Statistical Analysis Plan	
Study Code	D5136C00009
Edition Number	V3.0
Date	26 June 2020

A Randomised, Double-Blind, Parallel-Group, Multicentre, Phase III Study to Evaluate the Effect of Ticagrelor versus Placebo in Reducing the Rate of Vaso-Occlusive Crises in Paediatric Patients with Sickle Cell Disease (HESTIA3)

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SIGNATURE OF STUDY STATISTICIAN

Study Statistician

PPD

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SIGNATURE OF GLOBAL PRODUCT STATISTICIAN

Global Product Statistician

PPD

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ACS	Acute Chest Syndrome
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
aMean	Arithmetic Mean
APTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
ASCD	Acute SCD Complications
ATC	Anatomic Therapeutic Chemical
AUC	Area under the plasma concentration-time curve from zero to infinity
bd	Twice Daily
β-hCG	Beta-human Chorionic Gonadotropin
BLQ	Below the Limit of Quantification
BUN	Blood Urea Nitrogen
CI	Confidence Interval
CL/F	Oral Clearance
COVID-19	Coronavirus Disease 2019
CSED	Common Study End Date
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CTMS	Clinical Trial Management System
CV	Coefficient of Variation
DBP	Diastolic Blood Pressure
DL	Direct Likelihood Approach
DRMI	Drop-out Reason Multiple Imputation
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOS	End of Study
FAS	Full Analysis Set
FHS	Facial Hedonic Scale
FLACC	Face Legs Activity Cry Consolability Scale
FPS-R	Faces Pain Scale Revised
gCV%	% Geometric Coefficient of Variance

Abbreviation or special term	Explanation
gMean	Geometric Mean
gSD	Geometric Standard Deviation
Hb	Haemoglobin
HbS/β^0	Sickle beta-zero-thalassaemia
HBsAg	Hepatitis B Surface Antigen
HbSS	Homozygous Sickle Cell Anaemia
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HL	Hy's Law
HRQL	Health-related Quality of Life
IDMC	Independent Data Monitoring Committee
INR	International Normalised Ratio
IP	Investigational Product
ITT	Intent to Treat
IxRS	Interactive Voice/Web Response System
LDH	Lactate Dehydrogenase
LLN	Lower Limit of Normal
LLOQ	Lower Limit of Quantification
MAR	Missing at Random
Max	Maximum
MCMC	Markov chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
Min	Minimum
MNAR	Missing Not at Random
NBD	Negative Binomial Distribution
NC	Not Calculable
NQ	Non-quantifiable
NR	Not Reportable
NS	No Sample
NSAID	Non-steroidal Anti-inflammatory Drug
OAE	Other significant Adverse Events
PD	Pharmacodynamics
pDRMI	Partial Drop-out Reason Multiple Imputation

Abbreviation or special term	Explanation
PedsQL	Paediatric Quality of Life Inventory
PHL	Potential Hy's Law
PK	Pharmacokinetics
PP	Per Protocol
PRI	Platelet Reactivity Index
PT	Preferred Term
PTT	Partial Thromboplastin Time
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SC	Steering Committee
SCD	Sickle Cell Disease
SD	Standard Deviation
SI	Standard International
SMPA	Study Medication Palatability Assessment
SOC	System Organ Class
TBL	Total Bilirubin
TIA	Transient Ischemic Attack
ULN	Upper Limit of Normal
VASP	Vasodilator-stimulated Phosphoprotein
VOC	Vaso-occlusive Crisis
WHODD	World Health Organisation Drug Dictionary
ZINB	Zero-inflated Negative Binomial (distribution)
ZIP	Zero-inflated Poisson

AMENDMENT HISTORY

Date	Description of Change
26 June 2020	Changed IQVIA study statistician from PPD to PPD Updated SAP due to blind delivery review (BDR) comments review meeting (CRM) and due to protocol amendment related to COVID-19 such that the SAP is based on the clinical study protocol (CSP) V3.0 dated 20 April 2020. Changes made throughout to reflect sponsor's decision to terminate the study early. Minor edits that do not substantively alter the content of the document have been made for consistency and clarity where applicable and are not individually listed in this version history. Specifically: Section 1.3: Clarified that the randomisation codes will be computer-generated by Parexel and not AstraZeneca R&D Section List of Abbreviations, 2.2, 3.4.1, 3.4.7, 4.2.1, 4.2.4, 4.2.5, 4.2.5.2, 4.2.9.1 Appendix E: Added COVID-19 Section 3.1.4.1: Clarified EoS with the study having stopped. Section 4.2.4: Deleted + 7 days for medications so that concomitant definition is different Section 4.2.6.2: Added clarification on Wilcoxon rank sum test Section 4.2.6.4: Added age subgroups for overall adverse events (AEs) summary and AEs by system organ class (SOC)/preferred term (PT) Section 4.2.5.2: Changed compliance to be derived relative to actual exposure days (excluding missed exposure days due to study treatment interruptions) Section 4.2.8.3, 4.2.8.5, 4.2.10.1: Added clarification on durations (days) for painful crises, acute chest syndrome and hospitalisations for efficacy analysis Appendix C,D and E: Revised imputations in appendices due to BDR1

16 March 2020	Section 2.1 Table 1 Added in per protocol analysis set. Changed "major protocol deviations" to "important protocol deviations". Section 2.1 Table 2 Updated table to include SCD-related red blood cell transfusion endpoint. Footnotes added to include sensitivity analysis for VOC. Added remaining secondary endpoints. Deleted reference to PK parameters as this is not applicable. Changed "major" to "important" protocol deviations. Section 3.2 Added clarification for any patient who does not experience a VOC event. Count of events will be assumed to be 0. Section 3.3 Definition of on-treatment and off-treatment red blood cell transfusions added in. Section 3.4 Aligned Hy's Law with CSP, version 2.0, dated 29 August 2018. Section 4.2 Correction to number of years since SCD diagnosis to clarify this is from date of randomisation (Visit 2) and not date of birth. Updated "extent of disease" to "disease history". Added in category of < 1 VOC event experienced. Section 4.2 Treatment exposure and compliance revised to include total/actual treatment exposure (days), missed exposure days, total exposure years (across patients), treatment compliance (%) and weight (kg) versus dose level administration disagreement by individual dose level (15 mg/30 mg/45 mg [per tablet count]) and overall dose level. Section 4.2 Added in Wilcoxon rank sum test by subgroup. Added in category ≤ 1 VOC event in the last 12 months. Additional sensitivity analysis added including analysis based on PP analysis set and analysis based on baseline hydroxyurea use. Tipping point analysis added in. Section 4.2.8.6 Correction "worst evaluation" to "baseline to last on-treatment observation" for ECG summary. Section 4.2.9.2 Reference to PK parameter analysis is not within the scope of this SAP and has been deleted. Section 8 New appendices added to capture race mapping, partial or missing concomitant medication date imputations, missing or partial date of SCD diagnosis imputation and to detail sensitivity analyses of the primary efficacy endpoint.

1 STUDY DETAILS

1.1 Study Objectives

This statistical analysis plan (SAP) contains a more detailed description of the analyses described in the clinical study protocol (CSP), version 3.0 dated 20 April 2020. The primary, secondary, safety, and exploratory objectives (apart from the population pharmacokinetics [PK] model) are within the scope of this SAP. The population PK model will not be reported in the main clinical study report (CSR).

1.1.1 Primary Objective

Primary Objective	Outcome Measure
To compare the effect of ticagrelor vs placebo for the reduction of vaso-occlusive crises (VOCs), which is the composite of painful crisis and/or acute chest syndrome (ACS), in paediatric patients with sickle cell disease (SCD)	Number of VOCs

Primary endpoint as assessed throughout the treatment period which is defined from randomisation (Visit 2) to the end of study (EOS) visit or date of premature study discontinuation (refer to Sections 3.1.4 and 3.2.1 for further details).

1.1.2 Secondary Objectives

Secondary Objectives	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

Secondary Objectives	Outcome Measure
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 CSP Appendix I
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 recorded daily during VOC - For patients ≤ 4 years of age, observer-reported using the Face, Legs, Activity, Cry, Consolability Scale (FLACC) - For patients ≥ 5 years 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 3.3.4.
Secondary endpoints as assessed throughout the treatment period which is defined from randomisation (Visit 2) to the end of study (EOS) visit or date of premature study discontinuation (refer to Sections 3.1.4 and 3.1.4.1 for further details).

1.1.3 Safety Objectives

Safety Objective	Outcome Measure
To assess long-term safety and tolerability of therapy with ticagrelor vs placebo	Adverse events (AEs)/Serious adverse events (SAEs), including bleeding, vital signs and laboratory safety variables

1.1.4 Exploratory Objectives

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

[a] Not within the planned scope of this SAP.
[b] CL/F Apparent total clearance of the drug from plasma after oral administration. AUC Area under the plasma concentration-time curve.

1.2 Study Design

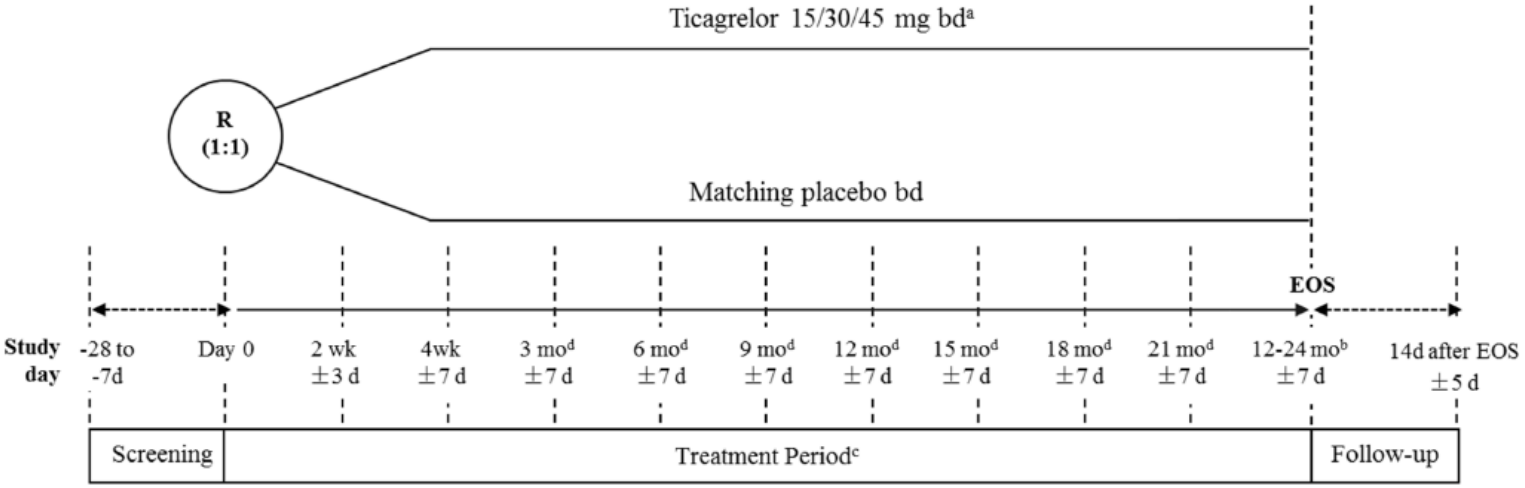
This is an international, multicentre, double-blind, randomised, parallel-group, placebo-controlled Phase III study to evaluate the effect of ticagrelor versus placebo in reducing the rate of vaso-occlusive crisis (VOC) events in paediatric patients with sickle cell disease (SCD). Patients will be monitored for occurrence of VOC events and other acute SCD complications.

Study participants should receive standard of care for SCD. In the treatment period, patients are to be followed for up to 24 months or until a common study end date (CSED) is reached, defined as 12 months after the last patient is randomised.

The target population is children aged ≥ 2 years to < 18 years and body weight of ≥ 12 kg diagnosed with homozygous sickle cell anaemia (HbSS) or sickle beta-zero-thalassaemia (HbS/β0). Patients that experienced at least two VOC events in the past 12 months prior to screening (Visit 1) and who fulfil the eligibility criteria will be enrolled in this study. At least 50 evaluable patients should be recruited in each of the age groups, ≥ 2 years to < 12 years and ≥ 12 years to < 18 years.

A schematic representation of the study design is shown in Figure 1.

Figure 1 Study Design



bd Twice daily. d Day. EOS End of Study. mo Month. R Randomisation. wk Week.
a Patients randomised to ticagrelor will receive doses based on weight-band (at randomisation [Visit 2]): ≥ 12 kg to ≤ 24 kg=15 mg, > 24 kg to ≤ 48 kg=30mg, > 48 kg=45 mg.
b EOS = Patients will be followed to common study end date defined as 12 months after the last patient is randomised, or up to 24 months.
c See CSP Table 2 for assessments during site visits (in-clinic) and CSP Table 3 for telephone visits that will occur monthly after Week 4 between site visits (in-clinic).
d Interval must not be more than 100 days to ensure tablet supply for all days.
NB. Only in-clinic visits are shown.

1.3 Number of Patients

The sample size was derived under the assumptions that the number of VOCs has a negative binomial distribution with shape parameter 0.8 and that the mean number of crises per year is 2.0 in the placebo group with reduction of 50% in the ticagrelor group. Considering that patients will be randomised in a 1:1 ratio, with minimum follow-up of 12 months and average follow-up of 18 months, 154 patients will provide about 90% power for a 2-sided test of the mean number of crises for ticagrelor versus placebo, at significance level 5%. Allowing for dropouts, the sample size is increased to 182. The calculations were based on simulation with 5,000 repetitions. Scenarios and simulations were evaluated to assess the risk with shorter and longer mean follow-up time. To ensure that the study is adequately powered the recruitment rate will be monitored and the sample size may be adjusted to a maximum of 200 patients. With a mean follow-up time of 13 months, 200 patients will provide 90% power to detect a reduction of 50% in the ticagrelor group.

The randomisation codes will be computer-generated by Parexel Informatics and loaded into the Interactive Voice/Web Response System (IxRS) database. Randomisation codes will be generated in blocks to ensure approximate balance (1:1) between the two randomised treatment groups (ticagrelor or placebo twice daily [bd]). Stratification for baseline hydroxyurea use (Yes/No) by country will be applied.

2 ANALYSIS SETS

2.1 Definition of Analysis Sets

Details of the analysis sets are presented in Table 1 and Table 2. Criteria defining the analysis sets, as detailed below, will be expanded in a separate study-specific protocol deviations and reasons for exclusion specifications plan.

Table 1 Analysis Sets

Analysis Set	Definition
All patients	All patients who provide written informed consent/assent (as relevant) prior to performing any specific study-related procedures.
All patients randomised/Full analysis set (FAS)	All randomised patients, regardless of study treatment received, will be included in the full analysis set. Patients will be analysed according to their randomised study treatment regardless of the study treatment they actually received.

Analysis Set	Definition
Safety analysis set	All randomised patients who receive at least one dose of randomised study treatment, ticagrelor or placebo, and for whom any post-dose data are available, will be included in the safety analysis set. Erroneously treated patients (e.g., those randomised to study treatment A but given study treatment B) will be accounted for in the actual study treatment received, where actual study treatment received is defined as: • Ticagrelor if a patient receives at least one dose of ticagrelor at any time during the treatment period, • Placebo, otherwise.
Per protocol (PP) analysis set	All randomised patients considered valid for safety, who comply with study course requirements per CSP and who, in addition, have no important protocol deviations/other factors impacting the efficacy outcome or treatment of the patient will be included in the PP analysis set. Patients will be analysed and presented by planned/actual study treatment. Patients with any study treatment deviations will be excluded from the PP analysis set such that for patients included in the analysis set, their randomised study treatment assignment = actual study treatment received. *Refer to latest version of the study-specific protocol deviations and reasons for exclusion specification plan for further details.*
Pharmacokinetics (PK) analysis set	All randomised patients who receive at least one dose of ticagrelor and provide at least one post-dose analysable plasma sample for PK analysis will be included in the PK analysis set. Patients with important 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 analysis may be excluded from the PK analysis set.
Pharmacodynamics (PD) analysis set	All patients who receive at least one dose of randomised study treatment, ticagrelor or placebo, and who provide at least baseline and one post-baseline (pre-dose and/or post-dose) analysable sample will be included in the PD analysis. Patients with important protocol deviations including changes to the procedures that may impact the quality of the data, or any circumstances that can alter the PD evaluation may be excluded from the PD analysis set.

