- An ACS is an acute illness characterized by fever and/or respiratory symptoms, accompanied by a new pulmonary infiltrate on a chest X-ray.

Objectives

Primary Objective:	**Outcome Measure:**
To compare the effect of ticagrelor vs placebo for the reduction of VOCs, which is the composite of painful crisis and/or ACS, in paediatric patients with SCD	Number of VOCs

Secondary Objective:	**Outcome Measure:**
To compare the effect of ticagrelor vs placebo for the reduction of painful crises	Number of painful crises
To compare the effect on ticagrelor vs placebo for the reduction of ACS	Number of ACSs
To compare the effect of ticagrelor vs placebo for the reduction of duration of painful crises	Duration of painful crises
To compare the effect of ticagrelor vs placebo on the number of VOCs requiring hospitalisation or emergency department visits	Number of VOCs requiring hospitalisation or emergency department visits
To compare the effect of ticagrelor vs placebo on reduction of days hospitalised for VOC	Number of days hospitalised for VOC
To compare the effect of ticagrelor vs placebo on the number of acute SCD complications[a]	Number of acute SCD complications
To compare the effect of ticagrelor vs placebo on reduction of days hospitalised for acute SCD complications[a]	Number of days hospitalised for acute SCD complications
To compare the effect of ticagrelor vs placebo on the number of sickle cell-related red blood cell transfusions	Number of sickle cell-related red blood cell transfusions
To describe the health-related quality of life (HRQL) and fatigue	HRQL total score and by dimension using Paediatric Quality of Life Inventory (PedsQL) SCD Module and Fatigue total score and by dimension using the PedsQL Multidimensional Fatigue Scale (age appropriate versions: 2-4 years; 5-7 years; 8-12 years; 13-18 years)
To describe absence from school or work due to SCD	Proportion of days of absence from school or work (only if going to school or work at randomisation)

Abbreviation or special term	Explanation
HbS/β^0	Sickle beta-zero-thalassaemia
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HRQL	Health-related quality of life
IATA	International Air Transport Association
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ICI	International Co-ordinating Investigator: If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the Investigators and/or activities internationally.
ID	Identification
IP	Investigational product
IXRS	Interactive Voice/Web Response System
LDH	Lactate dehydrogenase
LFT	Liver function test
MedDRA	Medical Dictionary for Regulatory Activities
NSAIDs	Non-steroidal anti-inflammatory drugs
$P2Y_{12}$	G protein-coupled platelet receptor for adenosine diphosphate (ADP)
PedsQL	Paediatric Quality of Life Inventory
P-gp	P-glycoprotein
PD	Pharmacodynamic
PI	Principal Investigator
PK	Pharmacokinetic
PRI	Platelet Reactivity Index
PRU	$P2Y_{12}$ reaction units
PT	Prothrombin time
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Steering Committee
SCD	Sickle cell disease
SD	Standard Deviation
TAMMV	Time averaged mean of the maximum velocity
TCD	Transcranial Doppler
TCDi	Transcranial Doppler imaging technique

PRU of 280 (which was the baseline PRU observed in HESTIA1, and similar to prasugrel Phase III DOVE study [Heeney et al 2016]).

The predicted platelet inhibition in HESTIA3 is similar to what was observed in the 45 mg bd dose group in the HESTIA2 study in young adults, where after 1 week of treatment the mean percentage decrease from baseline PRU was 48% before morning dose and 81% at 2 hours after dose. The 45 mg bd dose group was well tolerated and events of bleeding were of the same number and similar compared to the placebo and the 10 mg bd dose groups. Given the reversible mechanism of action for ticagrelor, the level of $P2Y_{12}$ inhibition during ticagrelor treatment is expected to vary within a dosing interval and peak around 2 hours after dosing.

When developing the dosing strategy for this study, the target for platelet inhibition was guided by the results from the recent prasugrel Phase III study in paediatric patients with SCD aged 2 to 17 years, showing insufficient efficacy with a mean PRU of 207 (ie, approximately 20% reduction from baseline) (Jakubowski et al 2017). The lack of therapeutic benefit with prasugrel may have been related to a too low platelet inhibition (Heeney et al 2016), and consequently, doses for HESTIA3 were selected to achieve a greater level of platelet inhibition. Moreover, a study with ticlopidine in adolescents and adult patients with SCD showing significant reductions in VOC (Cabannes et al 1984) used doses that generally provide <60% inhibition of platelet aggregation, which provides further support for the platelet inhibition target and the selected doses for the HESTIA3 study.

There are no other drugs approved for reduction of VOCs in children with SCD with a similar mechanism of action as ticagrelor. Hydroxyurea is approved for use in children with SCD in some markets and more recently, L-glutamine was approved by the US FDA. Evaluation of ticagrelor when given in addition to standard of care including these medications, where available and when considered medically appropriate, is considered acceptable for studying the efficacy and safety of ticagrelor in this patient group as compared with placebo.

Treatment duration is at least 12 months for study participants, but no longer than 24 months for any patients. The expected average follow-up is 18 months, assuming a uniformly distributed enrolment period of 12 months. Considering inclusion of patients with at least 2 VOCs in the past year, this treatment duration is considered long enough to evaluate effects on VOC events as well as to capture safety and tolerability data supporting a potential future long-term use of ticagrelor.

1.3 Benefit/risk and ethical assessment

The aim with ticagrelor treatment in paediatric patients with SCD is to reduce the rate of VOCs, with an acceptable safety profile. Considering that the anticipated benefit would be mostly symptom reduction and that patients with SCD suffer from anaemia, the acceptance for bleedings will be low.

Episodes with VOCs are the most common cause for emergency room visits for children with SCD. The pain associated with VOC can be excruciating and have a significant impact on the child's life, and significantly disturbs routine activities such as food intake, sleep and school

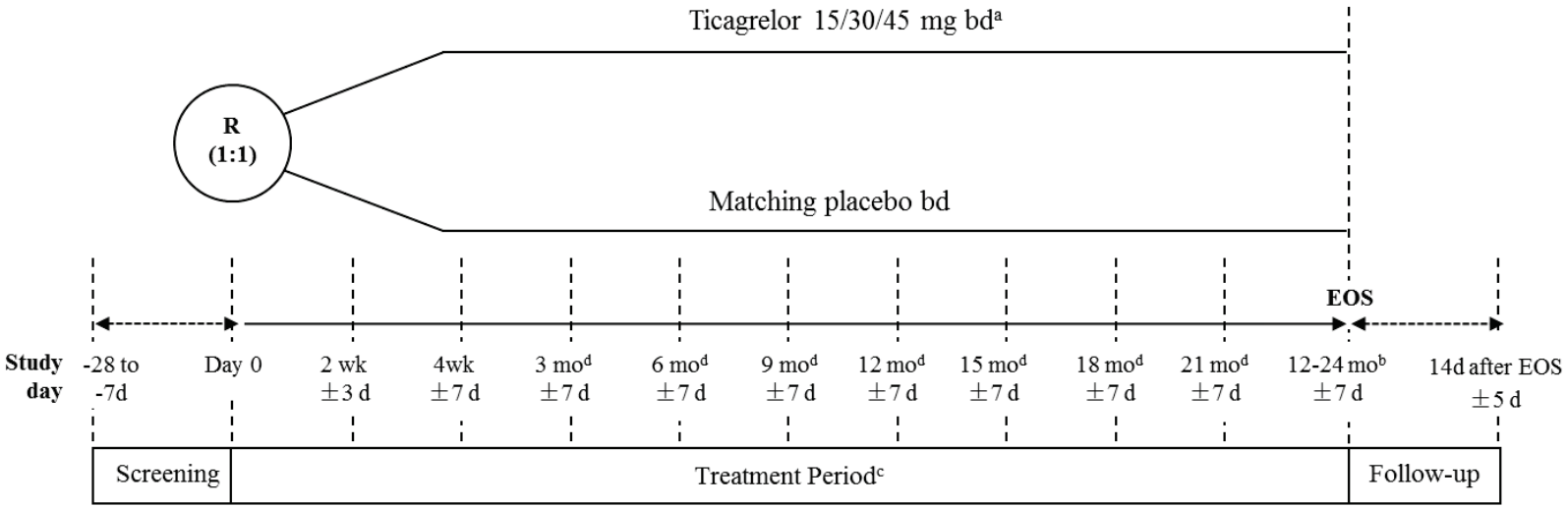

Table 2 for assessments during site visits and Table 3 for telephone visits that will occur monthly after Week 4 between site visits.

