg/kg or 0.25 mg/kg (see Section 8.6).

Part B:

Repeated dosing (Visit 4-8):

Randomisation to twice daily treatment with ticagrelor or placebo will occur at Visit 4. Patients will self-administer **0.125** mg/kg of ticagrelor dose or placebo for 4 weeks. Dose will be

administered twice daily within a 9-12 hours interval. The first dose will be administered in the evening the same day as Visit 4.

Revised text:

Part A:

Open-label single doses (Visit 2 and 3):

All patients will receive **0.75** mg/kg as their initial single dose, followed 7 days later by **1.125**mg/kg or **2.25** mg/kg. Single doses will be administered at the clinic by site staff. Patients are not allowed to eat 2 hours before and 1 hour after dosing at Visit 2 and 3.

Repeated dosing (Visit 3-4):

Patients will self-administer **0.75** mg/kg of open label ticagrelor for 1 week. Dose to be administered twice daily within a 9-12 hours interval. The first dose will be administered in the evening the same day as Visit 3.

Doses may be adjusted following assessment by AstraZeneca and the Steering Committee of open label Part A results in the first 6-12 patients. Dose adjustment decisions will be based upon a review of PK, PD and adverse events (see Section 8.6).

Part B:

Repeated dosing (Visit 4-8):

Randomisation to twice daily treatment with ticagrelor or placebo will occur at Visit 4. Patients will self-administer **0.75** mg/kg of ticagrelor dose or placebo for 4 weeks. Dose will be administered twice daily within a 9-12 hours interval. The first dose will be administered in the evening the same day as Visit 4.

Doses may be adjusted following assessment by AstraZeneca and the Steering Committee of open label Part A results in the first 6-12 patients. Dose adjustment decisions will be based upon a review of PK, PD and adverse events (see Section 8.6).

Section of protocol affected:

7.5 Compliance

Previous text:

Compliance will also be checked by measurement of PRU at Visit 8.

Revised text:

Compliance will also be checked by measurement of PRU at **Visit 4 and** Visit 8 **(if applicable)**.

Section of protocol affected:

8.5 Statistical analyses

Previous text:

A t-test will be performed for each of these variables at 5% significance level. The p-value and a 95% confidence interval for the difference between ticagrelor and placebo will be reported. There will be no adjustment for multiple comparisons. If it is inappropriate to assume a normal distribution, a Wilcoxon rank sum test may be performed. In case more than one adult equivalent dose is studied in Part B, the analysis will be repeated both for all ticagrelor doses versus placebo and for the dose the majority of patients received versus placebo.

Revised text:

A t-test will be performed for each of these variables at 5% significance level, **provided that the efficacy analysis set contains at least 30 patients, otherwise only descriptive statistics will be used.** The p-value and a 95% confidence interval for the difference between ticagrelor and placebo will be reported. There will be no adjustment for multiple comparisons. If it is inappropriate to assume a normal distribution, a Wilcoxon rank sum test may be performed. In case more than one adult equivalent dose is studied in Part B, the analysis will be repeated both for all ticagrelor doses versus placebo and for the dose the majority of patients received versus placebo.

Section of protocol affected:

8.6 Interim analysis

Previous text:

8.6 Interim analysis

An interim analysis will be conducted after 12 patients have completed Part A. **The average PRU reduction from baseline at 2 hours post-dose at Visit 4 will be used for a potential adjustment of the dose in the 7 days repeated dosing in Part A and in Part B for subsequent patients. PRU values from patients on 0.0625 mg/kg will not be included in the average. The new dose will be determined as follows:**

- **If mean PRU reduction >60% and ≤80%, a ticagrelor dose of 0.0625 mg/kg will be administered to the remaining patients**
- **If mean PRU reduction ≥30% and ≤60%, a ticagrelor dose of 0.125 mg/kg will be administered to the remaining patients**
- **If mean PRU reduction <30% and ≥20%, a ticagrelor dose equivalent to 0.25 mg/kg in adults will be administered to the remaining patients**
- **If mean PRU reduction <20% or >80%, an analysis integrating all data from the single doses and the repeated dosing in Part A will be used to adjust the dose. An amendment will be submitted with the new dose**

For more details on dose adjustment see Appendix E.

Revised text:

8.6 Interim analysis and potential further dose adjustments

An interim analysis was conducted per protocol after 12 patients had completed dosing in part A. The mean PRU reduction 2 hours post-dose at Visit 4 was <20%, and plasma ticagrelor concentrations were lower than expected. This triggered a protocol amendment to increase the weight-adjusted dosing in order to achieve a higher level of platelet inhibition.

Doses may be further adjusted following assessment by AstraZeneca and the Steering Committee of Part A results in the first 6-12 patients randomised under this amendment. Dose adjustment decisions will be based upon a review of PK, PD and adverse events and will apply only to patients randomised subsequent to the dose change decision.

For more details on **potential** dose adjustment see Appendix E.

Section of protocol affected:

9.3 Study timeline and end of study

Previous text:

The study is expected to start in Q3 2014 and to end by **Q2 to Q3 2015**.

Revised text:

The study is expected to start in Q3 2014 and to end by Q1 2017.