Table 2 Summary of Outcome Variables and Analysis Sets

Variable	Analysis Set
Baseline data	
Disposition	All patients

Variable	Analysis Set
Important protocol deviations	Full analysis set
Analysis sets	All patients randomised
Demography and baseline characteristics, medical history, disease characteristics, etc.	Full analysis set
Efficacy data	
Vaso-occlusive crises (VOCs)[a]	Full analysis set
Painful crises	Full analysis set
Acute chest syndromes (ACSs)	Full analysis set
Acute sickle cell disease (SCD) complications	Full analysis set
Health-related quality of life (HRQL)	Full analysis set
Absence from school/work due to SCD	Full analysis set
Pain intensity during VOCs	Full analysis set
Analgesics use during VOCs	Full analysis set
Duration of painful crises	Full analysis set
Duration of ACS	Full analysis set
VOCs requiring hospitalisation or emergency department visits	Full analysis set
Days hospitalised for VOC	Full analysis set
Days hospitalised for acute SCD complications	Full analysis set
Swallowability and palatability	Safety analysis set
SCD-related red blood cell transfusions	Full analysis set
Safety data	
Adverse events[b]	Safety analysis set
Bleeding events	Safety analysis set
Concomitant medications, procedures, and therapies	Safety analysis set
Laboratory measurements	Safety analysis set
Physical examinations	Safety analysis set
Electrocardiograms (ECGs)	Safety analysis set
Vital signs	Safety analysis set
Overdoses	Safety analysis set
Exposure	Safety analysis set
Pharmacokinetics data	

Variable	Analysis Set
Plasma ticagrelor concentration	PK analysis set (Listings will be based on Safety analysis set)
Plasma active metabolite (AR-C124910XX) concentration	PK analysis set (Listings will be based on Safety analysis set)
Pharmacodynamics data	
Plasma concentration of $P2Y_{12}$ reaction units (PRI [%]) measured by vasodilator-stimulated phosphoprotein (VASP) assay	PD analysis set (Listings will be based on Safety analysis set)

[a] Refer to Section 4.2.6.3 for information on the sensitivity analyses to be performed.
[b] Adverse events include any deaths.

2.2 Deviations

The study team and study physician/study clinical lead will review protocol deviations as recorded during the conduct of the study to assess whether these deviations are considered to impact the completeness, accuracy, and/or reliability of the study data or to significantly affect a patient's rights, safety, or wellbeing thus being deemed important. At a minimum, important protocol deviations may include:

- Patients who entered the study even though they did not fulfil the eligibility criteria.
- Patients who developed study treatment administration discontinuation criteria but continued with study treatment administration.
- Patients who received the wrong study treatment or incorrect dose.
- Patients who received a disallowed concomitant medication.
- Patients with other important protocol deviations determined in part by study design, the critical procedures, study data, patient protections described in the protocol, and the planned analyses of the study data, including those protocol deviations related to coronavirus disease 2019 (COVID-19)

This list is not intended to be exhaustive. Other factors/protocol deviations may be identified at any time and through various sources by the study team. Based on the latest version of the study-specific protocol deviations management plan, identified deviations, as included in the cumulative clinical trial management system (CTMS) report, will be reviewed by the study team and study physician/study clinical lead monthly and will be considered in the final evaluation of patient evaluability for inclusion in the relevant analysis sets. Details will be provided in a separate study-specific protocol deviations and reasons for exclusion specifications plan.

Prior to database lock and subsequent routine study unblinding, decisions on patient evaluability, assignment to the various analysis sets (with the exception of the PK analysis set finalised after routine study unblinding only) and identified important protocol deviations for

presentation purposes will be finalised in cross-functional collaboration between AstraZeneca and IQVIA.

3 PRIMARY AND SECONDARY VARIABLES

3.1 General Principles

3.1.1 Missing Data

In general, and unless specifically detailed in subsequent sections, variables will be analysed and/or summarised using available data only. Missing data will not be imputed.

Sensitivity analysis of the primary outcome to account for missing data will be performed. The data handling rules for these sensitivity analyses can be found in Appendix E Accounting for Missing Data.

For the handling of missing/partial start and stop dates of medications and therapies, including blood product transfusions, refer to Appendix C Missing/Partial Start and Stop Dates for Medications/Transfusions.

Similarly, for the handling of missing/partial date of birth, SCD diagnosis dates and for prior VOC events start and stop dates as captured on the VOC electronic case report form (eCRF), refer to Appendix D Missing/Partial Dates for Date of Birth, Diagnosis of Sickle Cell Disease, and Prior VOCs, and VOCs During the Study.

3.1.2 Baseline

Baseline is the last assessment collected (scheduled or unscheduled) prior to the first dose of study treatment, or last assessment collected prior to or at randomisation (Visit 2), for patients who are randomised but do not receive any study treatment. For in-clinic assessments with an assessment date equal to the first dose of study treatment, the assessment will be assumed to be pre-dose since all assessments are to be done prior to dispensing study treatment according to the protocol. For adverse events (AEs) and concomitant medications with start date equal to the first dose of study treatment, the event will be considered post-baseline.

3.1.3 Change and Percentage Change from Baseline

Change from baseline will be calculated as the post-baseline value minus the value at baseline:

- Change from baseline (unit) = (post-baseline value – baseline value)

Percentage change from baseline will be calculated as follows when appropriate:

- Percentage change from baseline (%) = (post-baseline value – baseline value)/baseline value × 100

If either the post-baseline value or the baseline value is missing, then both change from baseline and percentage change from baseline value will be set to missing and no imputation of missing values will be done. If the baseline value is zero, the percentage change will be set to missing.

3.1.4 Treatment Period

The double-blind randomised treatment period comprises of regular scheduled in-clinic visits as well as regularly scheduled telephone visits. The treatment period starts at randomisation (Visit 2) through the end of study (EOS) visit regardless of whether the patient prematurely discontinues study treatment. Refer to Section 3.1.4.1 for details on EOS visit. For patients who prematurely discontinue from study participation within this period, the double-blind randomised treatment period is defined through to the last available visit/assessment date or date of premature study discontinuation, whichever is latest.

3.1.4.1 End of Study Visit

Due to premature termination of the study by the sponsor, AstraZeneca, the end of study (EOS) visit is defined by a common study end date (CSED) corresponding to the date of communication to all investigators to immediately discontinue study treatment administration for all patients still ongoing on study treatment.

3.1.5 Safety Follow-up Period

The safety follow-up period follows the treatment period with the final visit, per schedule of assessments, up to a maximum of 19 days after the EOS visit.

3.1.6 Reference Dates (Relative Study Day)

Per the aforementioned periods, study day will be calculated relative to the reference date and will be used to show start/stop day of assessments and events in patient data listings.

Reference date: Defined as date of randomisation (Visit 2).

- If the date of the assessment/event is on or after the reference date, then:

Relative study day = (date of event – reference date) + 1

- If the date of the assessment/event is prior to the reference date, then:

Relative study day = (date of event – reference date)
Subsequently, randomisation as disposition event occurs on relative study Day 1 and Day 0 is not defined.

In the situation where the assessment/event date is partial or missing, relative study day and corresponding durations will appear partial or missing in the patient data listings.

3.1.7 On- and Off-treatment Periods

For safety and limited efficacy analyses, two additional periods are defined for analysis purposes:

3.1.7.1 On-treatment Period

The on-treatment period is defined as the period from first dose of study treatment up to and including last dose of study treatment + 7 days.

3.1.7.2 Off-treatment Period

The off-treatment period follows the end of the on-treatment period, 1 day after the "last dose of study treatment + 7 days" as defined in Section 3.1.7.1.

3.1.8 Retests and Unscheduled Assessments

By-visit summaries will be presented by scheduled eCRF visit (number and name) and no analysis visit windowing will be applied. Unscheduled assessments will only be listed and will not contribute to these by-visit summaries. Results from unscheduled laboratory, vital signs and ECG assessments will, however, be included in the identification of maximum and/or minimum values as well as in the identification of any treatment-emergent abnormalities or changes.

3.2 Primary Efficacy Variable

3.2.1 Vaso-occlusive Crises (VOCs)

A VOC event occurring during the study (following randomisation at Visit 2) and, as judged by the investigator to fulfil the definition of the primary endpoint event, should be recorded by the investigator both as a primary endpoint event on the VOC1 eCRF and as an adverse event (AE) on the AE eCRF.

The primary efficacy variable is the number of VOC events during the treatment period. The number of VOC events is defined as the count of VOC events experienced by a patient over the defined treatment period (refer to Section 3.1.4), as assessed by the investigator and collected on the VOC1 eCRF. Any VOC event identified outside the defined treatment period will not be included in the primary analysis.

A VOC is the composite of a painful crisis and/or an acute chest syndrome (ACS) event. 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 healthcare provider in a medical setting (such as a hospital, clinic or emergency room visit) or at home.

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

A VOC event is identified as follows:

- Within each of the two separate components: Event with an onset date ≤ 7 days of the previous event onset date will not be counted as a new event. It will be composed of the start date of the first occurrence of the component in the event to the stop date of the last occurrence of the component in the event.

  For example: Patient 1: *Counted as 2 events not 3 individual events*

PAINFUL CRISIS	2019-07-24	2019-07-28
PAINFUL CRISIS	2019-10-22	2019-10-23
PAINFUL CRISIS	2019-10-28	2019-10-30

- Across the two separate components: Event with an onset date ≤ 7 days of the previous event onset date will not be counted as a new event. It will be composed of the start date of the first component in the event to the stop date of the last component in the event.

  For example: Patient 2: *Counted as 4 events not 5 individual events*

ACUTE CHEST SYNDROME	2019-07-17	2019-07-23
PAINFUL CRISIS	2019-07-17	2019-07-23
PAINFUL CRISIS	2019-10-04	2019-10-04
PAINFUL CRISIS	2019-10-21	2019-11-05
PAINFUL CRISIS	2019-12-12	2019-12-12

3.3 Secondary Efficacy Variables

The secondary efficacy variables are:

- Number of painful crises
- Duration of painful crises

- Number of ACS events
- Number of VOC events requiring hospitalisation or emergency department visits
- Number of days hospitalised for VOC events
- Number of acute SCD complications
- Number of days hospitalised for acute SCD complications
- Number of sickle cell-related red blood cell (RBC) transfusions
- PedsQL SCD Module and PedsQL Multidimensional Fatigue Scale Scale: Total score and by dimension
- Proportion of days absent from school or work due to SCD
- Intensity of worst daily VOC-related pain (during VOC events)
- Analgesics administered for VOC events (opioids/non-opioids)
- Swallowability and palatability

3.3.1 Painful Crises

Painful crisis is one of the two components of VOC events. For the definition of painful crisis and identification of number of painful crises within the treatment period please refer to Section 3.2.1.

In addition to number of painful crises, the total duration (days) of painful crises will be derived as follows:

Total duration (days): Defined as the sum of the duration (days) (taking into account overlapping painful crisis days + 7-day onset rule as described below) of painful crises experienced by a patient over the defined treatment period, where:

- Duration of event (days) = (stop date of event – start date of event) + 1

  Total duration (days) will be calculated as the sum of the duration (days) of each event. If two or more events have overlapping durations, the overlapping days will only be counted once. Events with an onset date ≤7 days of the previous event onset date will not be counted as a new event (7-day onset rule). (refer to Section 3.2.1).

  For example: Patient 1: 2 events with total duration (taking into account overlapping days = 0 + 7-day onset rule) of 14 days: Derived as the sum = 5 + 2 + 3 + 4 = 14

1. PAINFUL CRISIS	2019-07-24	2019-07-28	5 days
2. PAINFUL CRISIS	2019-10-22	2019-10-23	2 days

3. PAINFUL CRISIS	2019-10-28	2019-10-30	3 + 4 intermission days

For example: Patient 2: 2 events with total duration (taking into account overlapping days = 1 + 7-day onset rule) of 16 days: Derived as the sum = (9 + 1 + 3 + 4) – 1 (overlapping day) = 16

1. PAINFUL CRISIS	2019-10-15	2019-10-23	9 days
2. PAINFUL CRISIS	2019-10-23	2019-10-23	1 day (overlaps with previous individual event so does not count toward total duration)
3. PAINFUL CRISIS	2019-10-28	2019-10-30	3 days + 4 intermission days

For summary purposes, patients who do not experience any painful crisis during the defined treatment period will have their duration of painful crisis set to 0 days.

3.3.2 Acute Chest Syndromes

Acute chest syndrome is one of the two components of VOC events. For the definition of ACS and identification of number of ACS events within the treatment period refer to Section 3.2. The total duration (days) of ACS events, is one the exploratory objectives of the present study, and will be calculated using the same rules as painful crises detailed in Section 3.3.1. Similarly, for summary purposes, patients who do not experience any ACS events during the treatment period will have their duration of ACS set to 0 days.

3.3.3 VOC Events Requiring Hospitalisation or Emergency Department Visits

For the definition of VOC events and identification of number of VOC events within the treatment period please refer to Section 3.2.1.

The number of VOC events requiring hospitalisation or emergency department visits is defined as the count of VOC events, experienced by a patient over the treatment period, for which the primary setting for VOC treatment is in-patient hospitalisation or emergency department as captured on the VOC1 eCRF.

In addition to number of VOC events requiring hospitalisation or emergency department visits, the total duration (days) hospitalised for all individual VOC events experienced by a patient during the treatment period will be derived as follows:

Total duration (days): Defined as the sum of the duration (days) of all individual hospitalisations (taking into account potential overlapping hospitalisation days of VOC components) during VOC events experienced by a patient over the treatment period for which the primary setting for VOC treatment is in-patient hospitalisation:

- Duration (days) = (individual hospital discharge date per VOC event – individual hospital admission date per VOC event) + 1
  Where:
  Hospital admission and discharge dates are captured on the AE eCRF.

For summary purposes, patients who do not experience any VOC event and patients who do not experience any VOC event requiring hospitalisation will have their number of days hospitalised for VOC events set to 0 days.

3.3.4 Acute Sickle Cell Disease Complications

Acute SCD complications are defined as any one or more of the following individual complications: Transient ischaemic attack (TIA)/ischaemic stroke, hepatic sequestration, splenic sequestration, priapism and dactylitis. Data, defining acute SCD complications, are collected on both the acute SCD complications (ASCD) eCRF and AE eCRF.

The number of acute SCD complications is defined as the count of all individual acute SCD complications experienced by a patient over the treatment period as collected on the ASCD eCRF.

In addition, the total duration (days) hospitalised for acute SCD complications will be derived as follows:

Total duration (days): Defined as the sum of the duration (days) of all individual hospitalisations (taking into account potential overlapping hospitalisation days) due to acute SCD complications experienced by a patient over the treatment period, for which hospitalisation is reported:

- Duration (days) = (individual hospital discharge date – individual hospital admission date) + 1
  Where:
  Hospital admission and discharge dates are captured on the ASCD eCRF.

Patients who do not experience any acute SCD complications, as well as patients who do not experience any acute SCD complications requiring hospitalisation will have their number of days hospitalised for acute SCD complications set to 0 days.

The individual events comprising acute SCD complications will be assessed as exploratory endpoints (TIA/ischaemic stroke, hepatic sequestration, splenic sequestration, priapism, and dactylitis) if reported by at least 10 patients in total across the two treatment groups.