[d] Interval must not be more than 100 days to ensure tablet supply for all days.

NB. Only on-site visits are shown.

2.2 Secondary objectives

Secondary Objective:	Outcome Measure:
To compare the effect of ticagrelor vs placebo for the reduction of painful crises	Number of painful crises
To compare the effect on ticagrelor vs placebo for the reduction of ACS	Number of ACSs
To compare the effect of ticagrelor vs placebo for the reduction of duration of painful crises	Duration of painful crises
To compare the effect of ticagrelor vs placebo on the number of VOCs requiring hospitalisation or emergency department visits	Number of VOCs requiring hospitalisation or emergency department visits
To compare the effect of ticagrelor vs placebo on reduction of days hospitalised for VOC	Number of days hospitalised for VOC
To compare the effect of ticagrelor vs placebo on the number of acute SCD complications[a]	Number of acute SCD complications
To compare the effect of ticagrelor vs placebo on reduction of days hospitalised for acute SCD complications[a]	Number of days hospitalised for acute SCD complications
To compare the effect of ticagrelor vs placebo on the number of sickle cell-related red blood cell (RBC) transfusions	Number of sickle cell-related RBC transfusions
To describe the health-related quality of life (HRQL) and fatigue	HRQL total score and by dimension using Paediatric Quality of Life Inventory (PedsQL) SCD Module and Fatigue total score and by dimension using the PedsQL Multidimensional Fatigue Scale as presented in Appendix I (age appropriate versions)
To describe absence from school or work due to SCD	Proportion of days of absence from school or work (only if going to school or work at randomisation)
To describe intensity of pain during VOC	Intensity of worst pain daily during VOC - For patients ≤4 years of age, observer reported using the Face, Legs, Activity, Cry, Consolability Scale (FLACC) - For patient ages 5 to 18 years of age, self-reported using the Faces Pain Scale Revised (FPS-R)
To describe analgesics use during VOC	Type of analgesics (opioid and non-opioid) use

To describe patient acceptability of the formulation (palatability and swallowability)	- For patients ≤4 years of age taking the tablet dispersed or whole, an observer assessment of palatability and swallowability will be undertaken - For patients ≥5 years of age taking the tablet dispersed or whole, palatability will be assessed and categorised using the Facial Hedonic Scale

[a] The acute SCD complications are defined in Section 5.1.5.

2.3 Safety objectives

Safety Objective:	**Outcome Measure:**
To assess long-term safety and tolerability of therapy with ticagrelor vs placebo	AEs/SAEs, including bleeding Vital signs and laboratory safety variables

2.4 Exploratory objectives

Exploratory Objective:	**Outcome Measure:**
To compare the effect of ticagrelor vs placebo for the reduction of duration of ACS	Duration of ACS
To assess the pharmacokinetics (PK) of ticagrelor and AR-C124910XX in paediatric patients with SCD using a population PK model	Population PK parameters such as oral clearance (CL/F) and ticagrelor exposure (AUC)
	Observed plasma concentrations of ticagrelor and the active metabolite AR-C124910XX
To assess the effect of ticagrelor on platelet aggregation	PRI measured by vasodilator-stimulated phosphoprotein (VASP) assay

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

Each patient must 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 must fulfil the following criteria:

1. Provision of signed and dated 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).
2. Male or female paediatric patients aged ≥2 to <18 years and body weight of ≥12 kg (at Visit 1), diagnosed with HbSS or HbS/β^0 as confirmed by high-performance liquid

chromatography or haemoglobin electrophoresis.
Note: Diagnosis of SCD (if not confirmed prior to screening and records available on the medical file) should be confirmed for HbSS or HbS/β^0 by high-performance liquid chromatography or haemoglobin electrophoresis, performed at the site's local lab, in order to confirm the type of mutation.

3. Have experienced at least 2 VOCs (painful crisis and/or ACS) as judged by the Investigator in the past 12 months prior to Visit 1. These VOCs need to be documented in the patient's medical records or in other documents that can be reconciled.
4. If ≤16 years old, 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.
5. If ≥10 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. If local guidelines dictate ophthalmological examination at younger ages, those local guidelines should be followed.
6. If treated with hydroxyurea, the weight-adjusted dose must be stable for 3 months before screening.
7. Suitable venous access for the study-related blood sampling
8. Prior to dosing on day of randomisation (Visit 2), a negative urine (dipstick) pregnancy test performed at Screening (Visit 1) and at Visit 2 must be available for female patients of childbearing potential.
9. Females of childbearing potential (after menarche) must not become pregnant during study. Sexually active females must use a highly effective method of contraception which results in a low failure rate (ie, less than 1% per year). If use of effective contraception cannot be secured in sexually active females, the patient cannot be included in this study. Refer to Section 3.8 for highly effective methods of contraception.

3.2 Exclusion criteria

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

1. History of transient ischaemic attack (TIA) or cerebrovascular accident (ischaemic 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. Patients with Conditional TAMMV values or higher (≥153 cm/sec using TCD imaging technique [TCDi] which is corresponding to ≥170 cm/sec by the non-imaging technique). Both the middle cerebral artery and the internal carotid artery should be considered. Any other criteria that would locally be considered as TCD indications for chronic transfusion would also exclude the patient.
3. Active pathological bleeding or increased risk of bleeding complications according to Investigator
4. Haemoglobin <6 g/dL from test performed at Screening (Visit 1)
5. Platelets <100 x 10^9/L from test performed at Screening (Visit 1)
6. Undergoing treatment with chronic red blood cell transfusion therapy

On visits with PedsQL, the instrument should be completed before any other study assessments.

Ensure that there are not more than 100 days between two planned visits containing dispensing of IP to ensure tablet supply for all days.

If feasible, study visits may take place at the patient's home or other setting if travel to the site is not possible due to the COVID-19 situation.

4.2.2 Telephone visits during treatment period

Descriptions of the procedures for this period are included in the Schedule of Assessments for telephone visits during the treatment period (Table 3).

Telephone visits should occur between the Investigator at the study site, and the caregiver for the patient. The Investigator may decide to speak directly with a patient in the late teenage period, if judged appropriate based on the Investigator's thorough knowledge of the patient.

Similar to on-site visits, the telephone visit should be documented in the patient's medical records. Notes are to include:

- Any AEs,
- Whether an AE fulfils criteria for VOC endpoint or not,
- Any changes of medications,
- Any use of contraceptives (applicable to females of childbearing potential).

See Appendix E, a Guide for Scheduled Telephone Visits for further details on conduct of the telephone visits.

4.2.3 End of study visit

Patients are to be followed up to 24 months or until a common study end date is reached defined as 12 months after the last patient is randomised. After the CSED have been communicated by AstraZeneca or representative, all patients still in the treatment period should be scheduled for the End of Study Visit (see Table 2). The End of Study Visit should be done within 30 days after CSED. The patients should return the eDevice and the IP bottles.

The Safety Follow-up Visit should be scheduled.

4.2.4 Safety follow-up visit

Descriptions of the procedures for this visit are included in the Schedule of Assessments (Table 2).

4.2.5 Unscheduled visits

For any safety or tolerability reasons, the patients may return to the clinic for an unscheduled visit.

The Investigator's evaluation should be documented in the source documents in the same manner as a regular planned visit. Procedures performed are at the discretion of the Investigator. Unscheduled visits should not affect the regular visit schedule and assessments.

5. STUDY ASSESSMENTS

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

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

An eDevice will be used by the patient/caregiver for electronic recording of pain according to FPS-R/FLACC when experiencing a VOC, analgesic use and absence from school/work due to SCD.

