



Statistical Analysis Plan

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

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SIGNATURE PAGE

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

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under Curve
AZ	AstraZeneca
BDRM	Blind Data Review Meeting
BP	Blood Pressure
CI	Confidence Interval
Cmax	Maximum Plasma Concentration
CL/F	Oral Clearance
DAE	Discontinuation of IP due to AE
DBP	Diastolic Blood Pressure
dp	Decimal places
EAS	Efficacy Analysis Set
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ePRO	Electronic Devices for Patient Reported Outcomes
FAS	Full Analysis Set
FHS	Faces Hedonic Scale
FLACC	Face, Legs, Activity, Cry, Consolability Scale
FPS-R	Faces Pain Scale - Revised
IP	Investigational Product
MedDRA	Medical Dictionary for Regulatory Activities
PD	Pharmacodynamic
PK	Pharmacokinetic
PRO	Patient Reported Outcomes
PRU	P2Y ₁₂ reaction units
PT	Preferred Term

Abbreviation or special term	Explanation
QTcB	Bazett Corrected QT Interval
QTcF	Fridericia Corrected QT Interval
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SBP	Systolic Blood Pressure
SCD	Sickle Cell Disease
SD	Standard Deviation
SOC	System Organ Class
TBL	Total Bilirubin
ULN	Upper Limit Normal
VOC	Vaso-Occlusive Crisis

AMENDMENT HISTORY

Date	Brief description of change
10-Jun-2016	<p>Signature page: Added author.</p> <p>List of abbreviations: Added terms.</p> <p>Section 1.3: Defined two sub-sections (1.3.1 and 1.3.2) where descriptions of study parts, flow charts, visit schedule and assessment plan are separately displayed for time up to time point when amendment 3 coming into effect and thereafter. End of 1.3: updated number of participating countries and sites and added rules for re-enrolment after amendment 3 coming into effect.</p> <p>Section 4.3: Described analysis of different dosages of IP in Part B.</p> <p>Section 4.3.7.3: Added restriction that t-tests will only be performed if at least 30 patients evaluated and changed wording of test procedure.</p>

Date	Brief description of change
13-Mar-2017	<p>Change in display of tables for Part A. Most tables will only be displayed for totals, no presentation by treatment dose groups.</p> <p>Due to CSP Amendment 3 most presentations by dose group are removed and instead displayed with a total column only.</p> <p>Modified wording of separate PK/PD analysis plan (section 1.1).</p> <p>Added Local Amendment Kenya in Reference List (section 1.3.2). Kenyan patients not randomised to Part B.</p> <p>Updated definition of safety analysis set (section 2.1.2).</p> <p>Approach used in case of treatment not as randomised in part B (section 2.1.2).</p> <p>Elimination of two Classification Meetings (section 2.2).</p> <p>General definition of time periods for Part A and Part B used in analyses (section 4.1).</p> <p>Updated definition of concomitant medication (section 4.3.5).</p> <p>Moved analysis of CL/F and PK concentrations to secondary efficacy summary (section 4.3.7.2).</p> <p>Drop table for percentage of days with pain in Part A for patients aged < 4 years (section 4.3.7.2).</p> <p>Added derivation of analgesics use for part A (section 4.3.7.2).</p> <p>Updated derivation of opioid analgesics use (section 4.3.7.2).</p> <p>Updated definition of absence from school or work (section 4.3.7.2).</p> <p>Drop analysis of other significant AEs (section 4.3.8.1).</p>

1. STUDY DETAILS

1.1 Scope of this Statistical Analysis Plan (SAP)

This SAP addresses the summaries, analysis and listings that need to be carried out for the efficacy and safety objectives based on the Revised Clinical Study Protocol, Lebanon Republic version 1.0, dated 18Mar2015 [1], eCRF version 2.0, dated 13Aug2014 [2], Daily Diary Data version 1.0, dated 04Apr2014 [3] and Data collection during Clinic visits to assess disease burden and Revised Clinical Study Protocol Edition Number 3, dated 22Dec2015 [10] and Revised Clinical Study Protocol For Kenya Edition Number 1, dated 03Feb2016 [11].

The PK/PD modelling is out of scope for this SAP and will be detailed in a separate PK/PD analysis plan.