Section of protocol affected:

Appendix E

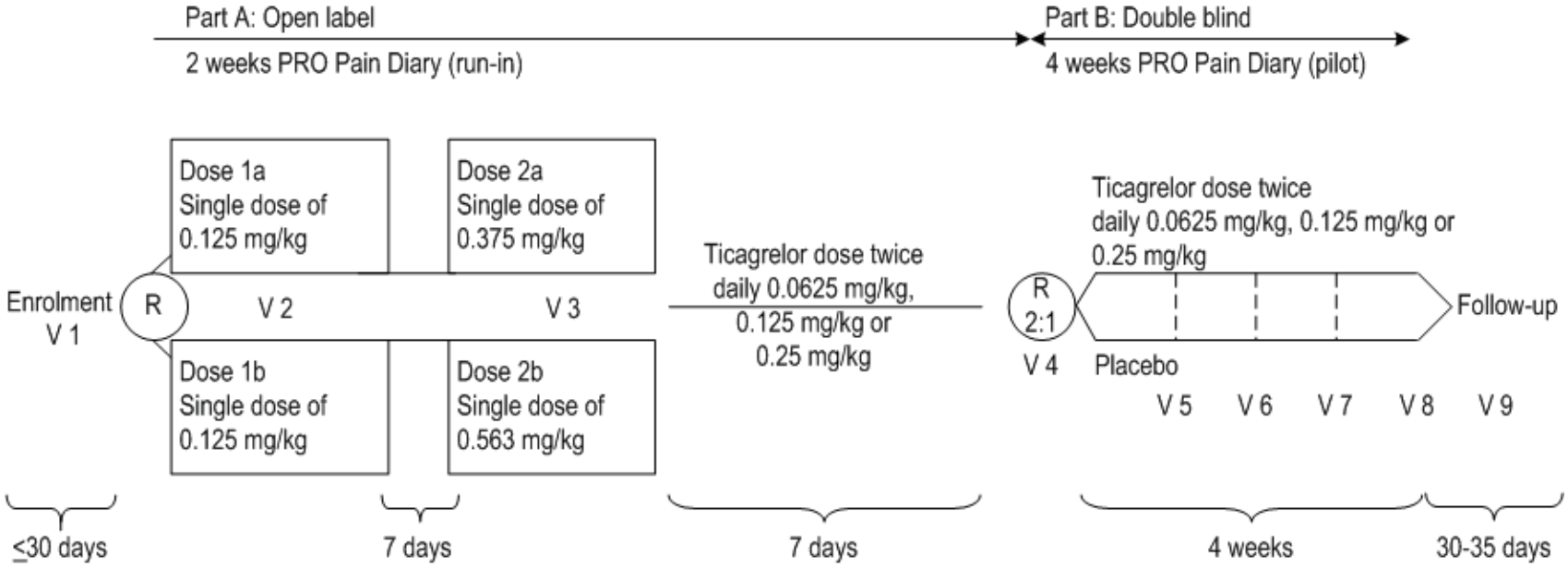
Previous text:

An interim analysis will be conducted after 12 patients have completed part A. The average PRU reduction from baseline at 2 hours post-dose at Visit 4 will be used for a potential adjustment of the dose in the 7 days repeated dosing in part A and in part B for subsequent patients. PRU values from patients on 0.0625 mg/kg will not be included in the average. The new dose and will be determined as follows:

- **If mean PRU reduction >60% and ≤80%, a ticagrelor dose of 0.0625 mg/kg will be administered to the remaining patients**
- **If mean PRU reduction ≥30% and ≤60%, a ticagrelor dose of 0.125 mg/kg will be administered to the remaining patients**
- **If mean PRU reduction <30% and ≥20%, a ticagrelor dose equivalent to 0.25 mg/kg in adults will be administered to the remaining patients**
- **If mean PRU reduction <20% or >80%, an analysis integrating all data from the single doses and the repeated dosing in part A will be used to adjust the dose. An amendment will be submitted with the new dose**

Figure 1 in this Appendix will replace Figure 1 in the main body of the Clinical Study Protocol after **the interim analysis**, see Section 1.4.

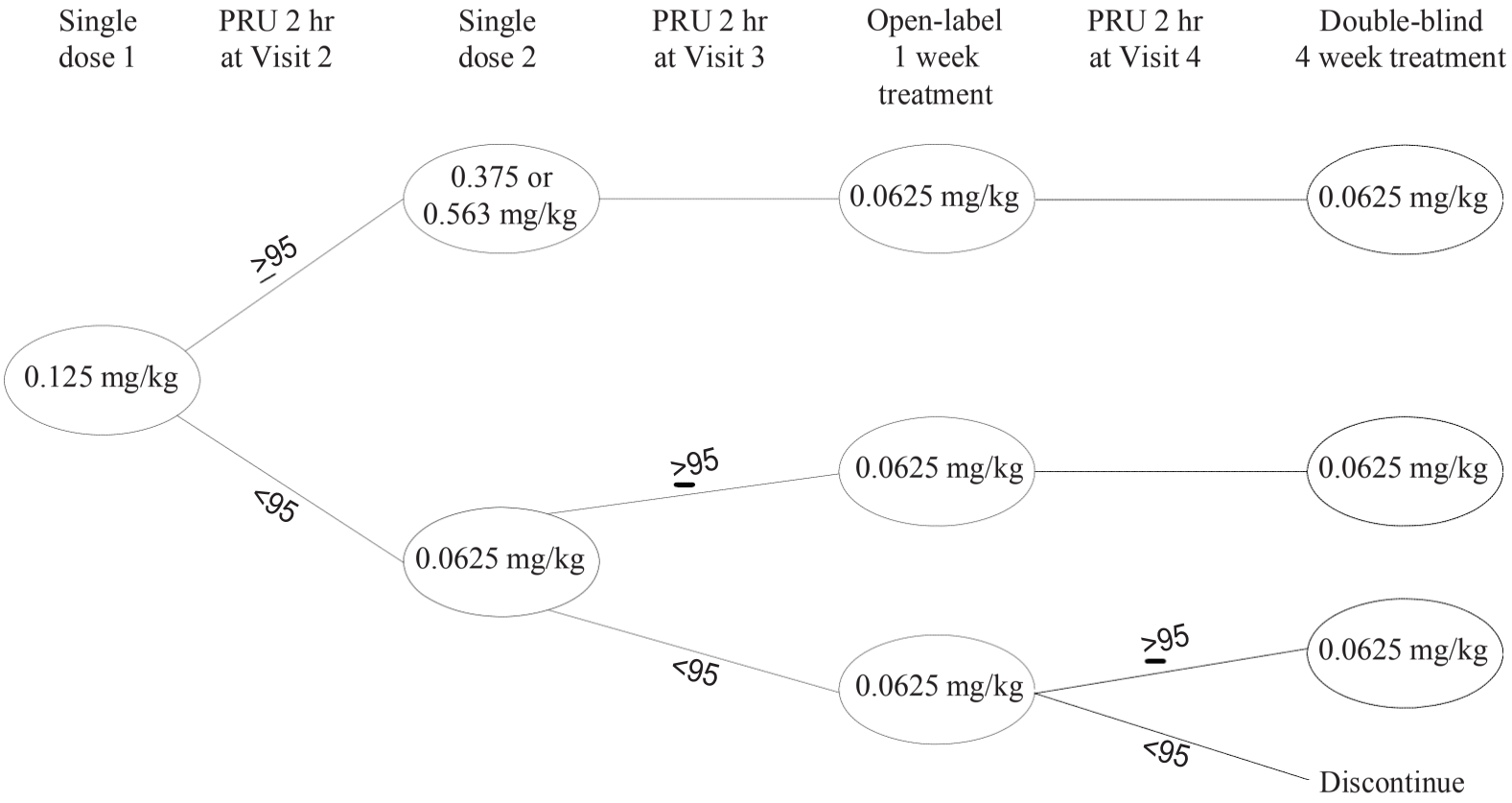
Figure 1 Study flow chart after interim analysis