5.1 Efficacy assessments

5.1.1 Vaso-occlusive crisis

A VOC is the composite of a painful crisis and/or an ACS (Howard et al 2015, Yawn et al 2014). Each component is defined as:

A painful crisis is an onset or worsening of pain that lasts at least 2 hours, for which there is no explanation other than vaso-occlusion and which requires therapy with oral or parenteral opioids, parenteral NSAIDs, or other analgesics prescribed by a health care provider in a medical setting (such as a hospital, clinic or emergency room visit) or at home.

An ACS is an acute illness characterised by fever and/or respiratory symptoms, accompanied by a new pulmonary infiltrate on a chest X-ray.

5.1.1.1 Collection of VOC

A VOC occurring during the study should be recorded by the Investigator both as a primary endpoint event, and also as an AE. A potential VOC judged by the Investigator not to fulfil the definition of the primary endpoint should be also recorded as an AE according to standard AE reporting procedures (see Section 6).

Collection of some information related to the potential VOC should be done by the patient/caregiver in real-time in the eDevice, and not based on recollection at the next planned visit. When information related to a potential VOC is entered in the eDevice, the Investigator will be alerted and should, unless a contact already occurred, call the caregiver within 72 hours from the onset of the potential event to enable a medical consultation and event data collection (see Appendix D, Interview Guide for VOC-triggered Telephone Calls). Families

will be instructed to call the site in case of a VOC, unless already contacted by the site within 72 hours.

Regardless of primary setting of treatment (eg, in-patient hospitalisation, short-stay outpatient unit, emergency department or self-treated), some VOC-related information outlined below must be documented by the caregiver in the patient's eDevice. The Investigator only, will judge if the potential VOC fulfil the definition of VOC (see Section 5.1.1 for definition). If needed, the Investigator should request medical records and/or other documents from other medical facility than the study site. It will be the Investigators' responsibility to document the VOC in medical records and ensure that the VOC data in the eCRF is correct.

Following information will be captured in the eDevice to be reviewed by the Investigator:

- Start and stop date/time of the VOC event
- Assessment of worst pain intensity will be done once daily throughout the duration the VOC event (Patient/Observer Reported), see Section 5.1.2.
- Report of anatomical location(s) of pain will be done once daily throughout the duration of the VOC event (Patient/Observer Reported).
- If analgesics are taken during the VOC (Yes/No) and the Investigator will enter details of the analgesics (ie, name, type, dose, routes of administration, frequency) into the eCRF.

The following data should be collected in the eCRF, based on review of eDevice entries, information from the medical consultation and copies from other medical facilities:

- Confirmation if the event fulfils the VOC definition
- Date of any telephone contact
- Start and stop date/time of the event
- Primary setting for VOC treatment (eg, in-patient hospitalisation, short-stay outpatient unit, emergency department or self-treated)
- Start and stop date/time of any in-patient hospitalisation
- Treatments administered of the event
- Complete AE/SAE form.

5.1.1.2 Training in the collection of VOC events

Patients will be supplied with a handheld eDevice for the treatment period. Caregivers must be willing to learn and use the eDevice and/or supervise the use of the eDevice. At Visit 2, all patients and their caregiver will be carefully instructed and trained on how to handle and complete the eDevice. Written information will be supplied to each patient and caregiver in an age-adapted way in their local language. Instructions for use of the eDevice will also be described in writing in the ICF for the caregiver, in age-adapted language in the paediatric assent form (if used in certain age groups), and in the ICF for any participants turning 18 years of age during the study period.

The patient and the caregiver will be instructed on how and where to request help if problems occur. The Investigator is responsible to ensure that this training is performed at Visit 2 and any subsequent visits as needed.

The patient/caregiver should be reminded to use the eDevice during a potential VOC event, regardless of primary setting of treatment (eg, in-patient hospitalisation, short-stay outpatient unit, emergency department or self-treated). The patients and caregiver must bring the eDevice to each visit for the Investigator to review of eDevice entries.

The patients and their caregiver should also be informed that pain during a VOC, location of pain and use of analgesic should be entered daily to the eDevice. The daily questions on pain intensity, pain localisation and analgesic use must be responded to on the actual day; these data cannot be entered for other dates. In case an already resolved VOC event was not registered in the eDevice, start and stop date are still possible to record retrospectively. Pain intensity, pain localisation and analgesic use cannot be recorded for these events in the eDevice. However, analgesic use during resolved events need to be recorded by the Investigator in the eCRF together with any other event details as for all VOC events.

When information related to a potential VOC is entered in the eDevice, the Investigator will be alerted and should, unless a contact already occurred, call the caregiver within 72 hours from the onset of the potential event to enable a medical consultation and event data collection. Families will be instructed to call the site in case of a VOC, unless already contacted by the site.

Expectations on Investigator's documentation of endpoint events will be discussed at the Investigators meetings. Before the first patient is enrolled into the study at a study site, an AstraZeneca representative will review and discuss the requirements of the Clinical Study Protocol and related documents again with the study staff in the Start-up Meeting, and train them in any study-specific procedures, including collection of data for the primary efficacy endpoint. Study monitoring will include review of data entered for the primary efficacy endpoint to ensure the data are complete. Re-training of study staff will take place as needed.

5.1.2 Pain during a VOC

Pain is commonly reported in clinical trials by having patients provide a rating of their own pain. In this study, pain rating will be done in the eDevice. 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.

For young children (2 to ≤4 years of age), subjective observation of pain-related behaviours is recommended. The Face, Legs, Activity, Cry, Consolability (FLACC) assessment tool is a measurement developed for and used to assess pain for children between the ages of 2 months and 7 years. The FLACC behavioural pain tool has shown good reliability and validity in assessing pain in critically ill adults and children (Voepel-Lewis et al 2010). The FLACC will be caregiver-reported for patients ≤4 years of age daily during the VOC event. Each of the

The clinical chemistry, haematology, virology and coagulation analyses will be performed at a central laboratory when possible or at an authorised/certified local laboratory as needed. All sampling, handling and transporting of samples will be in accordance with IATA Guidance Document (Appendix B).

Urinalysis is to be performed at the investigational site by dipstick. Urine pregnancy test will be taken at all visits for 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 visits.

The laboratory variables in Table 4 will be measured.

Table 4 Laboratory variables

Haematology/Haemostasis (whole blood)	**Clinical Chemistry (serum)**
B-Haemoglobin (Hb)	S-Creatinine
B-Haematocrit	S-Bilirubin, total
B-Leukocyte count	S-Bilirubin, direct
B-Leukocyte differential count (absolute count)	S-Alkaline phosphatase (ALP)
B-Platelet count	S-Aspartate transaminase (AST)
	S-Alanine transaminase (ALT)
Urinalysis (dipstick)	S-Lactate dehydrogenase (LDH)
U-Hb/Erythrocytes/Blood	S-Uric Acid
U-Protein/Albumin	S-Blood Urea Nitrogen (BUN)
U-Glucose	S-Albumin
U-beta-human chorionic gonadotropin (β-hCG)	S-Potassium
	S-Chloride
Virology Screen[a]	S-Sodium
Hepatitis B surface antigen (HBsAg)	S-Glucose
Hepatitis C virus (HCV)	S-Haptoglobin
HIV	
Malaria Screen (not mandatory)	**Coagulation**[a]
Microscopy (blood smear evaluation)	International normalised ratio (INR)
Rapid diagnostic tests	Prothrombin time (PT)
	Activated Partial Thromboplastin Time (APTT)

B blood; S serum; U urine.

[a] Virology screen and coagulation will be conducted at the Screening Visit only.

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed, dated and retained at centre

method. Full details of the analytical method used will be described in a separate Bioanalytical Report.

All samples still within the known stability of the analytes of interest (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

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

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

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

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

5.5 Pharmacodynamics

5.5.1 Vasodilator-stimulated phosphoprotein

Vasodilator-stimulated phosphoprotein is a critical protein that is expressed in platelets at high levels and plays a major role in negatively regulating secretory and adhesive events that are involved in platelet aggregation. The effect of ticagrelor on inhibition of platelet aggregation will be assessed by the VASP assay during treatment period (Voepel-Lewis et al 2010; Laine et al 2013).