3.3.5 Sickle Cell-related Red Blood Cell Transfusions

Information about blood product transfusions during the study is captured on the TRANSF eCRF. ll AEs resulting in the need for red blood cell transfusions will be done prior to database lock to determine if the transfusion is sickle cell related or not. The outcome of the medical review will be used to identify those sickle cell related red blood cell transfusions to be included in the subsequent efficacy analysis.

3.3.6 Health-related Quality of Life (HRQL) and Fatigue

The health-related quality of life (HRQL) will be assessed using the PedsQL SCD Module and PedsQL Multidimensional Fatigue Scale.

3.3.6.1 PedsQL SCD Module

The PedsQL SCD Module instrument has been developed (using a 5-point Likert scale) in age-specific versions and will be reported by age-specific groups accordingly (Panepinto et al 2013).

In the present study the child self-report forms for ages ≥5 years to <8 years, ≥8 years to <13 years, and ≥13years to ≤18 years and the caregiver proxy-report form specific for ≥2 years to <5 years will be used. A child's age at randomisation (Visit 2) defines which form should be completed, and this version remains the same throughout the duration of the study, regardless of whether the child changes age group during this period. For summary purposes, if the wrong version of the age-specific questionnaire is completed based on the patient's age at randomisation (Visit 2), the collected data will not be included in subsequent analyses at the given timepoint.

The PedsQL SCD Module consists of:

- General version (child + adolescent): 43 items
- Toddler version: 42 items
- Young child version: 40 items

The PedsQL SCD Module measures problems in the following categories across 9 sub-scales with an overall total score derived:

- Pain: 3 sub-scales:
  - Pain and hurt
  - Pain impact

  - Pain management/control
- Worry: 2 sub-scales:
  - Worry I
  - Worry II
- Emotions: 1 sub-scale
- Treatment: 1 sub-scale
- Communication: 2 sub-scales:
  - Communication I
  - Communication II
- Total score

PedsQL SCD Module items are reverse-scored and linearly transformed to a 0 to100 scale (0 = 100, 1 = 75, 2 = 50, 3 = 25, 4 = 0) so that higher scores indicate better quality of life. Sub-scale scores are computed as the sum of items' transformed scores divided by the number of items answered included in each sub-scale, this accounts for missing data. However, if more than 50% of the items in each sub-scale are missing (ie, >#items/2 – rounded down to the nearest integer) the sub-scale score is not computed.

To create the PedsQL SCD Module total score (43/42/40 items – depending on version completed) the arithmetic mean of the transformed scores is computed as the sum of the items' transformed scores divided by the number of items answered.

Per the aforementioned, 50% missing items for the PedsQL SCD Module total score would then be:

- General version (child + adolescent): 43 items: >21 items
- Toddler version: 42 items: >21 items
- Young child version: 40 items: >20 items

3.3.6.2 Multidimensional Fatigue Scale

The PedsQL Multidimensional Fatigue Scale instrument has been developed (using a 5-point Likert scale) in age-specific versions and will be reported by age-specific groups accordingly (Panepinto et al 2014).

In the present study the child self-report forms for ages ≥5 years to <8 years, ≥8 years to <13 years, and ≥13 years to ≤18 years and the caregiver proxy-report form specific for ≥2 years to <5 years will be used. A child's age at randomisation (Visit 2) defines which form should be completed, and this version remains the same throughout the duration of the study, regardless of whether the child changes age group during this period. For summary purposes, if the wrong version of the age-specific questionnaire is completed based on the patient's age

at randomisation (Visit 2), the collected data will not be included in subsequent analyses at the given timepoint.

The PedsQL Multidimensional Fatigue Scale measures problems in the following categories across 3 sub-scales with an overall total score derived:

- General (6 items)
- Sleep/rest (6 items)
- Cognitive fatigue (6 items)
- Total score (18 items)

PedsQL Multidimensional Fatigue Scale items are reverse-scored and linearly transformed to a 0 to 100 scale (0 = 100, 1 = 75, 2 = 50, 3 = 25, 4 = 0) so that higher scores indicate better quality of life. Sub-scale scores are computed as the sum of items' transformed scores divided by the number of items answered included in each sub-scale, this accounts for missing data. However, if more than 50% of the items in each sub-scale are missing (ie, >3 items in each sub-scale) the sub-scale score is not computed.

To create the PedsQL Multidimensional Fatigue Scale total score (18 items), the arithmetic mean of the transformed scores is computed as the sum of the items' transformed scores divided by the number of items answered.

3.3.7 Absence from School/Work Due to SCD

For patients attending school/work at randomisation (Visit 2), absence from school/work due to SCD will be recorded weekly by the patient in the eDevice with the help of the caregiver if needed.

The proportion of days absent from school/work due to SCD in the defined treatment period will be calculated as follows:

- Proportion of absent days = (total number of days reported)/ (total number of questionnaires answered × 7)

Where:

- Total number of days reported: Sum of days entered as based on the question "*How many days have you been at home from school/work during the last 7 days because of your disease?*".
- Total questionnaires answered: Defined as the number of absent days assessments completed as determined by a definitive response of "Yes/No" to the question *"Have you been at home from school/work during the last 7 days because of your disease?"* in addition to a complete and documented weekly diary assessment date (ddMMMyyyy).

For summary purposes, patients completing the weekly questionnaires, per the aforementioned definition, but who have not been absent from school/work due to SCD will have their number of absent days from school/work due to SCD set to 0 days.

For the handling of missing data from eDevice on absence from school/work due to SCD no further imputation will be done.

3.3.8 Pain During VOC Events

The Face, Legs, Activity, Cry, Consolability (FLACC) assessment tool is used to assess pain in children aged ≥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 is caregiver-reported and in the present study it will be used to assess pain daily during the VOC event for those patients <5 years of age as determined at randomisation (Visit 2). Each of the 5 behaviours observed are assigned a score of 0, 1 or 2. The total FLACC score ranges between 0 and 10, with 0 representing "no pain" and 10 representing "very much pain".

The Faces Pain Scale-revised (FPS-R) will be administered to assess pain daily during the VOC event by those patients aged ≥5 years as determined at randomisation (Visit 2). The FPS-R has been validated and has been judged as a well-established pain assessment tool in patients >4 years of age (Hicks et al 2001, Cohen et al 2008).

The FPS-R consists of six faces and scoring ranges between 0 and 10 (with an increase in numeric value by 2), where 0 is "no pain" and 10 is "very much pain". A body outline diagram will also be presented, and the patient/caregiver will be asked to indicate the location(s) of the pain.

These instruments will be assigned based on patients' age at randomisation (Visit 2), and the same version should be used throughout the study to assess intensity of pain, on a daily basis, during a VOC event. For summary purposes, if the wrong version of the questionnaire is completed as based on the patient's age at randomisation (Visit 2) the collected data will not be included in subsequent analyses at the given timepoint.

Worst pain ratings will be collected once daily throughout the duration of the VOC event using an eDevice. Intensity of pain during each VOC event over the defined treatment period will be based on the average of those available and reported worst daily pain values. Pain intensity will be summarised and presented separately for each instrument for those patients reporting VOC events within the defined treatment period.

For the handling of missing data from eDevice on pain during VOC events no imputation will be done.

3.3.9 Type of Analgesics Use During VOC Events

Analgesics use (opioid and non-opioid) during VOC events is captured by the investigator on the VOC1 eCRF.

3.3.10 Swallowability and Palatability Data

Palatability will be assessed by age group. The Facial Hedonic Scale (FHS) is a well-established method for assessing paediatric patients' responses to drug palatability for patients as young as 3 years of age (Davies and Tuleu 2008). The FHS consists of five faces with descriptions ranging from "Dislike very much" to "Like very much". The way in which the study treatment is taken, ie, whether the tablet is whole or dispersed, will be captured. No imputation will be done in case of missing formulation and a missing category will be presented, if relevant.

Patients ≥5 years of age at randomisation (Visit 2) will be asked to evaluate palatability using the FHS, directly after the patient has received the first dose of double-blind randomised study treatment at randomisation (Visit 2) and again at Visit 9 (Month 6).

For patients <5 years of age at randomisation (Visit 2) an observer's assessment of the patient's behaviour using the study medication palatability assessment (SMPA) eCRF, will be performed directly after the patient has received the first dose of double-blind randomised study treatment at randomisation (Visit 2) and again at Visit 9 (Month 6).

Willingness to swallow will be assessed and categorised as follows:

- Swallowed without a problem
- Some resistance but did swallow
- Spit out some/all of the medication
- Vomited up the medication.

Response to palatability will be assessed through the SMPA eCRF question *"Was any behaviour 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?"*. This will be presented as a binary outcome (ie, where "No" is no negative response and "Yes" is negative response). Further breakdown includes, whether the patient turned his/her head to reject the intake of the double-blind randomised study treatment or not, whether the patient twisted his/her face or mouth as an expression of displeasure and whether the patient displayed any other negative behaviour, including details of this behaviour. As such, negative response to palatability will be presented by the following categories:

- No (no negative response)
- Yes (negative response):
    - Turn head to reject intake of study treatment
    - Twist face or mouth in an expression of displeasure
    - Other

Questionnaire type will be assigned based on patients' age at randomisation (Visit 2), and the same version should be used throughout the study. For summary purposes, if the wrong version of the questionnaire is completed as based on the patient's age at randomisation (Visit 2) the collected data will not be included in subsequent analyses at the given timepoint.

3.4 Safety Variables

The safety variables which address the safety of ticagrelor are AEs including serious adverse events (SAEs), deaths, bleeding events, overdose, blood product transfusions, laboratory variables, ECG and vital signs.

3.4.1 Adverse Events

Serious adverse events will be collected from signing informed consent/assent, as relevant, throughout the treatment period and including the safety follow-up period. Adverse events will be collected from randomisation (Visit 2) throughout the treatment period and including the safety follow-up period. The Medical Dictionary for Regulatory Activities (MedDRA) (using the latest MedDRA version) will be used to code the AEs.

Adverse events will be categorised according to their onset date as follows:

- Pre-treatment: AEs occurring during screening ie, onset date < date of first dose of study treatment.
- On-treatment: AEs with onset date ≥ the date of first dose of study treatment and ≤ the date of last dose of study treatment + 7 days.
- Off-treatment: AEs occurring off-treatment ie, onset date > the date of last dose of study treatment + 7 days.

Although AE eCRF data collection mandates complete start/stop dates (or ongoing) for AEs collected following randomisation (Visit 2), in the exceptional case of missing/partial dates (and, as relevant, no indication of ongoing), no imputation will be done, and the event will be assumed to be "on-treatment" (worst-case approach). In case, for a specific event, severity or relationship is missing, no missing imputation will be performed, and a missing category will be presented in the relevant tables and listings.

Patients presenting clinical signs and symptoms consistent with COVID-19 infection will be managed as defined in Section 6.3.10 of the latest version of the CSP. Given the outcome of

the investigator's management of such patients AE/SAEs will potentially be identified as COVID-19 confirmed or suspected and will be presented as such in relevant safety analyses.

3.4.2 Other Significant Adverse Events (OAEs)

Other significant adverse events (OAEs) are events of particular clinical importance as determined by an AstraZeneca medically qualified expert in consultation with the Global Safety Physician. Based on these experts' judgement, AEs of particular clinical importance may be considered as OAEs and reported as such in the CSR only. There will be no pre-specification of OAEs.

3.4.3 Deaths

Deaths will be recorded as SAEs on the AE eCRF, with date of death, primary and secondary cause of death, as well as autopsy performed (Yes/No).

3.4.4 Bleeding Events

Bleeding events will be recorded as AEs on the AE eCRF (where AE category = bleeding event). In addition, the investigator will complete an assessment of the bleeding event on the BLEEDPED eCRF including specification of the nature of the event (spontaneous/trauma/procedural) and primary location.

For patients experiencing a bleeding event that fulfils criteria in more than one category, the bleed will be assigned, by the investigator, to the most severe category. The bleeding event categories are as follows:

- Major bleeding: Defined as any fatal bleeding, clinically overt bleeding associated with a decrease in haemoglobin (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.

3.4.5 Overdose

Study treatment overdose at any time during the defined treatment period will be captured on the OVERDOSE eCRF and if associated with an AE it will be noted as such. All cases of overdose will be presented in a listing for patients who have had an overdose at any time during the study.

3.4.6 Blood Product Transfusions

Information about blood product transfusions during the study is captured on the TRANSF eCRF.

The number of blood product transfusions is defined as the count of all blood product transfusions received by a patient at any time during the study and will be assigned, based on date of transfusion, to the on-treatment and off-treatment periods in accordance with the definitions detailed in Sections 3.1.7.1 and 3.1.7.2.

Date of transfusion should always be collected, however in case of partial/missing date, of transfusions refer to Appendix C Missing/Partial Start and Stop Dates for Medications/Transfusions for imputation rules resulting in a worst-case approach.

In addition, number of units transfused, and type of blood product will be presented for all patients in the safety analysis set receiving a blood product transfusion (regardless of reason for transfusion or blood product type transfused) at any time during the study.

3.4.7 Laboratory Variables

Blood samples for safety assessments (clinical chemistry, haematology, urinalysis and coagulation) will be taken as per schedule of assessments (refer to Table 2 of the latest version of the CSP). The list of laboratory variables to be presented in tables, listings and figures are included in Table 4 of the latest version of the CSP. Laboratory tests will be presented using the standardised name.

Laboratory assessments will be summarised and presented for all countries combined, in standard international (SI) units. Laboratory test results obtained from Egypt will be converted to the same SI units per central laboratory specification prior to summary and presentation. Similarly, due to COVID-19, the introduction of local laboratories necessitates the standardisation of local laboratory test results to the same SI units per central laboratory specification, such that data from central- and local laboratories will be combined for summary and presentation in relevant tables.

There will be no imputation for missing values. However, for values recorded with a leading "greater than" or "less than" (>/<) symbol, the reported numeric value will be used for analysis and the value with the qualifier will be included in the patient data listings, unless otherwise specified (e.g., a value of <0.01 will be analysed as 0.01 and listed as <0.01).

Change from baseline in haematology and clinical chemistry assessments (scheduled and unscheduled) will be derived as specified in Section 3.1.3.

Laboratory test results (scheduled and unscheduled) will be compared to the relevant laboratory reference range (lower limit of normal [LLN] to upper limit of normal [ULN]), specific to the patient's age (years) at the time of the assessment and gender as relevant, and categorised as:

- Low: Below lower limit of the laboratory reference range (<LLN)
- Normal: Within the lower limit and upper limit of the laboratory reference range, inclusive (≥LLN to ≤ULN)
- High: Greater than upper limit of the laboratory reference range (>ULN)

All observed values falling outside these reference ranges will be flagged.

Specifically, change from baseline to maximum/minimum values on-treatment, categorised as described above per laboratory reference range, will be presented, where maximum and minimum laboratory test results will be identified as:

- Maximum on-treatment: Highest test result (scheduled or unscheduled value) observed within the period from date of first dose of study treatment up to and including date of last dose of study treatment + 7 days.
- Minimum on-treatment: Lowest test result (scheduled or unscheduled value) observed within the period from date of first dose of study treatment up to and including date of last dose of study treatment + 7 days.

In addition to the aforementioned assessments, treatment-emergent change from baseline in observed values (scheduled and unscheduled) will be identified as compared to the relevant laboratory references range, where treatment-emergent is defined as follows:

- Treatment-emergent = Regarded as treatment-emergent if the post-baseline assessment on-treatment is "worse" than baseline (refer to Section 3.1.7.1 for further details).
  - Increase: In the identification of treatment-emergent high values, change from baseline categories "normal" AND "low" will be considered.
  - Decrease: In the identification of treatment-emergent low values, change from baseline categories "normal" AND "high" will be considered.

  For example: Patient 1

Alkaline Phosphatase	Baseline	Normal	
Alkaline Phosphatase	Visit 9	Normal	

Alkaline Phosphatase	Visit 15	High	Treatment-emergent high (increase)

3.4.7.1 Liver Function Tests, Potential Hy's Law and Hy's Law

For the following liver function tests, the multiple of the upper limit of normal (ULN) (reference range) will be calculated for each data point (scheduled and unscheduled): Aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, and alkaline phosphatase (ALP):

- Multiple = value/ULN
  For example: If the ALT value is 72 IU/L and the ULN 36 IU/L, then the multiple is 72/36 = 2.