Patients enrolled subsequent to the interim analysis will follow the dosing schedule shown in Figure 2 if mean PRU reduction in the interim analysis is >60% and ≤80%.

Figure 2 in this Appendix will replace Figure 2 in the main body of the Clinical Study Protocol after the interim analysis, see Section 4.2.

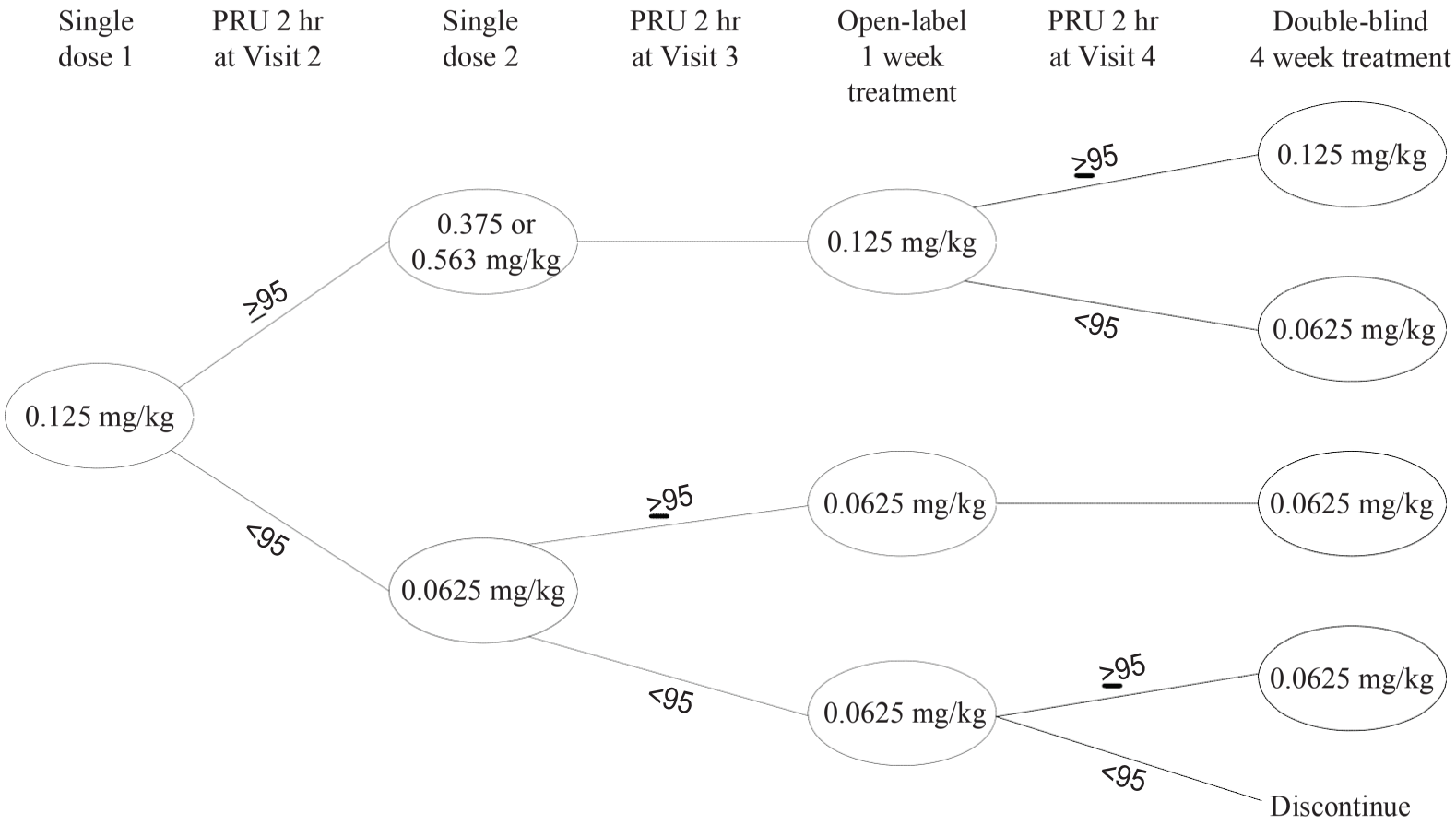
Figure 2 Dosing schedule after interim analysis, Repeated dose 0.0625 mg/kg



Patients enrolled subsequent to the interim analysis will follow the dosing schedule shown in Figure 3 if mean PRU reduction in the interim analysis is ≥30% and ≤60%.