5.5.2 Collection of samples

Blood samples for determination of platelet aggregation in whole blood will be taken at the time presented in Table 2. Except for the important PD sample taken prior to first dose of study drug at Visit 2 randomisation where no PK sample is taken, the collection of PD samples are thereafter matched with PK samples. To maintain the blinding of treatment allocation, the PD results will not be available to the site, and individual PD results will not be available to the Sponsor.

The time of last dose intake prior to any VASP visits (ie, the evening dose the day before the visit) needs also to be precisely recorded in the eCRF to be able to relate the predose VASP inhibition to time after ticagrelor dose intake.

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

Adverse events will be collected from the time of randomisation, and throughout the study, including the follow-up period. Any SAEs should be collected from when the ICF is signed.

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 electronic case report form (eCRF). AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

6.3.3 Variables

The following variables will be collected for each AE:

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

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

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

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

disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Section 6.2.

The definitions for intensity rating are:

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

6.3.4 Causality collection

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

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 A to the Clinical Study Protocol.

6.3.5 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or care provider or reported in response to the open question from the study site staff: *'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 eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

6.3.6 Adverse events based on examinations and tests

The results from the Clinical Study Protocol-mandated laboratory tests and vital signs will be summarised in the CSR. Deterioration as compared with baseline in protocol-mandated laboratory values, vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the IP.

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

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 Liver biochemistry and evaluation of Hy's Law

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥3 × ULN together with total bilirubin ≥2 × ULN need to be reported as SAEs, except if the elevation is caused by the underlying sickle cell disease, ie, haemolysis, as judged by the Investigator. Please refer to Appendix C for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

6.3.8 Assessment of bleeding events

Bleeding events will be recorded as AEs. The Investigator will do the classification of bleeding events. Bleeding events will be recorded in the eCRF.

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

- **Major bleeding:** defined as any fatal bleeding, clinically overt bleeding associated with a decrease in Hb of at least 20 g/L (2 g/dL), bleeding that is retroperitoneal, pulmonary, intracranial, or otherwise involves the central nervous system or bleeding that requires surgical intervention in an operating suite.
- **Clinically relevant non-major bleeding:** defined as overt bleeding for which a blood product is administered and which is not directly attributable to the patient's underlying medical condition, and bleeding that requires medical or surgical intervention to restore haemostasis, 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) and acute SCD complications

A VOC and acute SCD complications (TIA/ischaemic stroke, hepatic sequestration and splenic sequestration, priapism and dactylitis) occurring during the study should be recorded by the Investigator as AEs. For a definition and collection of VOCs, see Section 5.1.1 and for acute SCD complication, see Section 5.1.5.

- A VOC fulfilling the criteria should also be recorded as an adverse event with the diagnosis Sickle cell anaemia with crisis.
- If the VOC event includes symptoms of other acute SCD complications, these should also be recorded, but separately from the VOC event in the eCRF.

6.3.10 Procedures in relation to COVID-19 infection

If a patient presents with clinical signs and symptoms consistent with COVID-19 infection, the Investigator should request a test where possible and this should be recorded in the AE field of the eCRF as follows:

- If test is positive, record as "COVID-19 confirmed".
- If test is negative, record the AE/SAE signs and symptoms and/or other diagnosis.
- If test is not available and signs and symptoms, as judged by the Investigator, are highly suspicious of COVID-19 infection, record as "COVID-19 suspected".

If other concurrent diagnoses exist, eg, pneumonia, the Investigator should record as separate AEs.

If an AE/SAE is associated with COVID-19, the Investigator should determine whether the patient's IP should be continued, temporarily interrupted or permanently stopped. Refer to Section 3.9.4 for guidance on procedures in relation to COVID-19.

All AE reporting instructions in this section and SAE reporting in Section 6.4 also apply to any AE/SAE associated with COVID-19.

6.4 Reporting of serious adverse events

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

If any SAE occurs in the course of the study, other than mentioned in Section 6.3.9, then Investigators or other site personnel inform the appropriate AstraZeneca representatives within 1 day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it (see also Section 6.4.1).

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

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

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

If the WBDC system is not available, then the Investigator or other study site staff reports a SAE to the appropriate AstraZeneca representative by telephone. The AstraZeneca representative will advise the Investigator/study site staff how to proceed.

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

6.4.1 Reporting of SAEs that are also endpoints in the study

Efficacy endpoints in the study (VOCs and acute SCD complications [TIA/ischaemic stroke, hepatic sequestration and splenic sequestration, priapism and dactylitis]) fulfilling the criteria for SAE will not be reported by AstraZeneca to health authorities to avoid unnecessary unblinding of efficacy endpoints that are also SAEs.

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 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 CRF and on the Overdose CRF module.
- An overdose without associated symptoms is only reported on the Overdose CRF module.

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

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

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 6.4. For overdoses not fulfilling SAE criteria, AstraZenceca will ensure that the overdose is reported to the AstraZeneca data entry site within 30 calendar days of awareness.

6.6 Pregnancy

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

6.6.1 Maternal exposure

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

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

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

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

The same timelines apply when outcome information is available.

The eCRF is used to report the pregnancy. The outcome of the pregnancy is reported on a separate form outside the eCRF.

6.6.2 Paternal exposure

There is no restriction on fathering children or donating sperm during the study. Pregnancies in partners are not to be reported.

6.7 Medication error

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

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

Medication error includes situations where an error:

- Occurred
- Was identified and intercepted before the patient received the drug
- Did not occur, but circumstances were recognised that could have led to an error.

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

- Drug name confusion
- Dispensing error, eg, medication prepared incorrectly, even if it was not actually given to the patient

8.3.3 PK analysis set

All patients who receive at least 1 dose of IP and provide at least 1 post dose analysable plasma sample for PK analysis will be included in the PK analysis set.

Patients with major protocol deviations including changes to the procedures that may impact the quality of the data, or any circumstances that can alter the evaluation of the PK may be excluded from the PK analysis set.

8.3.4 PD analysis set

All patients who have receive at least 1 dose of IP and provide at least 1 postdose analysable sample for PD analysis will be included in the PD analysis set.

Patients with major protocol deviations including changes to the procedures that may impact the quality of the data, or any circumstances that can alter the evaluation of the PD may be excluded from the PD analysis set.

8.4 Outcome measure for analyses

See Section 2 for outcome measures.

8.5 Methods for statistical analyses

In general;

- Ticagrelor data will be pooled and analysed irrespective of dose.
- Safety, plasma concentrations of ticagrelor and active metabolite, HRQL variables will be presented using descriptive statistics and graphed as appropriate.
- Categorical variables will be summarised in frequency tables (number of patients and percentage), by treatment group.
- Continuous variables will be presented with descriptive statistics (n, arithmetic mean, standard deviation [SD], median, min, max), within treatment group. If appropriate, geometric mean and coefficient of variation (CV) will be used instead of arithmetic mean and SD, with CV (%) calculated as:
  $100 \cdot \sqrt{\left(\exp\left(s^2\right)-1\right)}$ where s is the SD of the data on a log scale.
- Data will also be presented in individual patient listings.
- Baseline values will be the closest observation prior to and including the randomisation visit.

8.5.1 Analysis of the primary variable

The primary analysis will be based on the intent-to-treat principle. Ticagrelor data will be pooled and analysed irrespective of dose.

The number of VOCs will be analysed using negative binomial regression. Any VOC event with an onset date within 7 days from a prior event onset date will not be counted as a new

episode. The response variable is the number of VOCs experienced by a patient over the treatment period. Patient follow-up time (log-transformed) will be included as an offset in the linear predictor to adjust for patients having different exposure times. Additional covariates to be adjusted for in the linear predictor will be treatment group (placebo as reference group) and baseline hydroxyurea therapy (Yes/No). The treatment effect will be tested at a 5% significance level.