1.2 Study objectives related to this SAP

1.2.1 Primary Objective

To summarise the Pharmacodynamic and Pharmacokinetic parameters of ticagrelor and its active metabolite (AR-C124910XX) using descriptive statistics.

1.2.2 Secondary Objectives

The secondary objectives of the study related to this SAP are:

- To summarise the pharmacokinetic concentrations of ticagrelor and its active metabolite (AR-C124910XX) using descriptive statistics.
- To investigate the efficacy of ticagrelor vs placebo in paediatric patients with Sickle Cell Disease (SCD) in reducing:
 - Number of Vaso-Occlusive Crisis (VOC)
 - Number of VOC requiring hospitalisation or emergency department visits
 - Days hospitalised for VOC or other complications of SCD
 - Days with pain (ages ≥ 4 years only)
 - Intensity of pain (ages ≥ 4 years only)
 - Days of analgesic use (ages ≥ 4 years only)
 - Days of opioid analgesic use
 - Days of absence from school or work (ages ≥ 6 years only).

1.2.3 Exploratory Objectives

The exploratory objectives of the study related to this SAP are:

- To investigate the efficacy of ticagrelor vs placebo in paediatric patients with SCD in reducing:
 - Days with pain (ages < 4 years only)
 - Intensity of pain (ages < 4 years only)

1.2.4 Safety Objectives

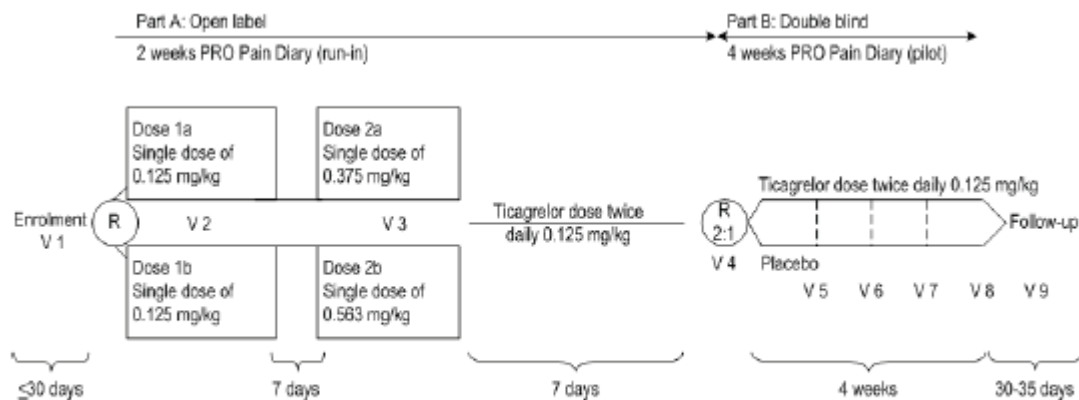
The safety objectives of this study are:

- To investigate the safety and tolerability of single and multiple doses of ticagrelor in paediatric patients with SCD.
- To determine the percentage of patients with haemorrhagic events requiring medical intervention

1.3 Study design

1.3.1 Study design before amendment 3 coming into effect

The study is a multicenter, open-label, dose-ranging study of ticagrelor followed by a double blind, placebo-controlled extension phase in paediatric patients with SCD.



R = randomisation; PRO = patient reported outcome

Part A:

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

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

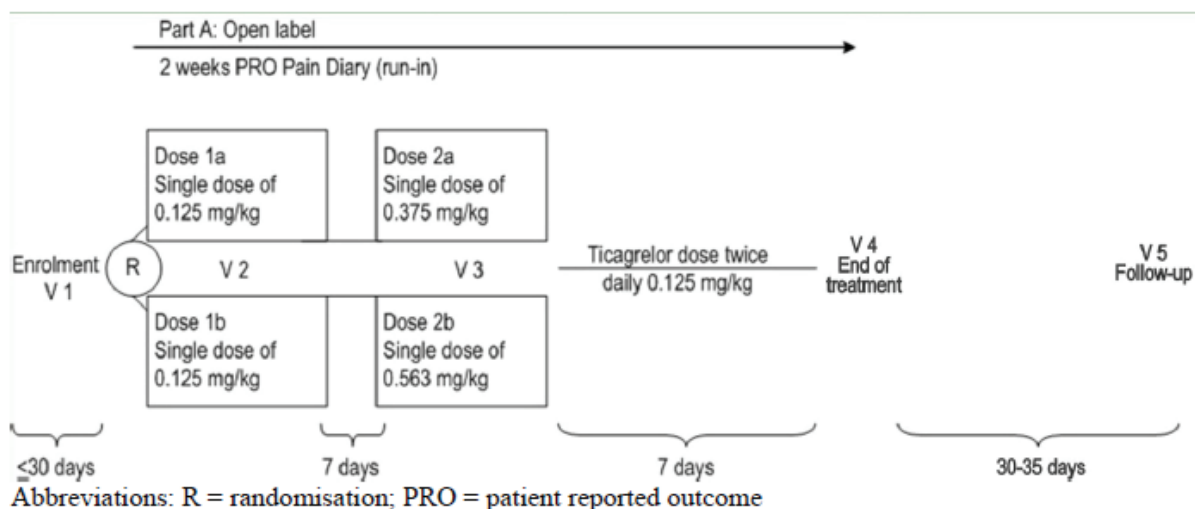
Part B (not applicable for Lebanon):

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

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

The study design in Lebanon is selected to support evaluation of the primary PK and PD objectives only, therefore only Part A will be conducted in Lebanon and patients will not be randomised to Part B. The patients will finish study treatment after one week open-label treatment and will visit site 30 days after treatment stopped for follow-up.

Study flow chart before interim analysis (for Lebanon centres)



Lebanon Centres:

Part A:

Visit 2, 3 & 4: Randomisation will take place 7 to 30 days after enrolment. Patients will be randomised 1:1 to receive one of two dosing schedules, with each dose separated by 7 days. Platelet aggregation will be measured using the VerifyNow™ P2Y12 assay and reported as PRU. PRU will determine continued dosing. Patients are not allowed to eat 2 hours before and 1 hour after dosing at these visits. Palatability assessment will be performed (Visit 2). A study nurse will assess palatability directly after administration of dose. The patients will be allowed to leave the clinic after all sampling has been completed. Following the 2 single doses, all patients will receive open-label one-week treatment with ticagrelor twice daily to determine tolerability. Dose to be administered twice daily within a 9-12 hours interval (starting in the evening the same day as Visit 3). The patient will register actual date and time of drug administration the morning and evening before Visit 4 in a Dosing Diary. He/she will be instructed to not take their dose at home in the morning of Visit 4. Study drug will be administered at the clinic and actual time of dosing should be recorded in the eCRF at Visit 4.

Part B will not be conducted in Lebanon.

Visit schedule and assessment plan

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

Table 1 Study Plan detailing the procedures

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

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

Abbreviations: AE = adverse event; BP = blood pressure; CRF = Case Report Form; ECG = electrocardiogram; eCRF = electronic Case Report Form; FLACC = the Face, Legs, Activity, Cry, Consolability form; INR = International Normalized Ratio; PK = pharmacokinetics; PRU = P2Y₁₂ reaction units; PTT = Partial Thromboplastin Time; SAE = serious adverse event; SCD = Sickle Cell Disease; VOC = vaso-occlusive crisis

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

Study Plan detailing the procedures (for Lebanon centres)

Assessment	Enrolment	Dose 1	Dose 2	End of treatment	Follow-up
Visit	1 ¹	2 ¹	3	4	5
Visit window:	Days -30 to -7 for Visit 1	±0 day for Visit 2	+ 7 days	+ 7 days	30-35 days following last dose for Visit 4 ^d
Week		0	1	2	6
Day		0	7	14	44-49
Signed Informed Assent/Consent	X				
Randomisation		X			
Inclusion/exclusion criteria	X	X ^a			
Relevant Medical and Surgical history, SCD characteristics and history	X				
Demographics	X				
Vital signs (BP, pulse)	X	X	X	X	X
Physical examination	X				X
Weight, height ^e	X	X	X	X	
Transcranial Doppler exam ^h	X				
Ophthalmological (Eye) exam ^h	X				
12-lead ECG ^o	X ^o			X	
Daily pain assessment ^g	X	X	X	X	
FLACC assessment ^g	X		X		
Daily recording of analgesic use ^g	X	X	X	X	
Days absent from school/work ^g	X	X	X	X	
Administration of IP at clinic ⁱ		X	X	X	
Treatment dispensed/returned ⁱ			X		
Compliance/ Drug accountability		X	X	X	
Acceptability/Palatability ^h		X			
Concomitant medication	X	X	X	X	X
Adverse event review (AEs and SAEs)	X ^f	X	X	X	X
Blood samples for haematology and clinical chemistry (incl uric acid)	X ⁿ			X ^k	
Blood samples for coagulation (INR and PTT)	X ^m				