Figure 3 in this Appendix will replace Figure 2 in the main body of the Clinical Study Protocol after the interim analysis, see Section 4.2.

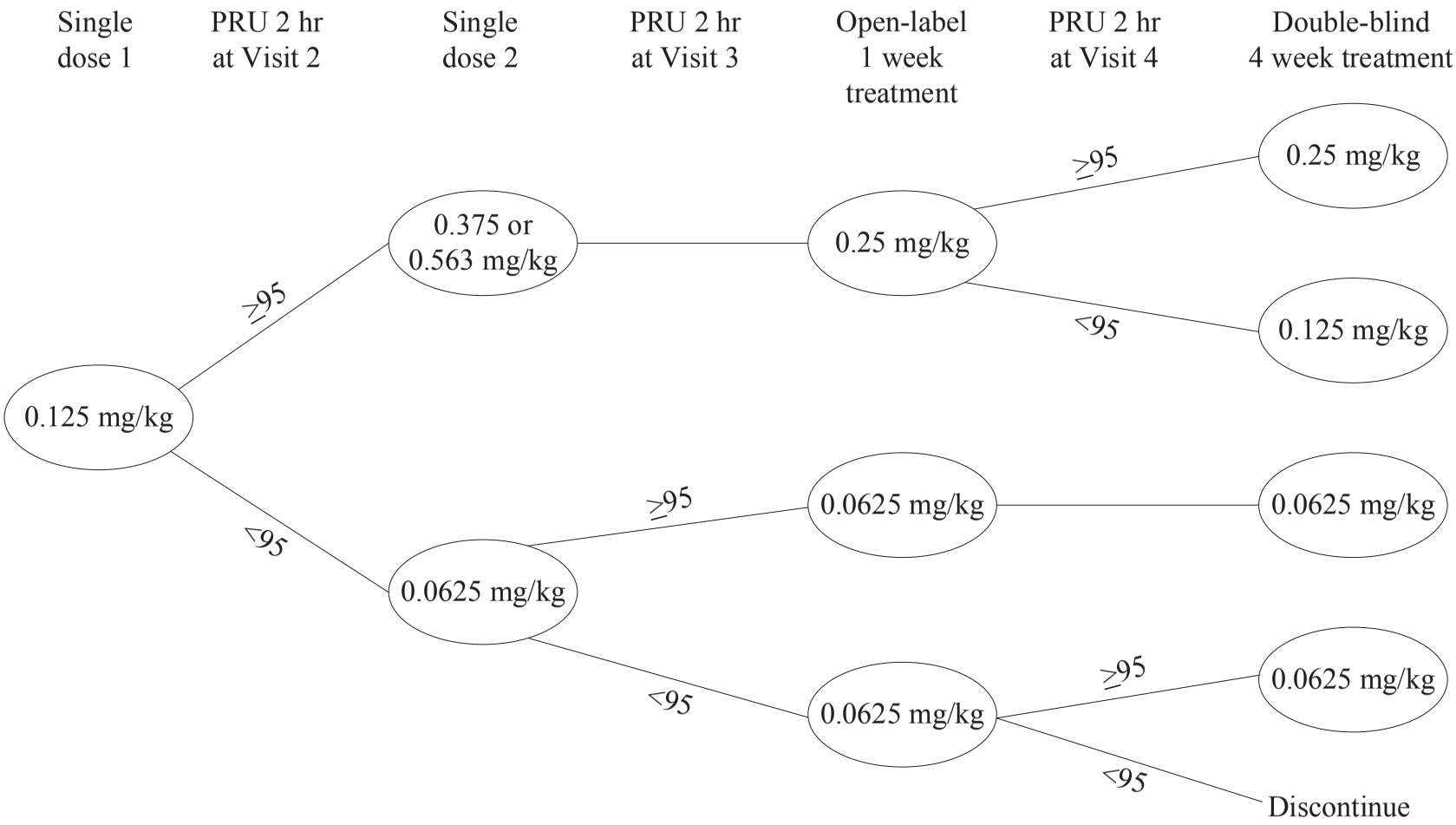
Figure 3 Dosing schedule after interim analysis, Repeated dose 0.125 mg/kg



Patients enrolled subsequent to the interim analysis will follow the dosing schedule shown in Figure 4 if mean PRU reduction in the interim analysis is <30% and ≥20%.

Figure 4 in this Appendix will replace Figure 2 in the main body of the Clinical Study Protocol after the interim analysis, see Section 4.2.

Figure 4 Dosing schedule after interim analysis, Repeated dose 0.25 mg/kg


Single dose 1
PRU 2 hr at Visit 2
Single dose 2
PRU 2 hr at Visit 3
Open-label 1 week treatment
PRU 2 hr at Visit 4
Double-blind 4 week treatment
0.125 mg/kg
≥95
<95
0.375 or 0.563 mg/kg
0.0625 mg/kg
0.25 mg/kg
0.125 mg/kg
0.0625 mg/kg
0.0625 mg/kg
0.0625 mg/kg
0.0625 mg/kg
Discontinue

Revised text:

An interim analysis was conducted per protocol after 12 patients had completed dosing in part A. The mean PRU reduction 2 hours post-dose at Visit 4 was <20%, and plasma ticagrelor concentrations were lower than expected. This triggered a protocol amendment to increase the weight-adjusted dosing in order to achieve a higher level of platelet inhibition.