If the negative binomial distribution is not appropriate, a Wilcoxon rank sum test will be used. As the Wilcoxon rank sum test cannot be adjusted for the patients follow-up time, sensitivity analyses will be performed to ensure robustness of the results.

The primary analysis (under the treatment policy estimand) includes all data until patients withdraw from the study regardless of if they discontinue from randomised treatment. The primary analysis uses the negative binomial regression model with logarithm of the observation period as an offset term and assumes that missing data is missing at random. Hence, the model assumes that the frequency-of-events during an unobserved period is the same as the frequency estimated using observed data.

To examine the sensitivity of the results and the robustness of this assumption analyses will be performed using controlled multiple imputation method. For this method, an underlying negative binomial stochastic process for the number of VOCs is assumed and post study withdrawal counts will be imputed based on the observed number of events prior to the withdrawal.

The following, but not limited to, missing data analysis will be performed:

- Missing counts in each arm are imputed assuming the expected event rate within that arm. This method corresponds closely to the original model and the results are expected to correspond closely to the primary analysis. This analysis is included to allow for comparison with the partial-DRMI method.
- Multiple imputation based on dropout reason (partial-DRMI); Missing counts will be imputed differently depending on the reason for dropout; meaning that counts for patients in the ticagrelor arm who withdraw consent for a potential treatment related reason are imputed based on the expected event rate in the placebo arm, whereas the remaining patients who have withdrawn consent are imputed assuming missing at random. Potential treatment related reasons include but are not limited to AEs, deaths and development of study specified reasons.

8.5.2 Analysis of the secondary variables

If numbers allow, the following will be analysed using the same analysis method as the primary endpoint: number of painful crises, number of ACSs, duration of painful crises, number of VOCs requiring hospitalisation or emergency department visits, number of days hospitalised for VOC, number of acute SCD complications, number of days hospitalised for acute SCD complications, and number of sickle cell-related red cell transfusions.

Table 2 Schedule of Assessments - Physical visits at study sites

	Screening period	Treatment period[a]										Follow-up period	For details see CSP Section
	Enrol-ment	Random-isation											
Visit Number	**1**	**2**	**3**	**4**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**End of Study (EOS)**	**Safety Follow-up**	
Day/Week/Month	**-7 d**	**0 d**	**2 wk**	**4 wk**	**3 mo[b]**	**6 mo[b]**	**9 mo[b]**	**12 mo[b]**	**15 mo[b]**	**18 mo[b]**	**21 mo[b]**	**{12 to 24 mo}**	**14d after EOS**	
Visit Window	**-28 to -7 d**	**N/A**	**±3 d**	**±7 d**	**±7 d**	**±7 d**	**±7 d**	**±7 d**	**±7 d**	**±7 d**	**±7 d**	**±14 d**	**±5 d**	
Blood samples for haematology and clinical chemistry	X	X[h]	X	X		X		X		X		X	X	5.2.1
Blood samples for coagulation (INR, PT and APTT)	X													5.2.1
Urine pregnancy Test[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	5.2.1
Urine for urinalysis (dipstick)	X	X[h]		X		X		X		X		X	X	5.2.1
Training and handout/collection of eDevice		X										X		
Review of eDevice device entries and reminder of use[j]			X	X	X	X	X	X	X	X	X	X		5.3.1
HRQL (PedsQL) assessment[k]		X				X		X		X		X		5.1.3
Palatability/swallowability[l]		X				X								5.3.1
Blood sampling for pharmacokinetics[m]		X		X		X		X		X		X		5.4
Blood sampling for pharmacodynamics (VASP)[m]		X		X		X		X		X		X		5.5
Dispense IP		X			X	X	X	X	X	X	X			7
Return IP and IP accountability			X	X	X	X	X	X	X	X	X	X		7.5 and 7.6
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	7.7
Adverse event collection (AEs and SAEs)	X[n]	X	X	X	X	X	X	X	X	X	X	X	X	6

AE Adverse event; APTT Activated partial thromboplastin time; BP Blood pressure; D Day; ECG Electrocardiogram; EOS End of study; eDevice Electronic device; FLACC Face, Legs, Activity, Cry, Consolability Scale; FPS-R Faces Pain Scale-revised; HBsAg Hepatitis B surface antigen; HCV Hepatitis C

4.1 Screening period

Procedures will be performed according to the Schedule of Assessments (Table 2).

Before any study-related assessments are performed, the informed consent/assent should be provided by the caregiver/patient, see Section 10.4.

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.

If the patient has had any serious illness after Visit 1 but before Visit 2, the need for repeated eligibility laboratory sampling must be evaluated before randomisation.

If the Visit 1 laboratory results are less than 10 days old at randomisation, they can replace randomisation safety laboratory sampling to minimise the blood volume drawn.

Unless done within previous 12 months, the Investigator must ensure TCD and ophthalmology examination are performed before proceeding in the study, see Section 3.2 for exclusion criteria related to these examinations. These examinations should thereafter be done annually during the study period.

4.2 Treatment period

4.2.1 Physical visits at study sites during the treatment period

Descriptions of the procedures for this period are included in the Schedule of Assessments for physical visits at study sites (Table 2).

At Visit 2, ensure the eligibility of the patient before continuing study-related assessments. The Paediatric Quality of Life Inventory (PedsQL) should be the first study assessment, ie, before blood sampling, electrocardiogram (ECG), etc. The patient will be administered his/her first dose of the double-blind treatment at the site. The collection of study assessments should be ensured before dispensing of the first dose. After the first dose is taken, assess palatability/swallowability.

For all on-site visits, remind the patient:

- To bring the IP bottles and the electronic Device (eDevice; including unscheduled visits) to the study site
- Not to take their dose at home in the morning of the visits with PK/PD sampling scheduled at the visit. The patient should be reminded on how to use the eDevice including during a potential VOC event, regardless of primary setting of treatment (eg, in-patient hospitalisation, short-stay outpatient unit, emergency department or self-treated), see Section 5.1.1.

Contraceptive method should be reviewed and monitored in females of childbearing potential.

1.5 Study governance and oversight

1.5.1 Steering Committee

A Steering Committee (SC) has been appointed for this study and has provided expert advice on, eg, the overall design, including the development of the protocol. The SC will continue to advice on any protocol amendments and will monitor study conduct, result interpretation and reporting of the study. The SC can propose to AstraZeneca their recommendations regarding study modifications or a potential early stop to the study based on the information received from the DMC. The SC is comprised of designated international academic leaders and non-voting members of the Sponsor, and will operate under a SC charter.

The Sponsor has the overall responsibility of the study.

1.5.2 Data Monitoring Committee

A DMC composed of independent SCD paediatric experts and including a platelet expert and statistician, will be appointed for this study and will report to the SC. The DMC 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. The DMC will have access to unblinded individual data and be able to evaluate these while the study is ongoing. The DMC meeting schedule is shown in Table 1. Additional meetings could be initiated by the DMC chair or the Sponsor as needed.

The DMC will consider recommending study termination for any episode of bleeding deemed related to the ticagrelor treatment that is fatal, or is a spontaneous intracranial haemorrhage, or if the accumulating data suggest a strong likelihood of excessive haemorrhagic events possibly related to ticagrelor that require medical intervention as reported by the Investigator. Study termination will also be considered if the number of fatal or life-threatening serious adverse events (SAEs), including but not limited to bleedings, is greater in ticagrelor-treated patients compared to placebo.

The DMC will make recommendations on the progression of the study based on the totality of data (eg, AEs, safety laboratory variables, ticagrelor exposure and platelet inhibition) or other findings putting patients at undue risk. The Sponsor has the final decision on study progression including amendments, etc.