Assessment	Enrolment	Dose 1	Dose 2	End of treatment	Follow-up
Visit	1 ^l	2 ^l	3	4	5
Visit window:	Days -30 to -7 for Visit 1	±0 day for Visit 2	+ 7 days	+ 7 days	30-35 days following last dose for Visit 4 ^d
Week		0	1	2	6
Day		0	7	14	44-49
VerifyNow TM PRU ^e		X	X	X	
Pregnancy test (dipstick) ^b	X		X	X	
Collection of VOC in CRF		X	X	X	X
Collection of transfusion data in CRF		X	X	X	X
Collection of bleeding events in CRF		X	X	X	X
Urinalysis	X ^m			X	
Blood sampling for pharmacokinetics ^e		X	X	X	

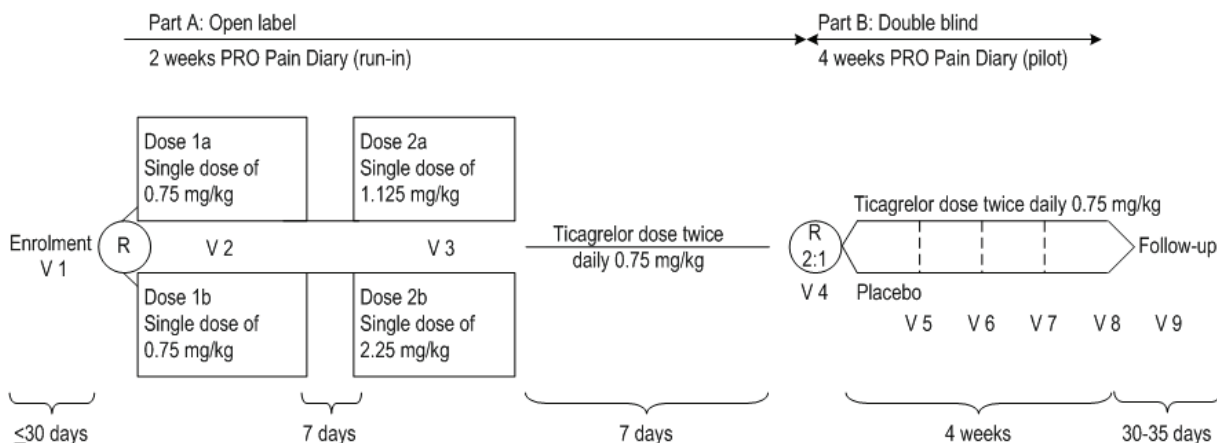
Abbreviations: AE = adverse event; BP = blood pressure; CRF = Case Report Form; ECG = electrocardiogram; eCRF = electronic Case Report Form; FLACC = Face, Legs, Activity, Cry, Consolability form; INR = International Normalised Ratio; PK = pharmacokinetics; PRU = P2Y₁₂ reaction units; PTT = Partial Thromboplastin Time; SAE = serious adverse event; SCD = Sickle Cell Disease; VOC = vaso-occlusive crisis

- a Results from local laboratory must have been received before first dose to check eligibility criteria.
- b In patient after menarche.
- c Actual time of PK and PRU sampling should be recorded in the eCRF.
- d May occur following earlier visits than Visit 5.
- e Height only at enrolment.
- f Only SAE assessed at this time.
- g Electronic diary recording by patient ≥4 years (when needed with parent/guardian help).
- h Questions assessed by nurse in children <6 years, Hedonic Faces Scale (HFS) for children ≥6 years
- i Actual time of dosing should be recorded in the eCRF.
- j The time of drug administration in the morning and evening before Visit 4 will be registered in a patient diary.
- k Blood sample for haematology and clinical chemistry (including uric acid) at Visit 4 will be collected 2h post-dose together with PK and PRU.
- l Visit 2 should be at least 7 days apart from Visit 1.
- m Laboratory testing performed prior to Visit 1 as part of usual clinical care does not need to be repeated as long as the values were obtained within 30 days prior to Visit 2.
- n The most recent examination must be performed within 12 months before Visit 1. If this is not the case, the examination must be done before proceeding in the study.
- o 12-lead ECG must be performed within 6 months before Visit 1. If this is not the case, the examination must be done before proceeding in the study.
- p FLACC for patients aged from 2 to <4 years only to be collected between Visit 1 and Visit 2 and between Visit 3 and 4.