Doses may be further adjusted following assessment by AstraZeneca and the Steering Committee of results in the first 6-12 patients randomised under this amendment. Dose adjustment decisions will be based upon a review of PK, PD and adverse events and will apply only to patients randomised subsequent to the dose change decision.

Alternative Dosing Schedule 1:

The dose for Visit 2, Part A and Part B may be reduced from 0.75 mg/kg to 0.563 mg/kg and the highest dose administered on Visit 3 may be reduced from 2.25 mg/kg to 1.69 mg/kg.

Refer to Figure 1: Alternative dosing schedule 1, reduced doses in Appendix E

Alternative Dosing Schedule 2:

If two or more patients exceed the paediatric exposure limit (Cmax 2000 ng/mL) after receiving 2.25 mg/kg as single dose on visit 3, this dose will be reduced from 2.25 mg/kg to 1.69 mg/kg.

Refer to Figure 2: Alternative dosing schedule 2, reduced top dose in Appendix E

Alternative Dosing Schedule 3:

The dose at visit 2 and during repeated dosing in Part A and Part B may be increased from 0.75 mg/kg to 1.125 mg/kg, and the single doses at visit 3 may be increased to 1.69 mg/kg and 2.25 mg/kg

Refer to Figure 3: Alternative dosing schedule 3, increased doses in Appendix E

Table 1 Adult equivalents of doses in the alternative dosing schedules

Weight-based Dose (mg/kg)	Adult equivalent dose (mg)
0.375	30
0.563	45
0.75	60
1.125	90
1.69	135
2.25	180

Figure 1 in this Appendix will replace Figure 2 in the main body of the Clinical Study Protocol if the **doses are reduced**, see Section 4.2

Figure 1 Alternative dosing schedule 1, reduced doses

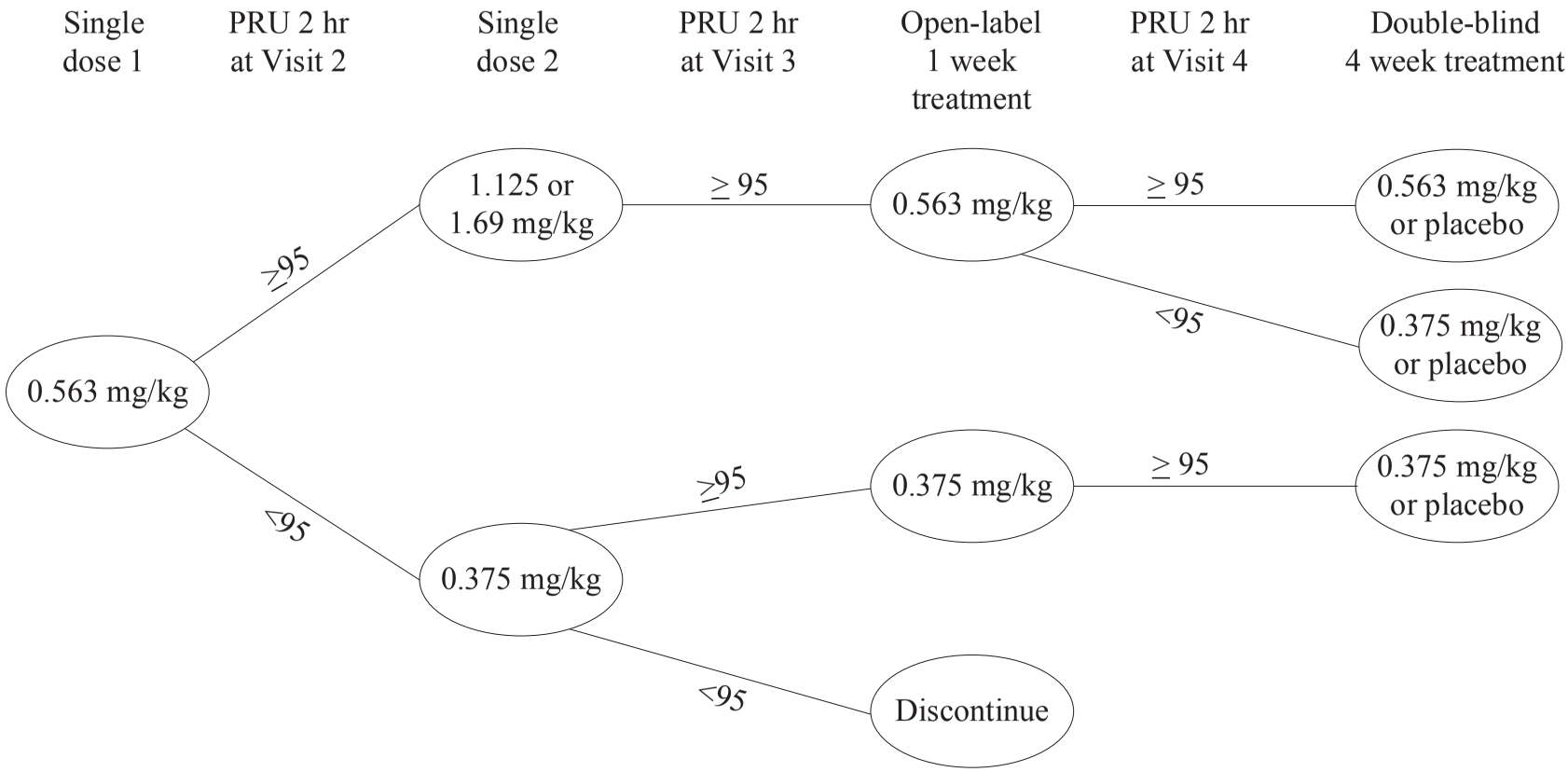


Figure 2 in this Appendix will replace Figure 2 in the main body of the Clinical Study Protocol if the **top dose is reduced**, see Section 4.2.