Potential Hy's Law (PHL)
AST or ALT ≥ 3× ULN **together with** total bilirubin ≥ 2× ULN at any point during the study following the start of study treatment irrespective of an increase in ALP.

Hy's Law (HL)
A Hy's Law case is defined as any patient with elevations in AST or ALT ≥ 3× ULN together with total bilirubin level ≥ 2× ULN, where no other reason, other than the study treatment, can be found to explain the combination of increases, e.g., elevated ALP indicating cholestasis, viral hepatitis, another drug.

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

Identification of Potential Hy's Law Cases
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 ≥ 3× ULN
- AST ≥ 3× ULN
- Total bilirubin level ≥ 2× ULN

3.4.8 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 performed as per schedule of assessments (refer to Table 2 of the latest version of the CSP) and will be recorded after the patient has been lying down to rest for at least 5 minutes. After the ECG recording, the investigator or designated physician will review each of the ECGs and record an overall evaluation (normal, abnormal not clinically

significant and abnormal clinically significant). Reasons for abnormal will be collected as part of a free text field.

Patients for whom the ECG assessment was not performed and/or patients with no ECG evaluation, as identified by a "not done" category on the ECG eCRF, will not be presented in subsequent summaries.

3.4.9 Vital Signs

Vital signs (blood pressure and pulse rate) will be measured after 5 minutes rest as per schedule of assessments (refer to Table 2 of the latest version of the CSP). Weight and height assessments will be performed at the visits as shown in Table 2 of the latest version of the CSP.

Change from baseline in vital signs to each post-baseline assessment (scheduled and unscheduled) will be calculated as described in Section 3.1.3.

Vital signs collected at any time during the study (scheduled and unscheduled) will be compared to the pre-defined abnormality assessment criteria reported in Table 4 (refer to Vital Signs Pre-defined Abnormality Assessment Criteria). The assessment of pre-defined abnormalities for systolic blood pressure (SBP), diastolic blood pressure (DBP) and pulse rate will be based on the upper/lower limits as relevant given the patient's age (years) at the time of the assessment and categorised as:

- Low: Below lower limit of the age-specific abnormality assessment criterion (< LL)
- Normal: Within the lower limit and upper limit of the age-specific abnormality assessment criterion, limits inclusive (≥ LL to ≤ UL)
- High: Greater than upper limit of the age-specific abnormality assessment criterion (> UL)

All observed values falling outside these criteria limits will be flagged.

Specifically, change from baseline to maximum/minimum values on-treatment (refer to Section 3.1.7.1), categorised as described above per abnormality assessment criteria, will be presented, where maximum and minimum vital signs results will be identified as:

- Maximum on-treatment: Highest vital signs result (scheduled or unscheduled value) observed within the period from date of first dose of double-blind randomised study treatment up to and including date of last dose of double-blind randomised study treatment + 7 days.
- Minimum on-treatment: Lowest vital signs result (scheduled or unscheduled value) observed within the period from date of first dose of double-blind randomised study treatment up to and including date of last dose of double-blind randomised study treatment + 7 days.

In addition to the aforementioned assessments, treatment-emergent change from baseline in observed vital signs values (scheduled and unscheduled) will be identified as compared to the relevant abnormality assessment criteria, where treatment-emergent is defined as follows:

- Treatment-emergent = Regarded as treatment-emergent if the post-baseline assessment on-treatment is "worse" than baseline (refer to Section 3.1.7.1 for further details).
  - Increase: In the identification of treatment-emergent high values, change from baseline categories "normal" AND "low" will be considered.
  - Decrease: In the identification of treatment-emergent low values, change from baseline categories "normal" AND "high" will be considered.

    For example: Patient 1

SBP	Baseline	Normal	
SBP	Visit 9	Normal	
SBP	Visit 15	High	Treatment-emergent high (increase)

3.4.10 Physical Examination

For physical examination, only information on whether the assessment was performed or not is recorded. Any abnormal findings are reported as either medical history or adverse events.

3.5 Exploratory Variables

3.5.1 Duration of ACS

Refer to Section 3.3.2 for relevant details.

3.5.2 Pharmacokinetic Parameters

The pharmacokinetic parameters which address the PK properties of ticagrelor and the active metabolite (AR-C124910XX) in oral dose administration are the observed plasma concentrations and the PK parameters, area under the plasma concentration-time curve (AUC) and apparent total clearance of the drug from plasma after oral administration (CL/F) for ticagrelor and AUC for the active metabolite obtained using population PK analysis approach.

PK samples will be collected at 0 hours (pre-dose) and 2 hours post-dose (no pre-dose sample at randomisation [Visit 2]) as per schedule of assessments and in case of changed dose due to weight increase (refer to Table 2 of the latest version of the CSP).

3.5.3 Pharmacodynamic Variables

The pharmacodynamic variable which addresses the PD properties of ticagrelor, as inhibitor of platelet aggregation, is the Platelet Reactivity Index (PRI [%]) measured by vasodilator-stimulated phosphoprotein (VASP) assay.

The PD samples will be collected at 0 hours (pre-dose) and 2 hours post-dose as per schedule of assessments (refer to Table 2 of the latest version of the CSP).

4 ANALYSIS METHODS

4.1 General Principles

4.1.1 General Methodology

The statistical analyses will be performed by IQVIA under the direction of Biometrics, BioPharmaceuticals R&D, AstraZeneca. The data analyses will be conducted using SAS® System (SAS Institute Inc., Cary, NC), version 9.2 or higher.

Continuous variables will be summarised for all countries combined, by treatment group by means of descriptive statistics including n (number of patients with available data), arithmetic mean, standard deviation (SD), median, minimum value and maximum value. Quartiles 1 and 3 may be included for some variables where appropriate. The mean and median will be presented with one more decimal place than the original data. Standard deviation with two more decimal places than the original data. Minimum and maximum values with the same number of decimal places as the raw data. In case of a single observation (n=1), SD will be presented as not calculable (set to NC [Not Calculable]) and in case of no observations (n=0) descriptive statistics will be left blank.

For natural log-transformed data, the following descriptive statistics will be presented:

- Number of observations (n)
- Geometric mean (gMean), calculated as exp[μ], where μ is the mean of the data on a natural logarithmic scale
- Geometric standard deviation (gSD), calculated as exp[s], where s is the SD of the data on a natural logarithmic scale
- Geometric coefficient of variance % (gCV%), calculated as $100 \sqrt{[\exp(s^2)-1]}$, where s is the SD of the data on a natural logarithmic scale
- Arithmetic mean (aMean)
- SD
- Median
- Minimum (min)
- Maximum (max)

Categorical variables will be summarised for all countries combined in frequency tables as number (n) of patients and percentage (%) of patients in each category by treatment group. Unless otherwise stated, percentages will be calculated relative to the total number of patients included in the relevant analysis set, by treatment group and overall (if applicable). Percentages will be rounded to one decimal place.

In statistical models, patients will be analysed according to the IxRS stratification level of baseline hydroxyurea use by country (Yes/No) even if this stratum assignment differs to that identified using the CM eCRF. This is in keeping with the intent to treat (ITT) principle.

The significance level for the primary endpoint will be 2-sided 5%; confidence intervals will be 95%. 2-sided p-value < 0.05 will be considered statistically significant.

No multiplicity adjustment will be included as no formal testing on secondary endpoints for statistical significance will be carried out. Statistical testing of secondary efficacy endpoints is only for exploratory purposes.

In general, and unless otherwise specified, ticagrelor data will be pooled and analysed irrespective of weight-based dose (15 mg/30 mg/45 mg bd). Therefore, all summaries will be presented by treatment group as follows:

Ticagrelor 15/30/45 mg bd	**Placebo**	**Total**

Study treatment exposure and compliance, as well as PK and PD data will be analysed according to pooled dose as well as separately per weight-band of dose, overall and/or at the time of assessment, as relevant. Summaries may, therefore, be presented by treatment group as follows, where relevant:

Ticagrelor 15/30/45 mg bd	**Ticagrelor 15 mg bd**	**Ticagrelor 30 mg bd**	**Ticagrelor 45 mg bd**

Individual data (scheduled and unscheduled) will be presented in patient data listings. Safety data, PK, and PD listings will be sorted by actual study treatment and E-code number. All other patient data listings will be sorted by patient identifier and planned treatment group.

4.2 Analysis Methods

4.2.1 Patient Disposition, Important Protocol Deviations and Analysis Sets

Patient disposition will be summarised for all patients providing written informed consent/assent (as relevant), by treatment group and overall. The number (n) and percentage (%) of patients will be presented for the following categories:

- Enrolled (number of patients only)
- Randomised/not randomised + reason
- Received study treatment/did not receive study treatment + reason
- Completed study treatment/did not complete study treatment + reason
- Completed study/prematurely discontinued study participation + reason

Patients prematurely discontinuing study treatment administration and/or study participation due to COVID-19 related reasons will be presented.

Reasons for not receiving the study treatment, for not completing study treatment, and for premature discontinuation of study participation will also be listed. The relative study day of premature discontinuation/withdrawal will also be presented. Patient disposition regards study participation, as well as study treatment impacted by COVID-19, will also be presented in patient data listings.

A flow diagram of patient disposition will be presented.

Patient enrolment will also be summarised by region, country and centre. The denominator for percentage (%) will be the total number of patients in the full analysis set, by treatment group and overall.

Important protocol deviations, including those protocol deviations related to COVID-19, will be summarised using the full analysis set (refer to Sections 2.1 and 2.2). Important protocol deviations will be finalised prior to database lock and routine study unblinding. The number (n) and percentage (%) of randomised patients with at least one important protocol deviation and within standardised important protocol deviation categories will be presented by treatment group and overall. Patients with important protocol deviations will also be listed.

The number (n) of patients included or excluded from each analysis set will be presented, including the reason(s) for exclusion from each analysis set. Patients can have one or more reasons for exclusion and will be counted in each category as relevant. Patients' assignment to the various analysis sets and reasons for exclusion will be presented in patient data listings.

Patients with identified treatment deviations (where planned study treatment assignment differs from actual study treatment received) and patients with unplanned emergency

unblinding of their blinded treatment code during the treatment period, will be identified in patient data listings. To note, in defining the PP analysis set, patients for whom the blind was broken during the double-blind randomised treatment period (emergency unblinding) introduce potential for bias in subsequent assessments. Should such patients be identified it will result in exclusion of the patients' data, in any analyses based on the PP analysis set, following the point of emergency unblinding, but will not necessarily lead to exclusion of such patients from the relevant analysis set, if otherwise valid.

The onset of the global COVID-19 pandemic potentially impacts a patient's ability to complete the study visits as initially planned per protocol. As such, the visit impacted by pandemic (VISITP) eCRF will be utilised to summarise, at a minimum, the number (n) and percentage (%) of patients in the full analysis set, by treatment group and overall:

- Number of visits impacted:
  - Partially completed
  - Fully completed
  - Delayed
  - Not done
- Reason for visit impact:
  - Patient decision
  - Pandemic-related logistic issue
  - Other/Specification
- Visit contact mode:
  - Remote-audio
  - Remote-video
  - In-clinic
  - Other/Specification

Patient visits (scheduled and unscheduled), identifying those visits impacted by COVID-19, will be presented, in patient data listings.

4.2.2 Demographic and Baseline Characteristics

With reference to the general principles and definitions detailed in Sections 2.1, 3.1 and 4.1.1, demographic and baseline characteristics will be summarised using FAS, by treatment group and overall.

Demographic summary includes presentation of:

- Age (years)at randomisation (Visit 2)

- Age group at randomisation (Visit 2):
  - < 12 years
  - ≥ 12 years
- Sex
- Race
- Ethnicity
- Country

In addition, summary of patient characteristics includes presentation of:

- Baseline height (cm)
- Baseline weight (kg)
- Baseline body mass index (BMI):
  - Calculated as the ratio of patient's baseline weight (kg) to the square of the patient's baseline height (m): BMI (kg/m^2) = (weight [kg])/(height [m^2])

    Where:

    Height is collected in cm and will be converted to meters prior to calculating BMI by dividing by 100.

Similarly, summary of additional patient characteristics at baseline includes presentation of:

- ECG
- Seated pulse (beats/min)
- Malaria
- Eye examination
- Transcranial doppler

Patients' history of SCD will be characterised by summary of the following as collected on the SCDHIS eCRF:

- SCD genotype (HbSS/HbSB Thalassaemia)
- SCD history of complications
- Age (years) at diagnosis of SCD: Calculated as follows:
  - Age (years) at diagnosis = (date of diagnosis – date of birth + 1)/365.25
- Number of years since SCD diagnosis: Calculated as follows:
  - Number of years since SCD diagnosis = (date of randomisation [Visit 2] - date of diagnosis + 1)/365.25

Similarly, patients' history of VOC events will be characterised by summary of the following as collected on the VOC eCRF:

- Number of VOC events in past 12 months relative to screening (Visit 1) and categorised as:
  - ≤ 1 VOC event in the last 12 months relative to screening (Visit 1)
  - ≥ 2 to ≤ 4 events in the last 12 months relative to screening (Visit 1)
  - > 4 VOC events in the last 12 months relative to screening (Visit 1)
- Primary setting for VOC treatment
- Duration (days) from start of the last prior VOC event (prior to randomisation [Visit 2]) to randomisation (Visit 2): Calculated as:
  - Duration (days) = (date of randomisation [Visit 2] – start date of last prior VOC event) + 1

For the handling of missing/partial date of birth, date of SCD diagnosis and for prior VOC events start and stop dates as captured on the VOC eCRF, refer to Appendix D Missing/Partial Dates for Date of Birth, Diagnosis of Sickle Cell Disease, Prior VOCs, and VOCs During the Study.

Demographic and baseline characteristics will be listed for all patients, (as defined in Section 2.1).

4.2.3 Past and Current Medical and Surgical History

Medical/relevant surgical history that occurred prior to screening (Visit 1) regardless of whether the condition is ongoing at the time of screening (Visit 1) will be summarised using FAS, by treatment group and overall (refer to Section 2.1). Medical/relevant surgical history will also be listed for all patients in patient data listings.

All medical/surgical history will be classified according to the latest version of the Medical Dictionary for Regulatory Activities (MedDRA).

Past medical history are those medical conditions/diseases which stopped prior to screening (Visit 1), while current medical records are those medical conditions/diseases that are still present or ongoing at the time of screening (Visit 1).

The number (n) and percentage (%) of FAS patients with any medical/surgical history (records) will be tabulated by MedDRA system organ class (SOC) and preferred term (PT). A patient will only be counted once within a particular SOC/PT, even if he/she has multiple conditions/diseases/surgeries in the same SOC/PT.

4.2.4 Prior, Concomitant, and Post-discontinuation Medications and Therapies

All medications will be coded using the latest AstraZeneca Drug Dictionary at the time of database lock and categorised as follows:

- Prior medication: Defined as those medications that were taken prior to the date of first dose of study treatment, regardless of whether medication use is ongoing.
- Concomitant medication: Defined as those medications taken at any time on or after the day of the first dose of study treatment up to and including the day of the last dose of study treatment, regardless of whether medication use is ongoing. A medication started prior to the first dose of study treatment that is ongoing at the time of first dose of study treatment will be identified as both prior and concomitant.
- Post-discontinuation medication: Defined as those medications started after the last dose of study treatment.

The handling of partial or missing medication dates is detailed in Appendix C Missing/Partial Start and Stop Dates for Medications/Transfusions.

All medications will be classified as allowed/disallowed following a physician review (prior to database lock) of the database and separate tables will be presented by treatment group and overall for patients who take allowed/disallowed concomitant medications.

Summary tables will present the number (n) and percentage (%) of patients in the safety analysis set, using at least one medication by generic term within anatomical therapeutic chemical (ATC) classification. Patients will be counted once at each level of summarisation (ATC classification/generic term).