Additionally, the DMC will do a formal interim PD assessment when 60 patients have had their PK/PD sampling after 4 weeks in the study. In this interim PD assessment, the mean of pre-dose and 2 hours post dose PRI values at 4 weeks will be calculated for each individual and compared to their respective baseline values. The population mean of the platelet inhibition in the ticagrelor arm is expected to be above 35% during the study. If there is a risk of not achieving the targeted inhibition level of 35% to 80% in the study, the first task of the DMC would be to investigate if the PK values and the PK/PD relationship are as expected and in line with earlier documented PK/PD data of ticagrelor. If any finding is deemed by the DMC to not be in accordance with expected PK and PD data and all other reasons for the unexpected findings are ruled out, they will contact the Sponsor and ask for proof of treatment

- Total bilirubin level ≥2 × ULN

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

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

- Notify the AstraZeneca representative
- Request a repeat of the test (new blood draw) by the central or local laboratory
- Complete the appropriate unscheduled laboratory case report form (CRF) module(s) with the original local laboratory test result.

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

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

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

- Notify the AstraZeneca representative
- Determine whether the subject meets PHL criteria (see Section 2 Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF.

Follow-up

Potential Hy's Law Criteria not met

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

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

Potential Hy's Law Criteria met

If the subject 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 subjects' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

Discussion item	Specific question (as applicable)
Collect any AEs with onset since last contact, and check status of ongoing AEs. As outlined in the corresponding eCRF modules, use follow-up questions as needed to cover: • Start/stop, • Outcome, • Any treatments provided, • Seriousness, • Severity, • Relationship to study drug or study procedures, • And any changes to study drug treatment	"What about the <<ongoing event (eg, cold, ankle sprain, etc.) >> we talked about last time? What happened with that?"
7. Collection of any VOC endpoints **Purpose:** To ensure any VOC events not yet reported to Investigator are captured. Questions should be tailored to ensure all the relevant data are collected for events meeting criteria for a VOC endpoint (painful crisis or ACS) so the eCRF can be completed*, examples: • Judge if event meets VOC definitions for this study • Start/stop • Treatment setting • Pain localisation • Type of analgesics taken (opioid/non-opioid) • Any other treatments given	*Unless already sorted out during the AE Discussion Item above, ask specifically about VOC events:* "Has <<patient name>> experienced any painful episodes or had any episodes with chest problems, fever, and often also breathing symptoms, since the last time we talked?"

Secondary Objective:	Outcome Measure:
To describe the intensity of pain during VOC	Intensity of worst pain daily during VOC - For patients ≤4 years of age, observer reported using the Face, Legs, Activity, Cry, Consolability Scale (FLACC) - For patient ages ≥5 to 18 years of age, self-reported using the Faces Pain Scale - Revised (FPS-R)
To describe analgesics used during VOC	Type of analgesics (opioid and non-opioid) use
To describe patient acceptability of the formulation (palatability and swallowability)	- For patients ≤4 years of age taking the tablet dispersed or whole, an observer assessment of palatability and swallowability will be undertaken - For patients ≥5 years of age taking the tablet dispersed or whole, palatability will be assessed and categorized using the Facial Hedonic Scale

[a] The acute SCD complications will be defined in Section 5.1.5 in Clinical Study Protocol.

Safety Objective:	Outcome Measure:
To assess long-term safety and tolerability of therapy with ticagrelor vs placebo	Adverse Events/Serious Adverse Events, including bleeding Vital signs and laboratory safety variables

Target subject population

The target population is children aged ≥2 to <18 years of age and body weight of ≥12 kg diagnosed with homozygous sickle cell anaemia (HbSS) or sickle beta-zero-thalassaemia (HbS/β^0).

Patients that experienced at least 2 VOC events in the past 12 months prior to Visit 1 and fulfil eligibility criteria will be enrolled in this study.

Duration of treatment

Eligible patients will receive double-blind ticagrelor or placebo twice a day (bd) for at least 12 months but no longer than 24 months. The expected average follow-up is 18 months, assuming a uniformly distributed enrolment period of 12 months.

Investigational product, dosage and mode of administration

The double-blinded study drug dose will be weight dependent:

- ≥12 to ≤24kg: Ticagrelor 15 mg or matching placebo, twice a day
- >24 to ≤48 kg: Ticagrelor 30 mg or matching placebo, twice a day
- >48 kg: Ticagrelor 45 mg or matching placebo, twice a day.

Abbreviation or special term	Explanation
TIA	Transient Ischemic Attack
ULN	Upper limit of normal
VASP	Vasodilator-stimulated phosphoprotein
VOC	Vaso-occlusive crisis
WBDC	Web Based Data Capture

activities during several days. The painful crises are repeatedly described as the most challenging symptom of their disease by patients with SCD. An ACS is a serious and potentially life-threatening condition that may lead to respiratory failure or multi organ failure, and is a common cause of death in SCD patients. Most cases of ACS require hospitalisation for >1 week (Vichinsky et al 2000). Besides the acute symptoms, the ischaemia during vaso-occlusion causes tissue damage that over time leads to impaired organ function (eg, renal failure) or complications such as bone necrosis, joint pain or cognitive impairment. Pharmacological treatments options to prevent VOC events in children are few and side effects can be dose-limiting (hydroxyurea). With previous studies of anti-platelet drugs suggesting potential to reduce VOCs (Cabannes et al 1984, Heeney et al 2016) and the high unmet need for new treatments, there is a clear value in continuing to investigate the role of anti-platelet therapies in the reduction of VOCs.

Inherent to their reduction in platelet reactivity, antiplatelet agents increase the risk of bleeding. Ticagrelor has been on the market since 2010 for use in adult patients with coronary artery disease to reduce the risk for cardiovascular events. The safety profile has been thoroughly evaluated in large trials. The PEGASUS study (D5132C00001) evaluated the combination of ticagrelor 60 or 90 mg bd with aspirin in adult patients with a history of myocardial infarction. This dual anti-platelet therapy resulted in more bleeding events overall compared to aspirin alone; however, the majority of these bleedings were of lesser severity (eg, epistaxis, bruising and hematomas). In the adult clinical programme for ticagrelor, including several large cardiovascular outcome studies, the number of reported events of fatal bleeding have been low and similar for ticagrelor and comparators (ie, clopidogrel, placebo, and aspirin). Doses in HESTIA3 have been selected to result in a less pronounced level of platelet inhibition (~35% to 80%) than doses used in adult patients with cardiovascular disease (>80%), and unlike in these patients, ticagrelor will not be combined with aspirin in HESTIA3. A lower bleeding risk is therefore anticipated in HESTIA3 than in previous adult cardiovascular outcome studies. Selected doses for HESTIA3 are within the range evaluated in children and young adults (HESTIA1 and HESTIA2). No safety concerns were raised from these studies, and there was no indication of an increased bleeding risk with ticagrelor.

Prasugrel and clopidogrel are other drugs in the $P2Y_{12}$ inhibitor class, but unlike ticagrelor, which reversibly inhibits the $P2Y_{12}$ receptors on platelets, these are irreversible $P2Y_{12}$ receptor inhibitors. The recent paediatric Phase III study with prasugrel in children with SCD (Heeney et al 2016) investigated doses resulting in around 20% platelet inhibition, with no significant difference in the safety endpoints, including the frequency of bleeding events requiring medical intervention, compared to placebo. Although not in children with SCD, the CLARINET study with clopidogrel randomised 906 infants aged ≤92 days with congenital heart disease to clopidogrel or placebo for a median of 5.8 months (Wessel et al 2013) using doses shown to give an average platelet inhibition of 45% to 50% (Wessel et al 2013, Li et al 2008). No increased bleeding risk was observed for clopidogrel compared to placebo in this study.