This study is planned to be conducted in approximately 5 countries (US, United Kingdom [UK], South Africa, Canada and Lebanon Republic) and approximately 8 to 20 sites, with a minimum of 36 patients and a maximum of 50 patients to be randomised in the study, depending on how many patients are required in order to have 36 evaluable patients. Of these 36 evaluable patients, at least 12 patients must be 2 to 11 years of age and 12 patients must be 12 to 18 years. In addition, a minimum of 12 evaluable patients must complete Part B (through Visit 8).

1.3.2 Study design after amendment 3 coming into effect

After amendment 3 coming into effect the following study flow chart and descriptions for study parts are valid:



R = Randomisation; PRO = Patient Reported Outcome.

Part A:

Visit 2, 3 & 4: Randomisation will take place 14 to 30 days after enrolment. Patients will be randomised 1:1 to receive one of two dosing schedules, with each dose separated by 7 days. Platelet aggregation will be measured using the VerifyNow™ P2Y12 assay and reported as PRU. PRU will determine continued dosing. Patients are not allowed to eat 2 hours before and 1 hour after dosing at these visits. Palatability assessment will be performed (Visit 2). A study nurse will assess palatability directly after administration of dose. The patients will be allowed to leave the clinic after all sampling has been completed. Following the 2 single doses, all patients will receive open-label one-week treatment with ticagrelor twice daily to determine tolerability prior to randomisation into Part B. Dose to be administered twice daily within a 9-12 hours interval (starting in the evening the same day as Visit 3). Patients only participating in Part A will complete Visit 4, which will be their last visit on treatment and after Visit 4 they will perform Visit 9 (30-35 days following last dose for Visit 4).

Part B (not applicable for Kenya [11]):

Visit 4, 5, 6, 7 & 8: Visit 4 will be performed in all patients, including those not continuing to Part B. Participation in Part B is optional. The patient will register actual date and time of drug administration the morning and evening before Visit 4 in a Dosing Diary. He/she will be

instructed to not take their dose at home in the morning of Visit 4. Study drug will be administered at the clinic and actual time of dosing should be recorded in the eCRF at Visit 4. For patients not participating in Part B, visit 4 will be the last visit on treatment. For patients continuing into Part B, patients will be randomised (2:1 ratio) to ticagrelor twice daily or placebo for a 4-week treatment phase and will return to the clinic on a weekly basis for study related procedures. Visit 5 and Visit 7 may optionally be performed as telephone contacts, based on the opinion of the Investigator (See [Table 2](#) , Visit 4-8). In some countries, Part B will not be performed.

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

For safety reasons the dosing schedule will be modified for individual patients as follows:

If PRU at 2 hr following dosing of 0.75 mg/kg is <95 , the subsequent maximum dose for this patient will be 0.563 mg/kg throughout the study. If PRU <95 following dosing of 0.563 mg/kg, the patient will be discontinued from further study drug.

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

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

Table 2 Study Plan detailing the procedures after amendment 3 coming into effect

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

Table 2 Study Plan detailing the procedures after amendment 3 coming into effect

Assessment	Part A				Part B				
	Enrolment	Dose 1	Dose 2	Repeated treatment phase			End of treatment	Follow-up	
Visit	1 ^m	2 ^m	3	4 ^l	5 ^r	6	7 ^r	8	9 ^l
Week		0	1	2	3	4	5	6	10
Day (Visit window)	-30 - -14	0	7 (+3)	14 (+7)	21 (+3)	28 (+3)	35 (+3)	42 (+3)	72-77 days following last dose for Visit 8 (or Visit 4) ^d
Pregnancy test (dipstick) ^b	X	X		X ^b				X	
Collection of VOC in CRF		X	X	X	X	X	X	X	X
Collection of transfusion data in CRF		X	X	X	X	X	X	X	X
Collection of bleeding events in CRF		X	X	X	X	X	X	X	X
Urinalysis	X ⁿ			X				X	
Blood sampling for pharmacokinetics ^c		X	X	X					