Prior, concomitant and post-discontinuation medications (allowed/disallowed) will be listed for all patients (as defined in Section 2.1). Medications administered due to COVID-19 confirmed/suspected AEs/SAEs will be identified utilising the *indication* variable on the CM eCRF, by means of the prefix "COVID-19" and will be listed in a separate patient data listing.

This study will evaluate ticagrelor efficacy and safety when added to standard of care treatments in SCD. Hence, patients are not withheld from any other treatments that may be used in SCD (e.g., hydroxyurea) during the study conduct, which is important considering the use of a placebo control group. Use of background standard of care, such as hydroxyurea, will be presented as follows:

- Number (n) and percentage (%) of patients in the FAS with background standard of care (regardless of type), as captured on the CM eCRF, and confirmed as ongoing at randomisation (Visit 2), as relevant: This will be based on ATC codes: *L01XX, A09AB, A05BA, A16AA and B06AX* as indicated by the study physician.
- Number (n) and percentage (%) of patients in the FAS with baseline hydroxyurea use (Yes/No) as assigned by IxRS.
- Number (n) and percentage (%) of patients in the FAS with stable hydroxyurea use for 3 months before enrolment in the study (screening [Visit 1]) and where stop date of hydroxyurea use is greater than randomisation (Visit 2)/date of first dose of study

treatment or is ongoing, as captured on the CM eCRF. This will be based on ATC code: *L01XX*.

- Number (n) and percentage (%) of patients in the FAS with hydroxyurea use started after randomisation (Visit 2)/date of first dose of study treatment and a duration of at least 6 months. Duration (months) will be derived as follows:
  - Duration (months) = (latest stop date of hydroxyurea use - earliest start date of hydroxyurea use [AFTER randomisation {Visit 2}]) + 1 (converted to months)

    Where:

    In case of ongoing medication use, study completion date or date of premature study discontinuation will be used to impute the latest stop date of hydroxyurea use in order to derive duration (months) within the context of the study course.

4.2.5 Study Treatment Exposure and Compliance

The following will be summarised by individual dose level (15 mg/30 mg/45 mg [per tablet count] bd) and overall dose level, by actual treatment group and overall, using the safety analysis set (refer to Section 2.1):

- Total study treatment exposure (days)
- Actual study treatment exposure (days)
- Number of study treatment interruptions, as reported by the investigator on the EX eCRF where *action taken with study drug* is indicated as "drug interrupted"
  - Main reason for study treatment interruption, as judged by the investigator, will be presented differentiating between COVID-19 related reasons and non-COVID-19 related reasons
- Total missed exposure days due to study treatment interruptions, as reported by the investigator on the EX eCRF where *action taken with study drug* is indicated as "drug interrupted"
  - Total missed exposure days due to COVID-19 related study treatment interruptions, as reported by the investigator on the EX eCRF where *action taken with study drug* is indicated as "drug interrupted"
- Total exposure years (across patients) based on total study treatment exposure (days)
- Study treatment compliance (%)
- Study treatment compliance (%) category:
  - < 80 %
  - ≥80 % to ≤120 %
  - >120 %
  - Missing

  - COVID-19 related reason
  - Non-COVID-19 related reason
- Weight (kg) versus dose level administration disagreement

Study treatment exposure and compliance will be based on the CSP weight-based specifications:

- ≥ 12 to ≤ 24 kg body weight: 15 mg dose level: 1 tablet of ticagrelor 15 mg or 1 tablet of placebo to match ticagrelor 15 mg twice daily
- > 24 to ≤ 48 kg body weight: 30 mg dose level: 2 tablets of ticagrelor 15 mg or 2 tablets of placebo to match ticagrelor 15 mg twice daily
- > 48 kg body weight: 45 mg dose level: 3 tablets of ticagrelor 15 mg or 3 tablets of placebo to match ticagrelor 15 mg twice daily

For patients with a weight increase exceeding 12.5% of the upper weight limit of the weight-band (≥ 27 kg and ≥54 kg, respectively), the dose will need to be increased according to the next weight-band. Decrease in dose level is not allowed and there will be no dose adjustments for decreasing weight.

The double-blind randomised treatment period comprises the following scheduled dispense/return visit intervals:

- Visit 2 (Week 0) to Visit 6 (3 Months)
- Visit 6 (3 Months) to Visit 9 (6 Months)
- Visit 9 (6 Months) to Visit 12 (9 Months)
- Visit 12 (9 Months) to Visit 15 (12 Months)
- Visit 15 (12 Months) to Next Scheduled In-clinic Visit/EOS[a]

[a] Only for patients completing the 24-month double-blind randomised treatment period or who are still ongoing within the double-blind randomised treatment period at the time of the CSED.

Study treatment dispense/return can, however, occur at any unscheduled timepoint within each of the scheduled dispense/return visit intervals and may also be impacted by COVID-19 with related reasons as captured on the drug accountability pandemic (DAP) eCRF.

Considering the aforementioned specifications, the following data handling conventions will therefore apply:

4.2.5.1 Study Treatment Exposure

Total duration of study treatment exposure (days) by dose level and overall dose level (includes missed exposure days due to study treatment interruptions):

- Exposure (days) = (date of last dose of double-blind randomised study treatment – date of first dose of double-blind randomised study treatment) + 1

  Where:

  Date of first dose of double-blind randomised study treatment equals:

  – Variable: *Start date of study drug administration*: Based on the EX eCRF, earliest administration date, at or after randomisation (Visit 2), at a given dose level and for each dose level received.
  – By overall dose level: Overall earliest of the aforementioned first dose of study treatment administration dates, over all dose levels received.

  Date of last dose of double-blind randomised study treatment equals:

  – Variable: *End date of study drug administration*: As captured on the EX eCRF and is the latest administration date, on or after randomisation (Visit 2), at a given dose level and for each dose level received regardless of temporary study treatment administration discontinuation (study treatment interruptions).
  – By overall dose level: Overall latest of the aforementioned last dose of study treatment administration dates, over all dose levels received. Patients may prematurely discontinue study treatment administration whilst continuing with scheduled assessments in the double-blind randomised treatment period. DOSDISC eCRF collects the variable, *date subject discontinued IP*. This date should equal the overall date of last dose of study treatment as captured on the EX eCRF but can be used in conjunction with EX data to accurately identify the overall date of last study treatment administration over all dose levels received in the double-blind randomised treatment period.

Total exposure years (across patients in a given treatment group) is defined as the sum of total double-blind randomised study treatment exposure (days) by overall dose level, including missed exposure days due to study treatment interruptions, for all patients in a given treatment group and is expressed in years as follows:

- Total exposure years (across patients) = Sum of (total study treatment exposure [days] by overall dose level)/360

  Where:

  Year = 360 days. .

Actual study treatment exposure (days) by dose level and overall dose level follows the same approach, however excludes all missed exposure days due to study treatment interruptions.

For example, *Patient 1: 30 mg dose level*:

Total study treatment exposure (days) = 238 days *(from 18 Apr 2019 to 11 Dec 2019)*

Missed exposure days = 9 days *(from 17 Nov 2019 to 25 Nov 2019) considering only the total number of missing exposure days due to study treatment interruptions (action taken with study drug on* EX eCRF indicated as "drug interrupted")

Actual study treatment exposure (days) = 238 – 9 = 229 days

	Dose	**Unit**	**Formulation**	**Freq**	**Reason for Action**	**Start Date**	**End Date**	**Action Taken with Study Drug**
1	30	mg	TABLET	BID	Adverse Event	2019-04-18	2019-11-16	Drug Interrupted
2	30	mg	TABLET	BID	Other	2019-11-26	2019-12-11	Dose Increased due to Weight Gain
3	45	mg	TABLET	BID		2019-12-12	ONGOING	

4.2.5.2 Study Treatment Compliance

Study treatment compliance (%) by dose level and overall dose level as based on actual study treatment exposure (days) (refer to Section 4.2.5.1):

- Compliance (%) = (actual tablets taken/expected tablets taken) × 100
  Where:
  - Actual tablets taken equals:
    - Per kit IDs for a given dose level: Difference between total tablets dispensed and total tablets returned, regardless of temporary study treatment administration discontinuation (study treatment interruptions) and noting that tablets may be returned after the end of the dose level administration.
    - By overall dose level: Sum of actual tablets taken over all dose levels received.

    If tablets returned amount is missing for any/all kit IDs dispensed, both dose level and overall dose level actual tablets taken will be missing, ie, no imputation assumptions of tablets taken will be applied and as such study treatment compliance will be missing.

  - Expected tablets taken equals:
    - Expected tablets to be taken per last available weight (kg) at the time of study treatment administration (planned) is based on actual study treatment exposure

(days) excluding missed exposure days due to study treatment interruptions, by each dose level received:

- 15 mg (>12 kg to ≤24 kg body weight): 1× 15 mg tablet bd: 2× actual study treatment exposure (days)
- 30 mg (>24 kg to ≤48 kg body weight): 2× 15 mg tablets bd: 4× actual study treatment exposure (days)
- 45 mg (>48 kg body weight): 3× 15 mg tablets bd: 6× actual study treatment exposure (days)

- By overall dose level: Sum of expected tablets taken over all dose levels received

In addition, study treatment compliance (%), as derived per the aforementioned, will be categorised as follows:

- < 80 %
- ≥80 % to ≤120 %
- >120 %
- Missing

Number (n) and percentage (%) of patients in the safety analysis set, per compliance category will be presented, by actual treatment group and overall. Percentage will be calculated relative to the total number of patients in the safety analysis set, by actual treatment group and overall. If, for at least 10 patients in total across the two treatment groups, compliance (%) cannot be calculated, the reason for missing compliance will be presented, if relevant, as:

- COVID-19 related reason
- Non-COVID-19 related reason

In addition to the aforementioned, weight (kg) versus dose level administration disagreement will be determined as follows:

Weight (kg) will be assessed every 6 months per the planned schedule of assessments. Weight (kg) (whether scheduled or unscheduled), as available at the start of study treatment administration at a given dose level, will be assessed in accordance with the CSP weight-based specifications and categorised as follows:

- Weight-based dose level agreement
- Weight-based dose level disagreement

The number (n) and percentage (%) of patients in the safety analysis set with weight-based dose level disagreement at any time over the course of the double-blind randomised treatment period and over all dose levels received will be presented. Percentage will be calculated

relative to the total number of patients in the safety analysis set, by actual treatment group and overall.

Details related to the administration of investigational product during the double-blind randomised treatment period will be presented in patient data listings.

4.2.6 Primary Efficacy Variable

4.2.6.1 Number of VOCs

The primary efficacy variable is the number of VOC events during the defined treatment period (refer to Section 3.1.4) and the primary analysis is to compare the VOC event rate of ticagrelor with placebo based on the intent to treat (ITT) principle. The primary efficacy analysis will be performed using FAS (refer to Section 2.1).

The null hypothesis is that the VOC event rate on ticagrelor is equal to the VOC event rate on placebo. The alternative hypothesis is that the VOC event rate on ticagrelor is not equal to the VOC event rate on the placebo, ie,

H_0: *Rate ratio (ticagrelor vs placebo)* $= 1$
H_a: *Rate ratio (ticagrelor vs placebo)* $\neq 1$

The VOC event rate on ticagrelor will be compared to the VOC event rate on placebo using a negative binomial model for the primary analysis. The response variable in the model will be the number of VOC events experienced by a patient during the defined treatment period, regardless of premature discontinuation of study treatment. The model will include covariates of treatment group and baseline hydroxyurea use (Yes/No) as covariates.

The logarithm of the patient's observed follow-up time per defined treatment period expressed in years (where a year = 360 days) will be used as an offset term in the model to adjust for patients having different follow-up times.

The estimated treatment effect (ie, the rate ratio of ticagrelor versus placebo), the corresponding Wald 95% confidence interval (CI) and the p-value for the rate ratio will be presented. In addition, the VOC event rate and the corresponding 95% CI within each treatment group will be presented. The VOC event rate will be computed using the OM option in the LSMEANS statement of PROC GENMOD.

An estimated value of the rate ratio < 1 will favour ticagrelor. The estimated dispersion parameter will also be noted.

4.2.6.2 Testing the Fit of Negative Binomial Distribution

The fit of the negative binomial distribution to the data will be tested by means of the Pearson goodness of fit test after estimating the parameters of the distribution and checking whether there are no convergence issues with the maximum likelihood estimation of the coefficients. The negative binomial model will be tested against the Poisson model in a likelihood ratio test to test the robustness of the model.

If the negative binomial distribution is not appropriate, a stratified Wilcoxon rank sum test will be used. As the stratified Wilcoxon rank sum test cannot be adjusted for the patient's follow-up time, the annualised number of VOC events will be used for the analysis rather than the number of VOCs as analysed for the primary efficacy. . By using annualised number of VOC events, it scales it allowing a comparison of VOC rates across patients with varying time in the study. Baseline hydroxyurea use (Yes/No) will be used as a stratification factor. Number of annualised VOC events is the count of VOC events experienced by a patient over the defined treatment period (refer to Section 3.1.5) as assessed by the investigator and collected on the VOC1 eCRF, multiplied by 360 days, and divided by the number of days in the defined treatment period.

$$Num\ VOCs\ Annualised = \frac{Number\ of\ VOCs}{(defined\ treatment\ period\ end\ date - randomisation\ date) + 1} * 360$$

A Wilcoxon rank sum test for each subgroup defined in Section 4.2.6.4 will also be presented. No stratification factor will be included in this analysis.

Median, median difference and 95% confidence interval for the median difference will be estimated using Hodges-Lehmann method. Summary statistics of the annualised VOC rate will also be presented.

4.2.6.3 Sensitivity Analyses

Sensitivity analyses to assess the robustness of the primary analysis results to missing data as outlined in Appendix E Accounting for Missing Data, may be conducted utilising the FAS, unless otherwise specified, depending on the amount of missing data due to patients who prematurely discontinue study treatment and/or study participation.

In addition to the sensitivity analyses outlined in Appendix E Accounting for Missing Data, the following analyses will also be performed:

1 The primary analysis will be repeated including only data from patients whilst being on study treatment ie, excluding data once patients discontinue from study treatment. For this analysis the patient's observed follow-up time will correspond to their actual "on-treatment" period defined as the period from first dose of study treatment (ticagrelor or

placebo) up to and including last dose of study treatment + 7 days. Refer to Section 3.1.7.1.

2 The primary analysis will be repeated where the response variable is the number of VOC events that occur during the defined treatment period, irrespective of the number of days between the onset of events.

3 The analysis will be repeated by replacing the factor for IxRS baseline hydroxyurea use (Yes/No) with a more inclusive indicator for hydroxyurea use defined as a combination of (a. and/or b.):

(a) IxRS baseline hydroxyurea use (Yes/No) **AND/OR**

(b) Hydroxyurea use:

(i) Start date after randomisation (Visit 2) AND

(ii) Duration of hydroxyurea use of at least 6 months during the study (latest stop date of hydroxyurea use record – earliest start date of hydroxyurea use record AFTER randomisation [Visit 2] + 1 [converted to months] ≥ 6 months).

Where:

In case of ongoing medication use, study completion date, as collected on the disposition eCRF, or date of premature study discontinuation will be used to impute the latest stop date of hydroxyurea use in order to derive duration (months) within the context of the study.

If both these criteria (i) and (ii) are met the value will be "Yes", otherwise it will be "No".