In HESTIA3, measures will be taken to minimise bleeding risk in participating patients. The eligibility criteria, restrictions and discontinuation criteria are tailored to exclude patients with increased risk for bleeding from participation, and other medications impacting platelet

7. Chronic use of NSAIDs defined as continuous intake >3 days per week that cannot be discontinued
8. Receiving chronic treatment with anticoagulants or antiplatelet drugs that cannot be discontinued
9. Moderate or severe hepatic impairment defined as laboratory values of alanine aminotransferase (ALT) >2 × upper limits of normal (ULN), total bilirubin >2 × ULN (unless judged by the Investigator to be caused by haemolysis), albumin <35 g/L (3.5 g/dL) and International normalised ratio (INR) >1.4, or symptoms of liver disease (eg, ascites) from test performed at Screening (Visit 1).
10. Renal failure requiring dialysis
11. 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.
12. Concomitant oral or intravenous therapy with strong cytochrome P450 3A (CYP3A) inhibitors, CYP3A substrates with narrow therapeutic indices, or strong CYP3A inducers (see full list in Appendix G), which cannot be stopped at least 5 half-lives before randomisation.
13. Active untreated malaria. Patients with suspected malaria at Screening (Visit 1) will be tested.
14. Known hypersensitivity or contraindication to ticagrelor
15. Patients who are currently pregnant or breastfeeding, or planning to become pregnant during the study or have given birth less than 3 months prior to Screening (Visit 1)
16. Any condition which, in the opinion of the Investigator, would make it unsafe or unsuitable for the patient to participate in this study
17. Concern for the inability of the patient or caregiver (defined as legally authorised representative) to comply with study procedures and/or follow-up
18. Previous randomisation in the present study
19. Participation in another clinical study with an IP or device during the last 30 days preceding screening.
20. Involvement of member of patient's family, or patient self, in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).

Procedures for withdrawal of incorrectly enrolled patients see Section 3.3.

3.3 Subject enrolment and randomisation

Investigator(s) should keep a record, the patient screening log, of patients who entered pre-study screening. Enrolment can occur 7-28 days before randomisation.

The Investigator(s) will:

1. Obtain signed informed consent/assent (per local requirements) from caregiver of the potential patient and from the patient (if applicable) before any study specific procedures are performed.
2. Assign (using the Interactive Voice/Web Response System [IXRS]) potential patient a unique enrolment number, beginning with 'E + 4-digit site number + 3-digit patient

5 behaviours observed are assigned a score of 0, 1 or 2. The total FLACC score will then range between 0 and 10, with 0 representing no pain.

The Faces Pain Scale - Revised (FPS-R) will be administered to all patients aged ≥5 years. When needed the caregiver can help the child with the assessment. It is important to train caregivers not to attempt to influence child's response in any way. The scale consists of 6 faces and scoring ranges between 0 and 10 (with an increase in numeric value by 2 [ie, 0, 2, 4, 6, 8, 10]), where 0 is no pain and 10 is very much pain. The FPS-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 years of age (Cohen et al 2008).

A body outline diagram will also be presented and the patient/caregiver will be asked to indicate the location(s) of the pain. See Appendix H for details of these pain assessments. Worst pain ratings will be collected once daily throughout the duration of the VOC event using an eDevice.

All instruments will be based on patients' age at baseline, and the same version should be used throughout the study.

5.1.3 Health-related quality of life (HRQL)

The HRQL will be assessed using the PedsQL SCD Module and Multidimensional Fatigue Scale. The SCD module consists of 43 items and measures problems with the patients' pain (severity, impact, management/control), worry, emotions, treatment and communication. The SCD module measures 9 sub-scales and a total score. The Multidimensional Fatigue Scale consists of 18 items measuring problems with general, sleep/rest and cognitive fatigue. The Multidimensional Fatigue Scale measure 3 sub-scales and a total score. The SCD module and the Fatigue Scale when used in SCD have shown acceptable to excellent measurement properties in both the patient-reported versions for ages 5 to 18 years and the parent-reported version for ages 2 to 4 years (Panepinto et al 2013, Panepinto et al 2014).

Both instruments have been developed in age-specific versions. In this study, the patient-reported versions are for patients ages 5 to 7, 8 to 12, and 13 to 18 years, respectively. For patients 2 to 4 years of age, the parent-reported version will be reported by a caregiver. See Appendix I for details of HRQL. Data will be collected using pen and paper at the site and will be administered at randomisation and every 6 months thereafter.

Appropriate procedures for minimising bias and enhancing compliance will be followed throughout the study. To ensure this, all study personnel will be trained to instruct the patient in a standardised way and further be responsible for providing all relevant instructions and training to the patients. A standardised procedure for the administration of the HRQL questionnaires should be applied.

Each centre must allocate responsibility for completion of the PedsQL questionnaires to a specific individual (eg, a Research Nurse). It is also important that the significance and relevance of the data are explained carefully to participating patients/caregivers so that they

as source data for laboratory variables. For information on how AEs based on laboratory tests should be recorded and reported, see Section 6.3.

NB. In case a patient shows an AST **or** ALT ≥3 × ULN **and** total bilirubin ≥2 × ULN, refer to Section 6.3.7 for further instructions.

5.2.2 Physical examination

A complete physical examination will 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 and neurological systems.

A brief examination of physical examination will include the following: general appearance, respiratory, cardiovascular and abdomen systems.

Physical examination will be performed at timelines as specified in the Schedule of Assessment in Table 2. Investigators should pay special attention to new or worsening abnormalities as they may qualify as AEs, see Section 6.3.6 for details.

5.2.3 ECG

5.2.3.1 Resting 12-lead ECG

A 12-lead ECG (standard ECG with a paper speed of 25 or 50 mm/second covering at least 6 sequential beats) will be recorded after the patient has been lying down to rest for up to 5 minutes. After ECG has been recorded, the Investigator or designated physician will review each of the ECGs and enter as 'Normal' or 'Abnormal' in the eCRF. If the ECG is evaluated as "Abnormal" the Investigator should document the specific abnormality as clinically significant or not.

A standardised ECG machine should be used and a paper copy of ECG tracing should be filed in the patient's medical records.

5.2.4 Vital signs

5.2.4.1 Weight and height

Weight and height assessments will be performed at the visits as shown in Table 2. Results available in medical records, as taken on the visit day, will be recorded in the eCRF.

The study site staff should use a digital precision scale if possible, and record the weight in kilograms or pounds to the first decimal point (eg, 95.3 kg). The same scale should be used and the patient should wear a standard hospital-type gown or equivalent light clothing and no shoes for the body weight measurement at each visit.

5.2.4.2 Pulse rate and blood pressure

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

The predose VASP sample also contains important information on the relationship of ticagrelor dose to exposure and platelet inhibition response and therefore, the correct time recording of the last dose the evening before the visit is equally important as the sample itself.

In case of increased dose due to increased weight, the PD sample will be collected at the following visit. The PD sample will be collected 0 hours (predose) and 2 hours postdose.

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

5.5.3 Storage and destruction of pharmacodynamics samples

Pharmacodynamic samples may be disposed of or destroyed and anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled pharmacodynamic samples to further evaluate and validate the analytical method before finalisation of the CSR. Any results from such analyses may be reported separately from the CSR.

Samples will be stored until the study is finalised, after which they will be destroyed. Detailed information about samples storage can be found in the Laboratory Manual. The results of any investigation will be reported either in the CSR itself or as an addendum, or separately in a scientific report or publication.

5.6 Genetics (Not applicable)

5.7 Biomarker analysis (Not applicable)

5.8 Volume of blood

The total maximum volume of blood that will be drawn from each patient at each study visit is listed in Table 5 below.

Table 5 Volume of blood to be withdrawn from each patient

	Total maximum volume (mL)	
	12 to 24 kg body weight	**>24kg body weight**
Visit 1 (Enrolment)	9,9	13,8
Visit 2 (Randomisation)	6,6	7,7
Visit 3 (2 weeks)	3,4	4,5
Visit 4 (4 weeks)	7,8	8,9
Visit 6 (3 months)	0	0
Visit 9 (6 months)	7,8	8,9
Visit 12 (9 months)	0	0
Visit 15 (12 months)	7,8	8,9
Visit 18 (15 months)	0	0
Visit 21 (18 months)	7,8	8,9
Visit 24 (21 months)	0	0

- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated, eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed, eg, kept in the fridge when it should be at room temperature
- Wrong patient received the medication (excluding IXRS errors)
- Wrong drug administered to patient (excluding IXRS errors).

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

- Errors related to or resulting from IXRS - including those which lead to 1 of the above listed events that would otherwise have been a medication error
- Patient accidentally missed drug dose(s), eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Patient failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open-label studies, even if an AstraZeneca product.