Abbreviations: AE = adverse event; BP = blood pressure; CRF = Case Report Form; ECG = electrocardiogram; eCRF = electronic Case Report Form; FLACC = Face, Legs, Activity, Cry, Consolability form;

INR = International Normalised Ratio; PK = pharmacokinetics; PRU = P2Y₁₂ reaction units; PTT = Partial Thromboplastin Time; SAE = serious adverse event; SCD = Sickle Cell Disease; VOC = vaso-occlusive crisis

a Results from local laboratory must have been received before first dose to check eligibility criteria.

b In patient after menarche. Pregnancy testing at Visit 4 is only applicable for patients NOT performing Part B.

c Actual time of PK and PRU sampling should be recorded in the eCRF. See description in Tables 2 and 3 in revised study protocol for PK sampling time points.

d May occur following earlier visits than Visit 9.

e Height only at enrolment.

f Only SAE assessed at this time.

g Electronic diary recording by patient ≥4 years (when needed with parent/guardian help).

h Questions assessed by nurse in children <6 years, Hedonic Faces Scale (HFS) for children ≥6 years

i Actual time of dosing should be recorded in the eCRF.

j The time of drug administration in the morning and evening before Visit 4 and 8 will be registered in a patient diary.

k Blood sample for haematology and clinical chemistry (including uric acid) at Visit 4 will be collected 2h post-dose together with PK and PRU.

l If patient only participates in Part A, the follow-up Visit 9 should be performed after Visit 4 according to schedule.

m Visit 2 should be at least 14 days apart from Visit 1.

n Laboratory testing performed prior to Visit 1 as part of usual clinical care does not need to be repeated as long as the values were obtained within 30 days prior to Visit 2.

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

- p 12-lead ECG must be performed within 6 months before Visit 1. If this is not the case, the examination must be done before proceeding in the study.
- q FLACC for patients aged from 2 to <4 years only to be collected between Visit 1 and Visit 2, and between Visit 4 and Visit 5.
- r Visit 5 and Visit 7 may be performed as telephone contacts, based on the opinion of the Investigator. Vital signs (BP and pulse) will only be measured if the patient visits the site.
- s If Visit 5 and/or Visit 7 are performed as telephone contacts, double kits of study treatment will be dispensed on Visit 4 and/or Visit 6 to cover the whole period.

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

As eligibility criteria have been changed with amendment 3, patients previously enrolled but not randomised may be reassessed for eligibility. Patients fulfilling all inclusion criteria and no exclusion criteria can be re-enrolled.

1.4 Number of patients

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

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

2. ANALYSIS SETS RELATED TO THIS SAP

2.1 Definition of analysis sets

The analysis sets are defined below.

2.1.1 Efficacy Analysis Set (EAS)

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

2.1.2 Safety Analysis Set (SAF)

All patients who received at least one single dose of ticagrelor will be included in the safety population (SAF) for Part A, all patients who received at least one dose of randomised investigational product, ticagrelor or placebo, will be included in the safety population for Part B. Analysis on the SAF will use the study medication actually received. Erroneously treated patients (eg. those randomised to ticagrelor but actually given placebo) will be accounted for in the actual treatment group. A patient who in error received both ticagrelor and placebo will be accounted for in the ticagrelor treatment group.

All summaries and analysis of safety data will be performed on the SAF, unless otherwise specified.

2.1.3 Pharmacokinetic Analysis Set (PK)

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

2.1.4 Pharmacodynamic Analysis Set (PD)

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

2.2 Deviations

A list of protocol deviations will be discussed and confirmed prior to database lock and unblinding.

3. PRIMARY/SECONDARY VARIABLES

3.1 PK/PD Variables

3.1.1 Primary PK/PD variables

PD Variable:

1. P2Y12 reaction units (PRU)

PK Variables:

1. Maximum Plasma Concentration (C_{max}) corresponds to the maximum observed plasma concentration. This variable will be derived by ICON Clinical Research.