4 The primary analysis will be repeated using the PP analysis set.

5 The primary analysis will be repeated for the following combination of covariates, if there are at least 5 patients within each stratum:

(a) Treatment group, baseline hydroxyurea use (Yes/No), age group at randomisation (Visit 2) (≥ 2 years to < 12 years, ≥ 12 years to < 18 years)

(b) Treatment group, baseline hydroxyurea use (Yes/No), prior VOC events in previous 12 months prior to study enrolment at screening (Visit 1) (≥ 2 to ≤ 4, > 4), as collected on the VOC eCRF

(c) Treatment group, baseline hydroxyurea use (Yes/No), and geographic region

(d) Where geographic region is defined as:

- North and South America (USA, Canada, Brazil)
- Europe (UK, Turkey, Spain, Italy, Greece, Belgium)
- Africa and Asia (Egypt, Ghana, India, Kenya, Lebanon, South Africa, Tanzania, Uganda)

(e) Treatment group, baseline hydroxyurea use (Yes/No), age group at randomisation (Visit 2) (≥ 2 years to < 12 years, ≥ 12 years to < 18 years), prior VOC events in previous 12 months prior to study enrolment at screening (Visit 1) (≥ 2 to ≤ 4, > 4), as collected on the VOC eCRF, and geographic region

6 Zero-inflated Poisson and zero-inflated negative binomial models will be run on the same data as used for the primary analysis to allow for over dispersion seen in the negative binomial and Poisson models. The models allow for the excessive zero counts in the data. The zero-inflated Poisson and negative binomial models split the data into two separate distributions where one distribution (either Poisson or negative binomial) that generate both zero and non-zero counts, the second distribution is a constant distribution that generates only zero counts. When a zero count is observed, there is some probability, called the zero-inflation probability, that the observation came from the always-zero distribution; the probability that the zero came from the Poisson/negative binomial distribution is 1 minus the zero-inflation probability. When the underlying count distribution is a Poisson distribution, the mixture is called a zero-inflated Poisson (ZIP) distribution; when the underlying count distribution is a negative binomial distribution, the mixture is called a zero-inflated negative binomial (ZINB) distribution (Hilbe 2007).

4.2.6.4 Subgroup analyses

To explore the uniformity of the detected overall treatment effect on the primary efficacy variable, subgroup analyses and statistical modelling including testing for interaction between treatment and covariates will be performed on the full analysis set for the factors below.

If there are issues with model convergence, only descriptive statistics by subgroup will be presented. Descriptive statistics by subgroup will be presented for all cases regardless of the model convergence. These analyses are exploratory and the results from these analyses will not affect the choice of terms used in the model for the primary analysis.

The following subgroups will be reported:

- Age by category:
  - ≥2 years to <12 years at randomisation (Visit 2)
  - ≥12 years to <18 years at randomisation (Visit 2)
- Number of VOC events within the previous 12 months prior to study enrolment at screening (Visit 1):
  - ≥2 to ≤4
  - >4
- Baseline hydroxyurea use: Based on IxRS
  - Yes
  - No

- Sickle cell genotype: HbSS and $HbSB^0$ Thalassaemia
- Geographic region:
  - North and South America (USA, Canada, Brazil)
  - Europe (UK, Turkey, Spain, Italy, Greece, Belgium)
  - Africa and Asia (Egypt, Ghana, India, Kenya, Lebanon, South Africa, Tanzania, Uganda)
- Gender: Male and Female
- Race as reported in Appendix B Race Mapping:
  - White
  - Black or African-American
  - Asian
  - Other

If the negative binomial regression model is judged to be appropriate, then for each subgroup analysis separately, where sufficient data allows, a negative binomial regression model will be fitted including as covariates treatment group, subgroup main effect and the treatment-by-subgroup interaction. The p-value for the treatment-by-subgroup interaction will be presented.

The logarithm of the patient's observed follow-up time per defined treatment period expressed in years (where a year = 360 days) will be used as an offset term in the model to adjust for patients having different follow-up times.

4.2.7 Time to Event Analyses

Pending number of events (as defined below), a time to event analysis may be considered utilising Kaplan-Meier methodology. Kaplan-Meier figures will be presented for the following:

- Time to first VOC event (days) in the defined treatment period: Based on the earliest start date of all VOC events, as collected on the VOC1 eCRF, experienced by a patient during the defined treatment period. Time (days) will be derived as the difference in days from randomisation (Visit 2) to the earliest start date of the VOC events. Patients not experiencing a VOC event will be censored at the end of their defined treatment period, derived as the latest of: Date of EOS visit, date of last available assessment within the defined treatment period or date of premature study discontinuation (regardless of the reason for premature study discontinuation)(refer to Section 3.1.4).
- Time to discontinuation of study treatment (days) (overall and by study treatment related/not study treatment related reason for discontinuation, as defined in Appendix E Accounting for Missing Data): Patients may prematurely discontinue study treatment administration whilst continuing with scheduled assessments. DOSDISC eCRF collects the variable, *date subject discontinued IP*. Time (days) will be derived as the difference in days from date of first dose of double-blind randomised study treatment to the date of

premature study treatment discontinuation. Patients randomised but not treated will be censored at date of randomisation (Visit 2) = Day 1. Patients completing double-blind randomised study treatment administration will be censored at the date of last dose of double-blind randomised study treatment administration.

4.2.8 Secondary Efficacy Variables

In general, and unless otherwise specified, the secondary efficacy analyses will be performed using the FAS (refer to Section 2.1) by planned treatment group. Palatability and swallowability will be performed using the safety analysis set by actual double-blind randomised study treatment received.

4.2.8.1 Number of Painful Crises

Descriptive statistics will be presented for the number of painful crises experienced by a patient over the treatment period by planned treatment group using the FAS. Descriptive statistics will also be presented for the number of individual painful crises irrespective of the number of days between the onset of painful crises.

The number of painful crises will be analysed using the negative binomial regression model, as described in Section 4.2.6.1 for the primary endpoint. Similarly, as sensitivity analysis, the same negative binomial regression model will be used on the number of individual painful crises irrespective of the number of days between the onset of painful crises.

4.2.8.2 Number of ACSs

Descriptive statistics will be presented for the number of ACSs experienced by a patient over the defined treatment period by planned treatment group. Descriptive statistics will also be presented for the number of individual ACSs irrespective of the number of days between the onset of ACSs.

If numbers allow, the number of ACSs will be analysed using the negative binomial regression model as described in Section 4.2.6.1 for the primary endpoint. Similarly, as sensitivity analysis, the same negative binomial regression model will be used on the number of individual ACSs irrespective of the number of days between the onset of ACSs.

4.2.8.3 Duration of Painful Crises

Descriptive statistics will be presented for the total duration (days) (taking into account overlapping painful crisis days + 7-day onset rule) of painful crises experienced by a patient over the defined treatment period by planned treatment group. Patients who do not experience any painful crisis will have their duration of painful crises set to 0.

If numbers allow, the total duration (days) (taking into account overlapping painful crisis days + 7-day onset rule) of painful crises will be analysed using the negative binomial regression model, as described in Section 4.2.6.1.

4.2.8.4 Number of VOC Events Requiring Hospitalisation or Emergency Department Visits

Descriptive statistics will be presented for the number of VOC events requiring hospitalisation or emergency department visits experienced by a patient over the treatment period by planned treatment group.

If numbers allow, the number of VOC events requiring hospitalisation or emergency department visits will be analysed using the negative binomial regression model, as described in Section 4.2.6.1.

4.2.8.5 Number of Days Hospitalised for VOC Events

Descriptive statistics will be presented for the total number of days hospitalised (taking into account potential overlapping hospitalisation days of VOC components) for VOC events experienced by a patient over the defined treatment period by planned treatment group. Patients who do not experience any VOC event as well as patients who do not experience any VOC events requiring hospitalisation due to VOC will have their number of days hospitalised for VOC set to 0.

If numbers allow, the total number of days hospitalised for VOCs (taking into account potential overlapping hospitalisation days of VOC components) will be analysed using the negative binomial regression model, as described in Section 4.2.6.1.

4.2.8.6 Number of Acute SCD Complications

Descriptive statistics will be presented for the number of acute SCD complications experienced by a patient over the treatment period by planned treatment group.

If numbers allow, the number of acute SCD complications will be analysed using the negative binomial regression model, as described in Section 4.2.6.1.

If reported by at least 10 patients in total across the two treatment groups, the individual events comprising acute SCD complications will be assessed descriptively as exploratory endpoints (TIA/ischaemic stroke, hepatic sequestration, splenic sequestration, priapism, and dactylitis).

4.2.8.7 Number of Days Hospitalised for Acute SCD Complications

Descriptive statistics will be presented for the total number of days hospitalised (taking into account potential overlapping hospitalisation days) for acute SCD complications experienced by a patient over the defined treatment period by planned treatment group. Patients who do not experience any acute SCD complication as well as patients who do not experience any acute SCD complications requiring hospitalisation will have their number of days hospitalised for SCD complications set to 0.

If numbers allow, the total number of days hospitalised (taking into account potential overlapping hospitalisation days) for acute SCD complications will be analysed using the negative binomial regression model as described in Section 4.2.6.1.

4.2.8.8 Number of Sickle Cell-related Red Blood Cell Transfusions

Descriptive statistics, including arithmetic mean, SD, median, min and max, will be presented for the number of sickle cell-related red blood cell transfusions received by a patient over the defined treatment period by planned treatment group.

If numbers allow, the number of sickle cell-related red blood cell transfusions will be analysed using the negative binomial regression model as described in Section 4.2.6.1.

4.2.8.9 Health-related Quality of Life (HRQL) and Fatigue

Descriptive statistics will be presented for patients in FAS, by planned treatment group and visit, for the PedsQL SCD Module considering the 9 sub-scales (refer to Section 3.3.6.1 for details) and the derived total score as well as the change from baseline in these scores to each post-baseline visit, based on scheduled eCRF visit (number and name).

Similarly, for the Multidimensional Fatigue Scale considering the 3 sub-scales (refer Section 3.3.6.2 for details) and the derived total score as well as the change from baseline in these scores to each post-baseline visit, based on scheduled eCRF visit (number and name)..

All descriptive statistics will be presented by age-specific category only. Individual patient data will be listed. It should be noted that child self-reported or caregiver-reported cannot be ascertained from the data collected and as such is not presented in relevant tables and listings.

4.2.8.10 Days Absent from School/Work Due to SCD

Descriptive statistics will be presented for the proportion of days absent from school/work due to SCD by planned treatment group, only for those patients who were going to school or work at randomisation (Visit 2).

4.2.8.11 Intensity of Pain During VOC Events and Number of VOC Events by Age Group

The number (n) and percentage (%) of patients experiencing at least one individual VOC event will be calculated based on FAS and will be presented by age group (<5 years and ≥5 years) and planned treatment group. Similarly, the total number of individual VOCs will be presented by age group (<5 years and ≥5 years) and planned treatment group.

Descriptive statistics of the average intensity of pain during VOCs will be presented by age group (<5 years by means of FLACC and for patients ≥5 years by means of FPS-R).

4.2.8.12 Type of Analgesics Used During VOC Events

Analgesics use during VOC events as well as the type of analgesics (opioid/non-opioid) will be summarised and presented, by planned treatment group, on both event and patient level:

- Number of (individual) VOC events occurring during the defined treatment period
- Analgesics use (during individual VOC events)
- Type of analgesics:
  - Opioid
  - Non-opioid

At event level, only the number of observations (n) in each category will be presented.

At patient level, the percentage (%) of patients reporting at least one VOC event will be calculated based on FAS. Percentage of analgesics use will be calculated based on the total number of patients in FAS with at least one VOC event reported in the defined treatment period. Patients with multiple analgesics used during VOC events will be counted only once in that category. Patients who used both types of analgesics (opioid/non-opioid) will be counted once in both categories.

4.2.8.13 Swallowability and Palatability Data

Swallowability and palatability data will be summarised taking into consideration the administration formulation. A summary table will be produced showing the number (n) and percentage (%) of patients with ease/difficulty of swallow based on the categories defined in Section 3.3.10.

In addition, the number (n) and percentage (%) of patients with a negative response to palatability will be presented. Percentage will be based on the total number of patients in the safety analysis set, per age group as determined at randomisation (Visit 2), who completed the correct age-specific assessment for study treatment palatability per formulation, by actual treatment group. Number of patients reporting a negative response will be also presented based on the categories defined in Section 3.3.10.

4.2.9 Safety

Safety summaries will be presented using the safety analysis set (refer to Section 2.1), unless otherwise specified, by actual study treatment received. No formal statistical analyses will be performed on safety data.

4.2.9.1 Adverse Events

Summary tables will include on-treatment/off-treatment AEs (refer to Section 3.4.1) only, unless otherwise specified. That is, pre-treatment AEs will be included in the patient data listings only.

Separate overall summary tables will be produced for AEs on-treatment and off-treatment showing the number (n) and percentage (%) of patients with at least one AE in each of the following AE categories: Any AE, any AE causally related to study treatment, maximum AE intensity, any AE with an outcome of death, any SAE and discontinuation of study treatment due to AEs. The overall summary tables will be repeated by age group as follows:

- ≥2 years to <12 years at randomisation (Visit 2)
- ≥12 years to <18 years at randomisation (Visit 2)

AEs/SAEs will be summarised by MedDRA SOC and MedDRA PT by actual study treatment received and by the same age group as previously defined. Events will be sorted by international order for system organ class (SOC) and alphabetically for PTs within each SOC. For each SOC/PT, the number (n) and percentage (%) of patients reporting at least one event at each level of summarisation (SOC/PT) will be presented ie, for a patient with multiple occurrences of the same AE, the event will only be counted once per PT/SOC. Patients with events in more than one SOC/PT are counted once per individual SOC/PT.

Most common AEs will be summarised separately by MedDRA PT, where most common is defined as a frequency > 5% in either of the two treatment groups and sorted by decreasing frequency based on the ticagrelor treatment group. Similarly, for presentation of non-serious AEs. In addition, AEs will be summarised by MedDRA PT and causality/relatedness. If a patient reports multiple occurrences of the same AE, the patient will be summarised only for the most related. Similarly, by MedDRA PT and maximum reported intensity. If a patient reports multiple occurrences of the same AE, the patient will be summarised only for the maximum reported intensity. In case of missing causality/relatedness and/or intensity, a missing category will be presented per relevant PT.

The event rate per 100 patient years will be presented by treatment group, where:

Event rate per 100 patient years = (number of patients with AEs/total exposure years) × 100 (refer to Section 4.2.5).

Where:
Year = 360 days.

Patient data listings of AEs leading to death, SAEs, SAEs causally related to study treatment and discontinuation of study treatment due to AEs will be presented. In addition, COVID-19 suspected AEs/SAEs and COVID-19 confirmed AEs/SAEs will be presented in a separate patient data listing. Dose level at onset of AEs/SAEs will also be presented in patient data listings.

4.2.9.2 Overdose

A listing will be provided of patients who experience at least one overdose over the study period. The listing will be sorted by actual study treatment taken and patient ID. Dose level at time of overdose and time to onset of overdose will also be presented.

4.2.9.3 Bleeding Events

For the safety analysis set, summary tables will include on-treatment/off-treatment bleeding events (refer to Sections 3.4.4) only. Pre-treatment bleeding events will be included in the patient data listings only. Any bleeding events occurring after premature study treatment discontinuation regardless of initiation of alternative therapy for SCD will be flagged in the patient data listings.

Total number of bleeding events (n only), frequency (n and %) of patients who have experienced at least one bleeding event on-treatment/off-treatment will be presented by actual study treatment received. Percentage of patients experiencing at least one bleeding event will be based on the safety analysis set, by actual treatment group.

Event-level and patient-level summary of bleeding characteristics: Severity of bleed, nature of the bleed and primary location of the bleed will also be presented. Percentage of bleeding events reported in each category will be based on the total number of bleeding events experienced by patients in the safety analysis set. Percentage of patients in each category will be based on the total number of patients in the safety analysis set who experienced at least one bleeding event, by actual treatment group.

All bleeding events at any time during the study will be presented in patient data listings. Dose level at onset of the bleeding event will also be presented.

4.2.9.4 Blood Product Transfusions

For the safety analysis set, summary tables will include on-treatment/off-treatment blood product transfusions (refer to Sections 3.1.7.1 and 3.1.7.2), unless otherwise specified. Transfusions (as defined in Section 3.4.6) including the number of patients who have had any AE leading to the need for a transfusion, the number of transfusions for each patient, and the number of units transfused along with the type of blood product transfused will be presented by actual study treatment received.