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

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

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

6.8 Management of IP-related toxicities

See Section 3.9.

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product(s)

Investigational product	Dosage form and strength	Manufacturer
Ticagrelor 15 mg tablet	Oral, plain, round, biconvex, white/off-white, uncoated, 15 mg	AstraZeneca
Placebo for ticagrelor 15 mg tablet	Oral, plain, round, biconvex, white/off-white, uncoated, containing no active ingredient	AstraZeneca

Number (%) of patients per type of analgesic use will be summarised. Number (%) of patients per palatability and swallowability category will be summarised. Descriptive statistics will be presented for the intensity of VOC-related pain, proportion of day's absence from school or work due to SCD and HRQL score; no statistical testing will be performed for these endpoints. The descriptive statistics will include n, arithmetic mean, SD, median, minimum and maximum.

8.5.3 Analysis of the exploratory variables

For categorical variables, the population size (N for sample size and n for available data) and the percentage (of available data) for each class of the variable will be presented. Continuous variables will be summarised using descriptive statistics, including n, arithmetic mean, SD, median, minimum and maximum values. If appropriate, geometric mean and CV will be used instead of arithmetic mean and SD.

A population PK and PK/PD analysis may be performed and include an investigation of the impact of (or lack of) relevant demographic and disease-related covariates. This analysis will be reported separate from the CSR.

8.5.4 Analysis of the safety variables

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Number of patients with events and percentages will be tabulated by preferred term and system organ class. An event that occurred once or more times during the treatment period will contribute 1 observation to the numerator of the proportion. The denominator of the proportion will comprise all patients in the safety set. Adverse events will also be summarised by intensity/severity and separately, by causality/relatedness (as determined by the Investigator). Should a patient report the same preferred term/system organ class within multiple intensity/severity or causality/relatedness categories, the patient's worst occurrence (most severe/most related) will be tabulated. Serious AEs, AEs leading to discontinuation of IP, and commonly occurring AEs will be summarised in a generally similar manner. Adverse events, SAEs, AEs leading to death, and AEs leading to discontinuation of IP will be summarised for each treatment group as applicable.

Laboratory data will be summarised by presenting shift tables from baseline to end of study using normal ranges and by presenting summary statistics of observed and change from baseline values (means, medians, quartiles, ranges). The incidence of clinically notable laboratory abnormalities will be summarised.

Vital sign data will be summarised by presenting summary statistics of observed and change from baseline values. The incidence of clinically notable vital sign abnormalities will be summarised.

For summarising of bleeding event, the number and percent of patients who experience (1) at least 1 bleeding event; (2) at least 1 major bleeding event; (3) at least 1 major or clinically relevant non-major bleeding event; (4) at least 1 minor bleeding event, will be presented by treatment group. The total number of events will also be provided.

virus; HIV Human immunodeficiency virus; HRQL Health-related quality of life; INR International normalised ratio; IP Investigational product; IXRS Interactive Voice/Web Response System; mo Month; PedsQL Paediatric Quality of Life Inventory; PD Pharmacodynamics; PK Pharmacokinetics; PT Prothrombin time; SAE Serious adverse event; SCD Sickle cell disease; TCD Transcranial Doppler; VASP Vasodilator-stimulated phosphoprotein; VOC Vaso-occlusive crisis; wk Week.

[a] Confirm patient still meets inclusion and exclusion criteria prior to randomising the patient in IXRS; SCD diagnostic testing not necessary if documented in medical records.

[b] Interval must not be more than 100 days to ensure tablet supply for all days.

[c] Age is required, but partial birthdate (year/month) is allowed if full data is not allowed or known.

[d] See inclusion criteria #4 for TCD and #5 for ophthalmology exam. Results must be available prior to randomisation and these examinations should thereafter be done annually during the study period.

[e] Only weight will be measured at Visit 2.

[f] A complete physical examination will be performed at Visit 1, EOS and Follow-up Visit and a brief examination at all other visits (see Section 5.2.2).

[g] Local/standard tests to be used for diagnosis of malaria for patients who are symptomatic at Screening.

[h] If the patient has had any serious illness after Visit 1 but before Visit 2, the need for repeated eligibility laboratory sampling must be evaluated before randomisation. If the Visit 1 laboratory results are less than 10 days old at randomisation, they can replace randomisation safety laboratory sampling to minimise the blood volume drawn.

[i] For females of childbearing potential.

[j] Electronic recording of worst pain according to FPS-R/FLACC and localisation of pain after experiencing a VOC, analgesic use and absence from school/work due to SCD.

[k] The HRQL (PedsQL) instruments are patient-reported if 5-7 years, 8-12 years, or 13-18 years and reported by a caregiver if the patient is ≤4 years.

[l] Morning dose of IP to be taken at the site. The palatability/swallowability questionnaire assessed by an observer in children ≤4 years, and by Facial Hedonic Scale (FHS) for children ≥5 years.

[m] Samples for PK and PD analysis will be taken 0 hour (predose) and 2 hours postdose at specified visits and in case of changed dose due to weight increase. No predose PK sample at Visit 2.

[n] SAEs should be collected from when the ICF is signed. AEs should be collected from time of randomisation.

Note: In case of modified follow-up when IP is discontinued, the study site visits can be replaced with telephone contact visits as per Table 3.

compliance and potentially escalate the issue the Steering Committee regarding a potential amending of the study in order to evaluate the need for a dose change based on new modelling and simulations including the new data.

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

Table 1 Data Monitoring Committee meeting schedule

Evaluation	Number of patients randomized	Completed visit (months)
1	40 patients completed Visit 4 or 10 patients completed Visit 6	4 (1) or 6 (3)
2	60 patients (formal interim PD assessment)	4 (1)
3	80 patients	6 (3)
4	80 patients	9 (6)
5	All patients	4 (1)
6	All patients	9 (6)
x	Patients remaining in study	As needed[a]

[a] As deemed necessary by the DMC chair and/or Sponsor.
PD pharmacodynamic.

2. STUDY OBJECTIVES

A VOC is the composite of a painful crisis and/or an ACS (Howard et al 2015, Yawn et al 2014). Each component is defined as:

A painful crisis is an onset or worsening of pain that lasts at least 2 hours, for which there is no explanation other than vaso-occlusion and which requires therapy with oral or parenteral opioids, parenteral non-steroidal anti-inflammatory drugs (NSAIDs), or other analgesics prescribed by a health care provider in a medical setting (such as a hospital, clinic, or emergency room visit) or at home.

An ACS is an acute illness characterized by fever and/or respiratory symptoms, accompanied by a new pulmonary infiltrate on a chest X-ray.

2.1 Primary objective

Primary Objective:	Outcome Measure:
To compare the effect of ticagrelor vs placebo for the reduction of VOCs, which is the composite of painful crisis and/or ACS, in paediatric patients with SCD	Number of VOCs

- Monitor the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Study Physician. This includes deciding which tests available in the HL lab kit should be used.
- Complete the 3 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.

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 Global Clinical Lead or equivalent 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 total bilirubin level 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 AstraZeneca standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and total bilirubin level 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.

Discussion item	Specific question (as applicable)
*Note that depending on where the event was treated, copies of medical records from other clinic or hospital may be needed.	
8. eDevice functionality and usage **Purpose:** To ensure that the eDevice is working OK and identify any need for re-training. Questions should be tailored based on entries made in StudyWorks, eg, if perfect compliance to weekly assessments of school/work absence but no VOC events, question could focus on ensuring no potential VOC events have been missed. Potential problems with using the eDevice should be further explored and resolved. Remind parent/caregiver of the self-training availability in the eDevice. Offer extra visits to site for hands-on re-training as needed.	"Have you and <<patient name>> experienced any issues with using the eDevice?" *If any expected data in StudyWorks is missing:* "I can see that you have not recorded much about <<pain intensity / absence from school/work>> in your eDevice." "Is there anything more relating to << pain intensity / absence from school/work>> that you haven't included?" "Is there anything else you haven't included?" "Please can you tell me if there is something we can do to help the eDevice recordings work better for you?"