Figure 2 Alternative dosing schedule 2, reduced top dose:

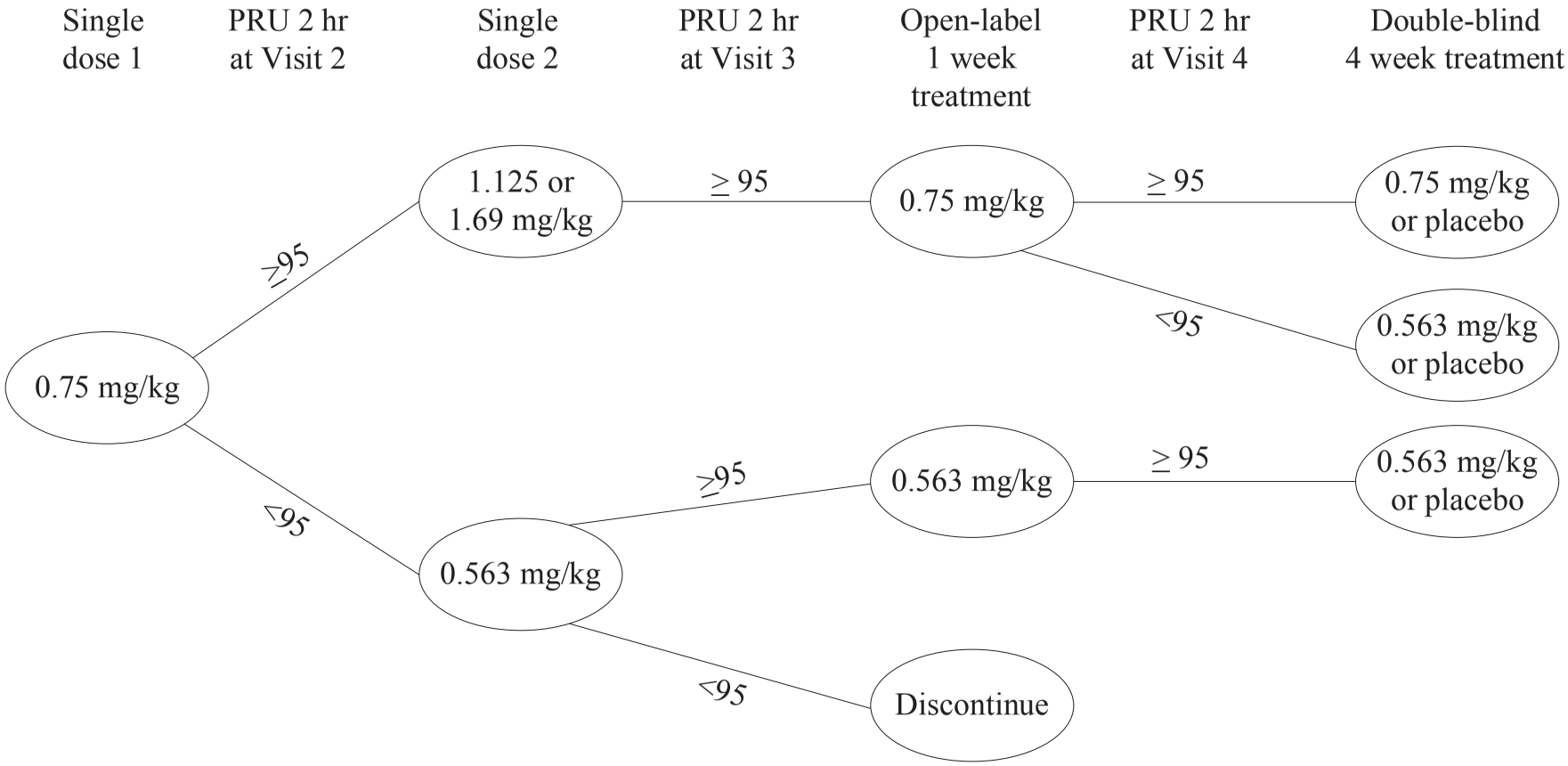
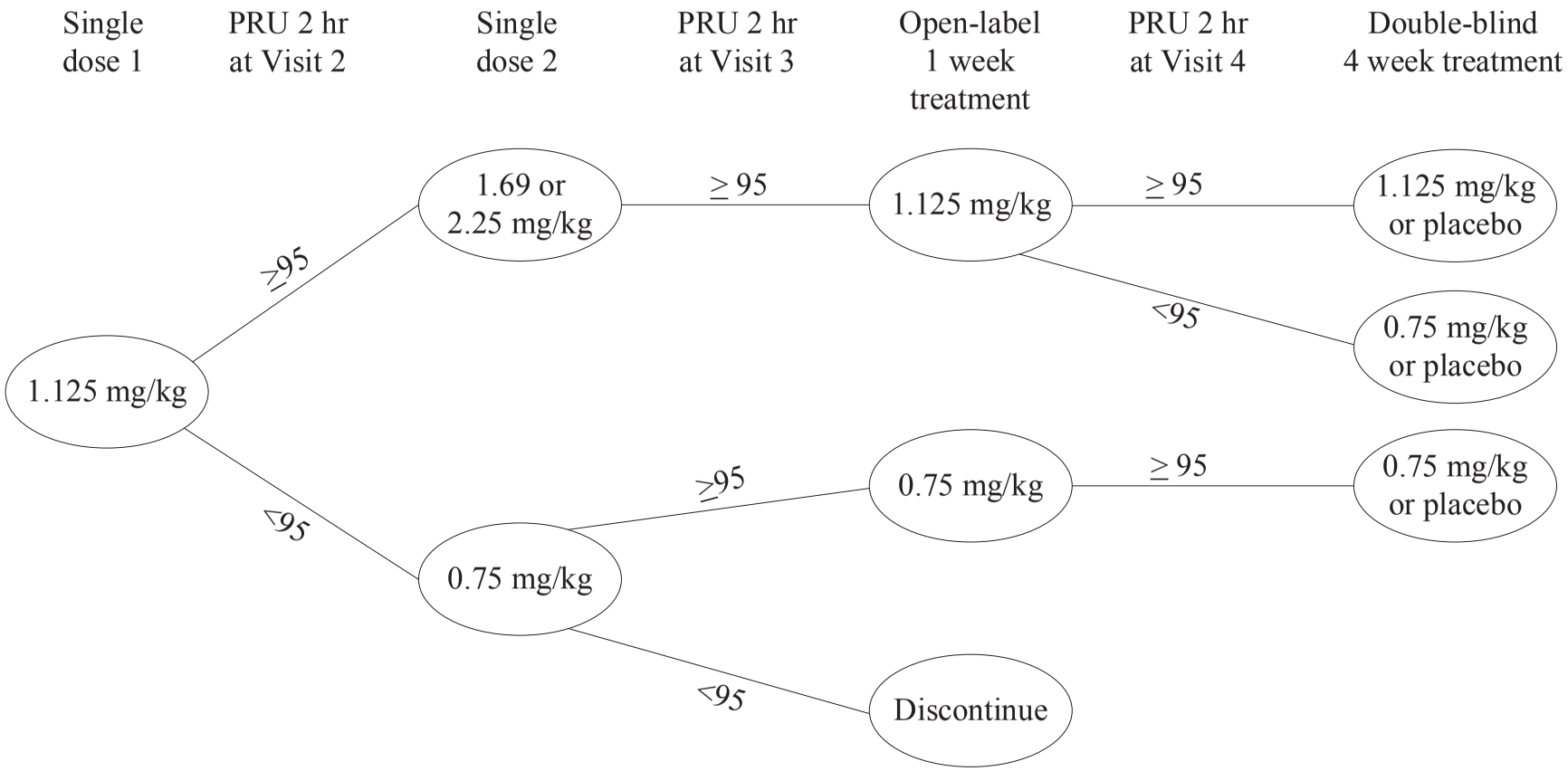