All blood product transfusions at any time during the study will be presented in patient data listings. Dose level at onset of the blood product transfusion will also be presented.

4.2.9.5 Laboratory Variables

With reference to the general principles and definitions detailed in Sections 2.1, 3.1 and 4.1.1, laboratory variables will be summarised using the safety analysis set, by actual treatment group. Relevant data will be presented in patient data listings.

For continuous variables, observed values and change from baseline will be summarised for each clinical chemistry, haematology, and urinalysis variable at each scheduled time point (per planned eCRF visit [number and name]). For categorical variables, shift tables will be presented for the change from baseline by actual treatment group.

Box plots of observed values and change from baseline will also be presented for each clinical chemistry, and haematology laboratory variable.

For each laboratory variable, a shift table will be produced presenting the baseline value classification according to laboratory reference range versus the minimum and maximum on-treatment value.

Descriptive statistics, summarising patients with at least one treatment-emergent change (high [increase]/low [decrease]) per laboratory variable, based on laboratory reference ranges, will be presented by actual treatment group (refer to Section 3.4.7). Where:

- n = Number of patients with at least one treatment-emergent change occurring on-treatment (patients with multiple occurrences on-treatment will only be counted once).
- % = Percentage of patients in the safety analysis set with at least one treatment-emergent change occurring on-treatment relative to the total number of patients in the safety analysis set, with a baseline and at least one post-baseline assessment on-treatment available.

4.2.9.5.1 Liver Enzyme Elevations and Hy's Law

The following summaries will include the number (n) and percentage (%) of patients in the safety analysis set with at least one post-baseline liver function assessment available in the defined double-blind randomised treatment period and identified as on-treatment or off-treatment (refer to Section 3.1.7.1 and 3.1.7.2), who have:

- Elevated ALT, AST, and total bilirubin over the defined treatment period
  - ALT <3, ≥3× to <5×, ≥5× to <10×, ≥10× ULN
  - AST <3×, ≥3× to <5×, ≥5× to <10×, ≥10× ULN
  - Total bilirubin <2×, ≥2× ULN
  - ALT or AST <3×, ≥3× to <5×, ≥5× to <10×, ≥10× ULN

- ALT or AST ≥3× ULN and total bilirubin ≥2× ULN (Potential Hy's law): The onset date of ALT or AST elevation should be prior to or on the date of total bilirubin elevation.

To identify potential Hy's Law cases, a listing of patients in the safety analysis set who have ALT or AST ≥3× ULN and total bilirubin ≥2× ULN at any time during the study (ie, not necessarily at the same time) following first dose of double-blind randomised study treatment administration will be provided. This listing will include all assessments (scheduled and unscheduled) for this subset of patients over the entire study course. Dose level at the time of liver function assessments will also be presented.

A shift plot will also present maximum on-treatment (refer to Section 3.4.7) ALT observed value by maximum on-treatment total bilirubin observed value, expressed as multiples of ULN. A similar plot will be presented for maximum on-treatment AST observed value. Reference lines will be included at 2× ULN for total bilirubin and 3× ULN for ALT/AST.

Additionally, a figure presenting the individual liver biochemistry test results over time for patients with elevated ALT or AST, and elevated total bilirubin at any time following first dose of double-blind randomised study treatment administration will be provided. Results will be expressed as multiples of ULN.

4.2.9.6 ECG Variables

Overall evaluation of ECG will be summarised at each timepoint/visit reporting the number (n) and percentage (%) of patients in the safety analysis set presenting with a normal, abnormal not clinically significant or abnormal clinically significant evaluation. A shift table from baseline to last on-treatment ECG evaluation (scheduled or unscheduled) will also be presented. Percentage will be based on the total number of patients in the safety analysis set, by actual treatment group, with a baseline and at least one post-baseline evaluable ECG assessment on-treatment available.

4.2.9.7 Vital Signs

For the safety analysis set, observed values and change from baseline to each scheduled visit (per planned eCRF visit [number and name]) will be summarised for each vital sign by actual treatment group.

For SBP, DBP and pulse rate, a shift table will be produced presenting the baseline value classification according to abnormality assessment criteria versus the minimum and maximum on-treatment value.

Descriptive statistics, summarising patients with at least one treatment-emergent change (high [increase]/low [decrease]), based on the abnormality assessment criteria, will be presented by actual treatment group. Where:

- n = Number of patients with at least one treatment-emergent change occurring on-treatment (patients with multiple occurrences on-treatment will only be counted once).
- % = Percentage of patients in the safety analysis set with at least one treatment-emergent change occurring on-treatment relative to the total number of patients in the safety analysis set, with a baseline and at least one post-baseline assessment on-treatment available.

4.2.10 Exploratory Variables

4.2.10.1 Duration of ACSs

Descriptive statistics will be presented for the total duration (days) (taking into account overlapping ACS days + 7-day onset rule) of ACSs experienced by a patient over the defined treatment period by planned treatment group. Patients who do not experience any ACS will have their duration of ACS set to 0 (see Section 3.3.2).

4.2.10.2 Pharmacokinetic Data

4.2.10.2.1 Statistical Analysis of Pharmacokinetic Data

The PK analysis set is defined in Table 1.

All available plasma concentration-time data for ticagrelor and active metabolite (AR-C124910XX) will be listed for the safety analysis set with any data to be excluded from the summary tables and figures for the PK analysis set indicated. Any PK data excluded from the summary tables (either individual time points or entire treatment period) will also be excluded from the associated figures.

For those patients eligible for inclusion in the PK analysis set the plasma concentration-time data will be summarised by protocol-scheduled timepoint for each dosing regimen.

The levels of precision for reporting PK concentration data in the listings and for each descriptive statistic in the summary tables are detailed in the PK Order Form provided by the PK Scientist on which the tables, figures and listings shells are based.

Descriptive statistics used for summarising the PK data, ie, plasma concentrations of ticagrelor and active metabolite (AR-C124910XX), at each timepoint for each visit will follow from general methodology (refer to Section 4.1.1).

Plasma concentrations that are below the limit of quantification (BLQ) will be reported as follows:

Individual concentrations below the lower limit of quantification (LLOQ) of the bioanalytical assay will be reported as non-quantifiable (NQ) in the listings with the LLOQ defined in the footnotes of the relevant tables, figures, and listings. Individual plasma concentrations that are not reportable will be reported as not reportable (NR) and those that are missing will be

reported as no sample (NS) in the listings. Plasma concentrations that are NQ, NR or NS will be handled as follows in the presentation of descriptive statistics:

- Any values reported as NR or NS will be excluded from the summary tables and figures. At a timepoint where less than or equal to 50% of the concentration values are NQ, all NQ values will be substituted with the LLOQ concentration, and all descriptive statistics will be calculated accordingly.
- At a timepoint where more than half (but not all) of the values are NQ, the gMean, gCV% and SD will be reported as not calculable (NC). The maximum value will be reported from the individual data and the minimum and median will be set to NQ.
- If all concentrations are NQ at a timepoint, the gMean, min, median and max will be reported as NQ and the SD and gCV% will be reported as NC.

The number of values above LLOQ (n >LLOQ) will be reported for each timepoint together with the total number of collected values.

Three observations > LLOQ will be required as a minimum for PK plasma concentrations to be summarised. For consistency, the same plasma concentration values will be used in the mean data graphs as those given in the descriptive statistics summary table for each timepoint.

The plasma PK concentration data for ticagrelor and active metabolite (AR-C124910XX) will be displayed graphically. Displays will include:

1 Individual patient plasma concentration-time profiles on the linear scale showing ticagrelor and active metabolite (AR-C124910XX) on the same plot.
2 Individual patient plasma concentration-time spaghetti plots of ticagrelor on the linear scale for each dose level showing all patients on the same plot. This will be repeated for active metabolite (AR-C124910XX).
3 Geometric mean (gMean) pre-dose plasma concentrations of ticagrelor (with gSD error bars) and active metabolite (AR-C124910XX) on the same plot versus visit (visit number as X-axis) for the pooled weight-bands/doses and for each weight-band/dose level.
4 Geometric mean (gMean) 2-hour plasma concentrations (with gSD error bars) of ticagrelor and active metabolite (AR-C124910XX) on the same plot versus visit (visit number as X-axis) for the pooled weight-bands/doses and for each weight-band/dose level.

4.2.10.3 Pharmacodynamic Variable

Pharmacodynamic analysis, by actual treatment group, will be performed utilising patients considered evaluable for inclusion in the PD analysis set and who provide at least baseline and one post-baseline (pre-dose and/or post-dose) analysable sample (refer to Section 2.1).

All available data will be listed for the safety analysis set with any PD data to be excluded from the summary tables and figures indicated by means of a flag.

PRI (%) values will be presented by actual study treatment received for each week/month and timepoints (pre-dose and 2 hours post-dose). Descriptive statistics will be presented for each observed result including:

- gMean: Calculated as exp[μ], where μ is the mean of the data on a natural logarithmic scale
- gSD: Calculated as exp[s], where s is the SD of the data on a natural logarithmic scale
- gCV%: Calculated as 100 √ [exp(s^2)-1], where s is the SD of the data on a natural logarithmic scale
- aMean
- SD
- Median
- Minimum (min)
- Maximum (max)

and for change from baseline (refer to Section 3.1.3) by means of:

- aMean
- SD
- Median
- Minimum (min)
- Maximum (max)

In addition, PRI (%) will be presented graphically as follows:

- Individual patient PRI-time spaghetti plots for the pooled weight-bands/doses and for each weight-band/dose level. Pre-dose and 2-hours post-dose PRI values will not be averaged and will be presented separately.
- Mean (geometric and arithmetic) pre-dose PRI values versus visit (visit number as X-axis) for the pooled weight-bands/dose level and for each weight-band/dose level.
- Mean (geometric and arithmetic) 2-hours post-dose PRI values versus visit (visit number as X-axis) for the pooled weight-bands/dose level and for each weight-band/dose level.

If considered relevant, the same data handling conventions detailed for the PK analyses will be applied for those PRI (%) values that are NQ, NR or NS.

5 INDEPENDENT DATA MONITORING COMMITTEE

An independent data monitoring committee (IDMC) composed of independent SCD paediatric experts and including a platelet expert and statistician, will be appointed for this study and will report to the Steering Committee (SC). The IDMC 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 IDMC will make

recommendations on the progression of the study based on the totality of unblinded data or other findings putting patients at undue risk. Please refer to Section 1.5.2 of the CSP for further details.

Additionally, the IDMC 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-hour post-dose PRI (%) values at 4 weeks will be calculated for each individual patient 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 for not achieving the targeted inhibition level of 35 to 80% in the study, the first task of the IDMC would be to investigate the PK values and that 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 IDMC not to 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 study treatment compliance and potentially escalate the issue to the SC 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.

6 CHANGES/CLARIFICATIONS OF ANALYSIS FROM PROTOCOL

Table 3 Summary of Changes/Clarifications from Protocol

Reference	Protocol	Change	Justification
Sec 2.1	V2.0 29AUG2018	*Added PP analysis set*	Missing from protocol but needed for outputs
Appendix E and Sec 4.2.6.1	V2.0 29AUG2018	*Added tipping point and other sensitivity analysis*	Needed to explore more end points than protocol specified

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8 APPENDIX

Appendix A Vital Signs Pre-defined Abnormality Assessment Criteria

As far as vital signs are concerned, the following pre-defined abnormality assessment criteria will be considered:

Table 4 Vital Signs Pre-defined Abnormality Assessment Criteria

Years	Systolic Blood Pressure		Diastolic Blood Pressure		Pulse	
	Lower	Upper	Lower	Upper	Lower	Upper
≥ 2 to < 4	80	110	55	75	70	130
≥ 4 to < 6	80	115	55	75	70	120
≥ 6 to < 8	85	115	55	75	65	115
≥ 8 to < 12	90	120	60	80	60	110
≥ 12 to < 14	95	125	65	85	60	110
≥ 14 to < 16	95	130	65	85	55	100
≥ 16 to < 18	95	135	70	85	50	90

Appendix B Race Mapping

Analysis Race	Race as Collected
AMERICAN INDIAN OR ALASKA NATIVE	AMERICAN INDIAN OR ALASKA NATIVE
ASIAN	ASIAN
ASIAN	ASIAN AMERICAN
BLACK OR AFRICAN AMERICAN	AFRICAN
BLACK OR AFRICAN AMERICAN	AFRICAN CARIBBEAN
BLACK OR AFRICAN AMERICAN	BAHAMIAN
BLACK OR AFRICAN AMERICAN	BARBADIAN
BLACK OR AFRICAN AMERICAN	BLACK CENTRAL AMERICAN
BLACK OR AFRICAN AMERICAN	BLACK OR AFRICAN AMERICAN
BLACK OR AFRICAN AMERICAN	BLACK SOUTH AMERICAN
BLACK OR AFRICAN AMERICAN	BOTSWANAN
BLACK OR AFRICAN AMERICAN	DOMINICA ISLANDER
BLACK OR AFRICAN AMERICAN	DOMINICAN
BLACK OR AFRICAN AMERICAN	ETHIOPIAN
BLACK OR AFRICAN AMERICAN	HAITIAN
BLACK OR AFRICAN AMERICAN	JAMAICAN
BLACK OR AFRICAN AMERICAN	LIBERIAN
BLACK OR AFRICAN AMERICAN	NAMIBIAN
BLACK OR AFRICAN AMERICAN	NIGERIAN
BLACK OR AFRICAN AMERICAN	TOBAGOAN
BLACK OR AFRICAN AMERICAN	TRINIDADIAN

BLACK OR AFRICAN AMERICAN	WEST INDIAN
BLACK OR AFRICAN AMERICAN	ZAIREAN
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER
WHITE	ARAB
WHITE	EASTERN EUROPEAN
WHITE	EUROPEAN
WHITE	MEDITERRANEAN
WHITE	MIDDLE EASTERN
WHITE	NORTH AFRICAN
WHITE	NORTHERN EUROPEAN
WHITE	RUSSIAN
WHITE	WESTERN EUROPEAN
WHITE	WHITE
WHITE	WHITE CARIBBEAN
WHITE	WHITE CENTRAL AMERICAN
WHITE	WHITE SOUTH AMERICAN
OTHER	OTHER

Appendix C Missing/Partial Start and Stop Dates for Medications/Transfusions

Partial start dates are allowed for medications per the CM eCRF design.

Start dates missing the day or both the day and month of the year will adhere to the following conventions to classify prior/concomitant medications:

- The missing start day of a medication will be set to the first day of the month that the medication was taken.
- If the start date of a medication is missing both the day and month, the start date will be set to January 1 of the year of onset of medication use.

If the start date of a medication is unknown, but the medication was known to have been started more than 1 month prior to screening (Visit 1) , sites can select "treatment started more than 1 month prior to study start" in the CM eCRF *in lieu* of entering a start date (implies prior medication for patients in the safety analysis set at a minimum).

If the start date of a medication is not recorded and has not been checked in the CM eCRF as having started "more than 1 month prior to study start", and the stop date is a complete date:

- in case the stop date is after the date of first dose of double-blind randomised study treatment then the start date will be set to the date of the first dose of double-blind randomised study treatment.
- otherwise the start date will be set to the stop date of the medication.

Partial stop dates for concomitant medications are not allowed per CM eCRF design. Fully missing concomitant medication stop dates will not be imputed and such medications will be regarded as ongoing, implies concomitant medication for patients in the safety analysis set.

Date of blood product transfusion is required per TRANSF eCRF design and partial/completely missing blood product transfusion dates will not be imputed. In case of partial/completely missing blood product transfusion date then the transfusion date will be regarded as the start date of the relevant adverse event as identified by AEID (AE Number) captured on the TRANSF eCRF. Otherwise if it is not possible to link the blood product transfusion to an adverse event, the blood product transfusion will be reported as follows:

- For patients with at least one double-blind randomised study treatment administration, the transfusion will be assumed to be "on-treatment" (worst-case approach) when considering the safety analysis set.