Figure 3 in this Appendix will replace Figure 2 in the main body of the Clinical Study Protocol if the **doses are increased**, see Section 4.2.

Figure 3 Alternative dosing schedule 3, increased doses:



Section of protocol affected:

Appendix F

Previous text:

Before each dosing occasion the granules will be constituted with a **fixed volume** of purified water to form a homogenous suspension suitable for oral dosing. Dosing will be weight based and a suitable volume of suspension should be withdrawn from the bottle using a syringe suitable for oral dosing. The dose volume to be given to the patient is defined in Table 1-Table 5. The dose tables are based on predefined weight brackets in order to ensure dose accuracy (only whole mL to be given) and that the correct treatment **strength** is given to patient. All patients will receive a handling instruction together with study drug at each visit starting at Visit 3. The investigator will enter the individual volume to be given in the handling instruction before the patient leaves the clinic. For more information, please see Section 7.2 in the Clinical Study Protocol.

Table 1 0.0625 mg/kg

Weight (kg)	Bottle strength (mg)	Dose volume (mL)	Actual dose (mg)
16-27	10	1	1
28-41	10	2	2
42-55	10	3	3
56-69	10	4	4
70-120	10	5	5

Table 2 0.125 mg/kg

Weight (kg)	Bottle strength (mg)	Dose volume (mL)	Actual dose (mg)
16-27	10	2	2
28-41	10	4	4
42-55	10	6	6
56-69	10	8	8
70-120	10	10	10

Table 3 0.250 mg/kg

Weight (kg)	Bottle strength (mg)	Dose volume (mL)	Actual dose (mg)
16-27	10	4	4
28-41	10	8	8
42-55	45	3	13.5
56-69	45	4	18
70-120	45	5	22.5

Table 4 0.375 mg/kg

Weight (kg)	Bottle strength (mg)	Dose volume (mL)	Actual dose (mg)
16-27	10	6	6
28-41	45	3	13.5
42-55	45	4	18
56-69	45	5	22.5
70-120	45	7	31.5

Table 5 0.563 mg/kg

Weight (kg)	Bottle strength (mg)	Dose volume (mL)	Actual dose (mg)
16-27	45	2	9
28-41	45	4	18
42-55	45	6	27
56-69	45	8	36
70-120	45	10	45*

*** The highest dose in this study is 45 mg, even if the patient weight is >120 kg**

Revised text:

Before each dosing occasion the granules will be constituted with **10 mL** of purified water to form a homogenous suspension suitable for oral dosing. Dosing will be weight based and a suitable volume of suspension should be withdrawn from the bottle using a syringe suitable for oral dosing. The dose volume to be given to the patient is defined in **Table 1-Table 6**. The dose tables are based on predefined weight brackets in order to ensure dose accuracy (only whole mL to be given, **except for the 0.375 mg/kg dose**) and that the correct treatment **dose** is given to patient. All patients will receive a handling instruction together with study drug at each visit starting at Visit 3. The investigator will enter the individual volume to be given in the handling instruction before the patient leaves the clinic. For more information, please see Section 7.2 in the Clinical Study Protocol.