Appendix D Missing/Partial Dates for Date of Birth, Diagnosis of Sickle Cell Disease, Prior VOCs, and VOCs During the Study

Date of birth is required, however a partial date is allowed and as such the complete date will be imputed as:

- the 15th day of the month if only the day is missing
- 1st January if both day and month are missing

In case of completely missing date of birth no imputation will be done, and any age derivation will be set to missing.

A partial date is allowed for the diagnosis date of sickle cell disease. The complete date will be imputed as:

- the 15th day of the month if only the day is missing
- 1st January if both day and month are missing

If the imputed date is prior to the date of birth, it will instead be set to the date of birth. In case of completely missing date, SCD diagnosis date will be set to the date of birth.

A partial date is allowed for prior VOCs as collected on the VOC eCRF. The complete date will be imputed as:

- the 15th day of the month if only the day is missing

In case of completely missing date or if only a year is reported, prior VOC event date will be set to the day before screening (Visit 1).

Those VOCs occurring during the study will be collected on the VOC1 eCRF. Data collection pe the VOC1 eCRF mandates complete start/stop dates for VOC events collected during the study, in the exceptional case of missing/partial dates, no imputation will be done. The following conventions will apply:

- VOC events collected on the VOC1 eCRF during the double-blind randomised treatment period with missing/partial dates will be assumed to be on-treatment (worst-case).

- VOC events collected during the double-blind randomised treatment period cannot be pooled if there is no complete start/stop date to link it to another VOC event within 7 days, but these events will be counted as individual VOC events.

- Similarly, for the handling of missing/partial dates when calculating the total duration (days) of VOC events and total duration (days) of hospitalisation, no imputation will be

done. Example of such an exceptional case may be events with a fatal outcome and hence no stop date of event.

Appendix E Accounting for Missing Data

Accounting for missing data for recurrent events (VOC event rate endpoint)

In this study some patients dropping out of the study potentially leads to unobserved events. The amount of missing data is minimised in this study as patients are encouraged to remain in the study after premature discontinuation of double-blind randomised study treatment and complete visits according to the protocol schedule of assessments.

This section describes the plan to account for missing data in the sensitivity analyses to assess the robustness of the treatment effect under different underlying assumptions to account for missing data.

Missing data descriptions

Tabular summaries for the percentage of patients by the reason for premature discontinuation of double-blind randomised study treatment as well as for early withdrawal from the study will be presented by double-blind randomised treatment group to describe why patients prematurely discontinue from double-blind randomised treatment or withdraw prematurely from the study.

Primary analysis under the Treatment Policy Estimands using the Missing at Random (MAR) assumption

The primary analysis is under the treatment policy estimand which allows for differences in outcomes over the entire defined double-blind randomised treatment period to reflect the effect of initially assigned randomised study treatment as well as if subsequent alternative treatments for SCD are taken. This primary analysis includes all data until patients withdraw from the study regardless of whether they prematurely discontinue from double-blind randomised study 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 (MAR) and is a direct likelihood approach (DL).

Sensitivity analyses under the Treatment Policy Estimands using both MAR and MNAR assumptions

To examine the sensitivity of the results of the primary analysis to departures from the underlying assumptions, additional analyses will be performed using controlled multiple imputation (MI) methods which allow for different underlying assumptions to be used. As with the primary analysis the sensitivity analyses include all data until patients withdraw from the study regardless of whether they prematurely discontinue from double-blind randomised study treatment.

For this method an underlying negative binomial stochastic process for the rate of VOCs is assumed and post-withdrawal counts will be imputed conditional upon the observed number of events prior to the withdrawal. This allows various assumptions about the missing data to be analysed by modifying the post-withdrawal model assumption.

The method involves first fitting the primary analysis (in addition to each analysis described in Section 4.2.6.3, bullet numbers 5 [if there are at least 5 patients in each strata]) ie, negative binomial regression model to the observed data and then imputing post-withdrawal counts by sampling from the conditional negative binomial probability relating post-withdrawal counts and observed prior-withdrawal counts based on various assumptions;

$$\Pr\left(Y_{ij,2} = y_2 \middle| Y_{ij,1} = y_1\right) = \frac{\Gamma(\gamma+y_1+y_2)}{\Gamma(y_2+1)\Gamma(\gamma+y_1)} p_j^{y_2}(1-p_j)^{\gamma+y_2} \qquad (1)$$

Here y_1 is number of counts prior to withdrawal from the study, y_2 is number of counts after withdrawal from the study, γ is the dispersion parameter and is assumed to be the same for the different double-blind randomised treatment groups, j denotes the treatment group and i denotes the patient identifier. Furthermore, $p_j = \frac{p_{j,2}-p_{j,1}p_{j,2}}{1-p_{j,1}p_{j,2}}$ (2) where $p_{j,1}$ is the negative binomial distribution (NBD) rate parameter prior to withdrawal from the study, and $p_{j,2}$ is the rate parameter after withdrawal from the study as determined based on various assumptions. The imputed number of VOC events that would have been seen is then combined with the observed VOC events and data is analysed using the primary analysis methodology (DL). This analysis is repeated 1000 times and the results combined using Rubin's formulae (Rubin 1987).

The following default assumptions that will be used to impute the missing data for patients who prematurely discontinue from the study are as follows:

1 MAR: Missing counts in each double-blind randomised treatment group are imputed assuming the expected event rate within that treatment group.

2 Partial Dropout Reason-based Multiple Imputation (pDRMI): Missing counts will be imputed differently depending on the reason for dropout; counts for patients in the Ticagrelor groups who dropped out for a study treatment-related reasons are imputed based on the expected VOC event rate in the placebo treatment group, whereas the remaining patients who have dropped out are imputed assuming MAR. Study treatment-related reasons may include (1) AEs, (2) Death and (3) Development of study-specified reasons.

3 Dropout Reason-based Multiple Imputation (DRMI): As for pDRMI with study treatment-related reasons and including "severe non-compliance with the protocol".

A review of each patient who withdraws from the study will be carried out prior to database lock and routine study unblinding. The review will include assessment of the reason for

discontinuation of double-blind randomised study treatment for those patients who discontinued the double-blind randomised study treatment and then withdrew from the study and free text for when the reason for withdrawal or discontinuation of double-blind randomised study treatment is "subject decision" or "other". Based on this review the default assumptions for pDRMI and DRMI may be changed. A list of these patients and the assumptions made under pDRMI and DRMI will be documented prior to database lock and routine study unblinding.

A summary of reasons for patients withdrawing from the study and the corresponding treatment group used to calculate the imputation VOC event rate under MAR, pDRMI, and DRMI is given in Table 5.

Table 5 Reasons for patients withdrawing from the study and the corresponding treatment group used to calculate the imputation VOC event rate under MAR, pDRMI, and DRMI

Reason for withdrawal[a]	MAR	pDRMI	DRMI
Death	Ticagrelor	Placebo	Placebo
Severe non-compliance to protocol	Ticagrelor	Based on review of important protocol deviations prior to study unblinding	Based on review of important protocol deviations prior to study unblinding
Patient lost to follow-up	Ticagrelor	Based on review prior to study unblinding	Based on review prior to study unblinding
Withdrawal by patient	Ticagrelor	Based on review prior to study unblinding	Based on review prior to study unblinding
Other[b]	Ticagrelor	Based on review prior to study unblinding	Based on review prior to study unblinding

[a]All patients withdrawing from placebo have VOC event rate imputed using the placebo treatment group rate.
[b]All patients withdrawing for a COVID-19 related reason, regardless of which category of reason is collected for them, will be reviewed prior to study unblinding

In addition, a tipping point analysis will be performed (if appropriate, ie, the primary efficacy was a favourable result) using the same model as above and where:

- Missing counts for a patient will be imputed, according to the rate of the double-blind randomised treatment group that the patient belongs to multiplied by a factor delta (δ).
- A series of analyses will be performed with a range of increasing deltas for the two treatment groups (δ_P and δ_T for placebo and ticagrelor groups respectively) so that one can assess at which point the study conclusions would change from favourable to unfavourable; ie, to identify a tipping point.

In this assessment, the ticagrelor group is assumed to worsen after withdrawal. Therefore, deltas will be increased starting from 1 in increments of 0.025, until a favourable primary efficacy result is no longer favourable. If statistical significance is maintained among the matrix of possible δ combinations, the comparison is deemed robust to missing data.

Together with the primary analysis the sensitivity analyses are considered to cover the range from realistic to plausible worst-case assumptions about missing data. The MAR multiple imputation approach is expected to correspond closely to the primary analysis and is included to allow for comparisons with MNAR assumptions using the same multiple imputation methodology.

The pDRMI/DRMI approach was selected as the most conservative approach because placebo patients are potentially receiving standard of care and are not expected to change to a substantially more effective treatment after withdrawing from study or double-blind randomised study treatment. For patients receiving ticagrelor who withdraw from the study due to study treatment-related reasons it is assumed that at worst they would be on the standard of care treatment ie, the placebo group.

On-treatment Analyses (Efficacy and Effectiveness estimands)

In addition, primary and sensitivity analyses described previously, two alternative estimands will be estimated using only the initial randomised study treatment data:

- Efficacy estimand: What would the outcome have been if all patients had stayed on study treatment: This will be estimated using the primary analysis method but including only data from patients whilst being on initial randomised study treatment, and assuming MAR subsequently.
- Effectiveness estimand with assumed loss of effect post-discontinuation of ticagrelor: This will be estimated using the pDRMI and DRMI controlled imputation approaches including only data from patients whilst on study treatment.

Therefore, the primary analyses and sensitivity analyses will be repeated including only data from patients whilst being on initial randomised study treatment ie, excluding data once patients discontinue from randomised study treatment.

A summary of reasons for patients withdrawing from the ticagrelor and the corresponding treatment group used to calculate the imputation VOC event rate under MAR, DRMI and pDRMI are presented in Table 6. As for patients who withdraw from the study, a review of each patient who discontinued double-blind randomised study treatment will be carried out prior to database lock and routine study unblinding, where the default assumptions for pDRMI and DRMI as described in Table 5 may be changed. Again, a list of these patients and the assumptions made under pDRMI and DRMI will be documented prior to database lock and routine study unblinding.

Table 6 Reasons for patients discontinuing from the ticagrelor and the corresponding treatment group used to calculate the imputation VOC event rate under MAR, pDRMI and DRMI

Reason for discontinuation of treatment[a]	MAR	pDRMI	DRMI
Subject decision	Ticagrelor	Based on review prior to study unblinding	Based on review prior to study unblinding
Adverse event	Ticagrelor	Placebo	Placebo
Severe non-compliance to protocol	Ticagrelor	Ticagrelor	Placebo
Condition under investigation worsened	Ticagrelor	Placebo	Placebo
Development of study-specific discontinuation criteria	Ticagrelor	Placebo	Placebo
Subject lost to follow-up	Ticagrelor	Ticagrelor	Ticagrelor
Other[b]	Ticagrelor	Based on review prior to study unblinding	Based on review prior to study unblinding

[a]All patients withdrawing from placebo have VOC event rate imputed using the placebo treatment group rate.
[b]All patients withdrawing for a COVID-19 related reason, regardless of which category of reason is collected for them, will be reviewed prior to study unblinding

Using on-treatment data is easier to interpret as it is not impacted by any subsequent pattern of alternative therapies for SCD once patients discontinue from double-blind randomised study treatment. The efficacy estimand together with the reason for and timing of why a patient might not tolerate the study treatment allows for the simplest interpretation as it describes the treatment effect for patients who adhere to study treatment together with why and when they might not adhere to study treatment. Sensitivity analyses using the effectiveness estimands under the pDRMI and DRMI allow for alternative assumptions to be made based on reasons for discontinuation.

Overall summary of analyses to account for missing data

A summary of the different analyses to be carried out under different estimands and assumptions are described in Table 7.

Table 7 Summary of analysis under various estimands and assumptions

	Treatment Policy Estimand					**On-treatment Analyses (Efficacy and Effectiveness Estimands)**			
	DL	**MAR**		**pDRMI**	**DRMI**	**DL**	**MAR**	**pDRMI**	**DRMI**
	Double-blind randomised treatment period					**On-treatment**			
Estimand	**Treatment policy (MAR)**			**Treatment policy (MNAR)**		**Efficacy (MAR)**		**Effectiveness (MNAR)**	
VOC event rate for imputation in Ticagrelor arm**	No explicit imputation *	Ticagrelor rate assumed for all reasons for withdrawal	Ticagrelor rate assumed for all reasons for withdrawal	Placebo rate assumed for AEs, Death and development of study specified reasons to withdraw from study , otherwise Ticagrelor rate assumed. Reasons are subject to review prior to study unblinding	Placebo rate assumed for AEs, Death, development of study specified reasons to withdraw from study and Severe non-compliance to protocol, otherwise Ticagrelor rate assumed. Reasons are subject to review prior to study unblinding	No explicit imputation *	Ticagrelor rate assumed for all reasons for discontinued study treatment	Placebo rate assumed for AEs, and development of study specified reasons to stop study treatment, otherwise Ticagrelor rate assumed. Reasons are subject to review prior to study unblinding	Placebo rate assumed for AEs, development of study specified reasons to stop study treatment and Severe non-compliance to protocol, otherwise Ticagrelor rate assumed. Reasons are subject to review prior to study unblinding

Default definition for $p_{j,1}$ and $p_{j,2}$ based on formula (2). ***		$p_{j,2} = p_{j,1}$ For all treatment groups j=T and P	$p_{j,2} = p_{j,1}$ For all treatment groups j=T and P with δ multiplied by imputed values. incrementing δ by 0.025 at each iteration	$p_{B,2} = p_{B,1}$ $p_{B,2} = p_{P,1}$ $p_{P,2} = p_{P,1}$ for reasons above otherwise $p_{B,2} = p_{B,1}$	$p_{B,2} = p_{B,1}$ $p_{B,2} = p_{P,1}$ $p_{P,2} = p_{P,1}$ for reasons above otherwise $p_{B,2} = p_{B,1}$		$p_{j,2} = p_{j,1}$ For all treatment groups j=T and P	$p_{B,2} = p_{B,1}$ $p_{B,2} = p_{B,1}$ $p_{B,2} = p_{P,1}$ $p_{P,2} = p_{P,1}$ for reasons above otherwise $p_{B,2} = p_{B,1}$	$p_{B,2} = p_{P,1}$ $p_{P,2} = p_{P,1}$ for reasons above otherwise $p_{B,2} = p_{B,1}$

P Placebo. T Ticagrelor.

* Implicitly assumes unobserved rate is the same as observed.

** All patients withdrawing from placebo have VOC event rate imputed using the placebo treatment group rate. (i.e. $p_{P,=,2} = p_{P,1}$).

*** Note can be over written by review prior to database lock and routine study unblinding.

Forest plots will be used to show the primary analysis results along with the missing data sensitivity and alternative estimand analysis results.

It is noted that if the primary analysis is statistically significant, it is not necessarily expected that all sensitivity analyses will also give statistically significant results. If the results of the sensitivity analyses provide reasonably similar estimates of the treatment effect to the primary analysis, this will be interpreted as providing assurance that neither the lost information nor the mechanisms which cause the data to be missing have an important effect on primary analysis conclusions. Based on these outputs and the study treatment's mechanism of action, the plausibility of the assumptions made about missing data in the different analyses will be considered and described in the CSR.

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Document Name: d5136c00009-sap-ed-3		
Document Title:	Statistical Analysis Plan Edition 3	
Document ID:	CCI [redacted]	
Version Label:	2.0 CURRENT LATEST APPROVED	
Server Date **(dd-MMM-yyyy HH:mm 'UTC'Z)**	**Signed by**	**Meaning of Signature**
30-Jun-2020 18:06 UTC	PPD [redacted]	Content Approval
30-Jun-2020 11:20 UTC	PPD [redacted]	Author Approval

Notes: CCI [redacted]