Table 1 0.375 mg/kg

Weight (kg)	Bottle strength (mg)	Dose volume (mL)	Actual dose (mg) *
16-27	**45**	**1.3**	6
28-41	45	3	13.5
42-55	45	4	18
56-69	45	5	22.5
≥70	45	7	31.5

Table 2 0.563 mg/kg

Weight (kg)	Bottle strength (mg)	Dose volume (mL)	Actual dose (mg) *
16-27	45	2	9
28-41	45	4	18
42-55	45	6	27
56-69	45	8	36
≥70	45	10	45

Table 3 0.75 mg/kg

Weight (kg)	Bottle strength (mg)	Dose volume (mL)	Actual dose (mg) *
16-27	45	3	13.5
28-41	45	6	27
42-55	45	8	36
56-69	45	10	45
≥70	45	13	58.5

Table 4 1.125 mg/kg

Weight (kg)	Bottle strength (mg)	Dose volume (mL)	Actual dose (mg) *
16-27	45	4	18
28-41	45	9	40.5
42-55	45	12	54
56-69	45	16	72
≥70	45	20	90**

Table 5 1.69 mg/kg

Weight (kg)	Bottle strength (mg)	Dose volume (mL)	Actual dose (mg) *
16-27	45	6	27
28-41	45	13	58.5
42-55	45	18	81
56-69	45	23	103.5
≥70	45	30	135

Table 6 2.25 mg/kg

Weight (kg)	Bottle strength (mg)	Dose volume (mL)	Actual dose (mg) *
16-27	45	8	36
28-41	45	17	76.5
42-55	45	24	108
56-69	45	31	139.5
≥70	45	40	180**

* Actual doses were calculated using the mean weight in the weight bands ((Upper weight-Lower weight)/2+Lower weight) except for the highest and lowest weight bands, where 80kg and the 16kg was used respectively.

** The highest dose in this study is **180** mg for **single doses, and 90 mg for repeated doses.**

Reason for Amendment:

Change in Dosing Scheme:

Study D5136C00007 (HESTIA1) was initiated with ticagrelor doses ranging from 0.125-0.563 mg/kg (equivalent to adult doses of 10-45 mg). The protocol provided for an interim analyses of PK and PD with protocol-specified criteria for dose adjustments. Analysis of the first 12 randomised patients shows that the exposure to ticagrelor was lower than predicted and the platelet inhibitory effect was also lower than intended. The doses administered were predicted to result in approximately 10-75% platelet inhibition, but the observed mean reductions were 13-30%. In order to accomplish the primary study objective of characterising the relationship between ticagrelor dose and inhibition of platelet aggregation to support dose selection for Phase III, the doses studied in the remaining patients will be increased by this protocol amendment.

Moreover, recently published results from a Phase III study in children with SCD with another P2Y12 inhibitor, prasugrel, suggest that the low degree of platelet inhibition achieved so far in this Phase 2 study with ticagrelor cannot be expected to provide any clinically meaningful effect on pain crises (ref Heeney et al, NEJM, online before printed, Dec 8, 2015).

The interim data from HESTIA1 do not raise any safety concerns, and in fact no bleeding adverse events have been reported. The most commonly reported adverse events were sickle cell anemia crisis (4 patients), vomiting, arthralgia and pain in extremities (3 patients each). Three serious adverse events occurred in 2 patients (acute chest syndrome, sickle cell anemia crises). None of the non-serious or serious adverse events were judged as related to study drug by the investigator.

This amendment will provide for higher doses for patients enrolled following this amendment in order to fully characterize the dose-response for ticagrelor in children. Doses proposed in this amendment on a mg/kg basis are all less than or equivalent to the currently approved doses for adult cardiovascular diseases (single loading dose of 180 mg followed by 90 mg twice daily) and the predicted highest exposure, taking individual variability into account, are well below pediatric exposure limits (Cmax 2000 ng/mL and AUC 19000 ng*hr/mL).

The 10 mg bottle strength has been removed because this bottle strength is no longer needed for the revised dosing schedule.

Changes in Inclusion and Exclusion Criteria:

Inclusion criteria #2 concerning the history of VOC in the prior 12 months was removed to enable characterization of PK and PD in a broader patient population of patients with SCD.

The requirement for stable hydroxyurea dosing was changed from 3 months to 1 month since this is considered sufficient to establish steady state.

As the eligibility criteria have been changed with this amendment, previously enrolled but not randomized patients may be re-enrolled and evaluated for participation under the new study protocol, at the discretion of the investigator.

Changes to Part B of the study:

The amended protocol allows for patients to opt out of participation in Part B. HESTIA1 is a complex study with a high study burden to paediatric patients and their families. The primary objective of the study is to determine the PK/PD relationship, which can be determined in Part A of the amended protocol. This change will allow those patients interested in a longer double-blind treatment to participate in both parts of the study, but also to enable participation in part A only for those patients and families who otherwise would completely deny study participation because Part B is too time-consuming and burdensome for them.

Since Part B is now optional, the PK/PD determinations previously scheduled for Visit 8 have been moved to Visit 4 in order to assure that steady state PK/PD is obtained in all study patients.

The pregnancy urine testing has been moved from Visit 3 to Visit 2 to insure that all patients are tested prior to first dose. A pregnancy test has been added to Visit 4 for the patients only completing Part A to insure that all patients are tested following repeated dosing.

Changes to the statistical analyses section:

If most of the remaining patients decline participation in part B, the patients in the efficacy analysis set are prone to selection bias. Results of statistical tests conducted under such circumstances are not generalizable and hence only descriptive statistics will be used.

Changes to Visit Schedule:

The minimum number of days between Visit 1 and Visit 2 was increased from 7 days to 14 days to ensure that 30 days elapse between Visit 1 and Visit 4. This ensures that the volume of blood to be drawn within 30 days is not higher than 3% of blood volume. The visit window between the treatment visits has been shortened to better fit the visit schedule and to avoid requiring patients to bring home large volumes of study medication.

Changes to List of References:

Heeney et al 2015
Heeney MM, Hoppe CC, Abboud MR, Inusa B, Kanter J, Ogutu B et al. A multinational trial of prasugrel for sickle cell vaso-occlusive events.
NEJM, online before print Dec 8, 2015

Persons who initiated the Amendment:

AstraZeneca Study Team, with concurrence of study Steering Committee.