2. Area Under the Plasma Concentration Time Curve (AUC). This parameter will be derived by AstraZeneca (AZ).

3.1.2 Secondary PK/PD variables

PK Variables:

1. Concentration of ticagrelor and its active metabolite.
2. Population PK parameters: AUC and CL/F will be derived by AZ.

3.2 Efficacy Variables

3.2.1 Secondary efficacy variables

1. VOC

- Number of VOC
- Number of VOC requiring hospitalisation or emergency department visits (Part B only)
- Percentage of Days hospitalised for VOC or other complications of SCD (Part B only). See section 4.3.7.2 for the derivation of the percentage.

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

2. Pain

- Percentage of Days with pain (ages ≥ 4 years only). See section 4.3.7.3 for the derivation of the percentage.
- Intensity of pain (ages ≥ 4 years only)

As additional exploratory analysis:

- Percentage of Days with pain (ages < 4 years only). See section 4.3.7.3 for the derivation of the percentage.
- Intensity of pain (ages < 4 years only)

Pain is commonly reported in clinical trials by having patients provide a rating of their own pain. Different measures of numerical rating scales have demonstrated good psychometric properties but are not fit for purpose for the

youngest age groups due to their limited understanding of number concepts. Therefore, pain-rating scales with a series of faces depicting different levels of pain have been developed. The Faces Pain Scale – Revised (FPS-R) was validated by [4] in 3 studies and has been judged as a well-established pain assessment tool in patients 4 to 16 years of age [5] and will be administered to all patients in this study age ≥ 4 years. When needed, a parent/guardian can help the child with the assessment.

The Faces Pain Scale will be collected daily at bedtime using an electronic device. The scale consists of six faces and scoring ranges between 0-10 (with an increase in numeric value by 2 i.e. (0, 2, 4, 6, 8, 10)), where 0 is no pain. If the patient answers that he/she has pain a body outline diagram will be presented and the patient will be asked to indicate the location of the pain [6].

For patients aged from 2 to <4 years, a FLACC form will be used for recording daily pain. The FLACC form will be completed daily at bedtime by the primary caregiver, with the assessment of the time when the child is under the caregiver's care. If possible, the reporter should be the same caregiver during the reporting period [6].

The FLACC [9] form consists of five items with each item categorised on a 0-2 scale resulting in a total score between 0 and 10 points.

Other efficacy variables:

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

- Percentage of Days of analgesic use (ages ≥ 4 years only). See section 4.3.7.3 for the derivation of the percentage.
- Percentage of Days of opioid analgesic use. See section 4.3.7.3 for the derivation of the percentage.

Patients will be asked about their use of analgesics. When needed a parent/guardian can help the child with the assessment. The question 'Have you taken any medication because of your pain today' will be administered daily in the electronic device. Response options will be dichotomous, i.e. 'Yes' or 'No'. The question should be answered daily at bedtime. Specification of whether analgesics have been opioid or non-opioid will be done at follow-up site visit. For analysis, all medications entered in the concomitant medication module with ATC code N02A will be considered.

- Percentage of Days of absence from school or work (ages ≥ 6 years only), excluding days of absence due to long study visits. See section 4.3.7.3 for the derivation of the percentage.

For patients aged ≥ 6 years, absence from school/work, excluding days of absence due to long study visits will be recorded. The question ‘Have you been at home from school/work the last 7 days because of your disease’ will be administered weekly in the electronic device. If the reply is ‘Yes’ the patient will be prompted to answer how many days he/she has been absent. Days off school due to study visits will not be recorded.

4. Palatability measures will be collected for Part A.

Palatability will be assessed using the Facial Hedonic Scale (FHS) (completed by patient) at Visit 2. Patients ≥ 6 years old will be asked to evaluate palatability immediately after dosing using the Hedonic Faces Scale. For patients under 6 years of age a nurse’s assessment of the patient’s behavior, including willingness to swallow, will be performed directly after the patient has received the investigational product.

3.3 Safety Variables

Safety outcome variables are:

- Adverse Events
- Laboratory Assessments: Clinical chemistry, haematology, coagulation and urinalysis.
- Vital Signs: Height (cm) at enrolment, Weight (kg), Sitting Pulse (beats/min), Sitting Systolic Blood Pressure (SBP) (mmHg) and Sitting Diastolic blood pressure (DBP) (mmHg).
- 12-Lead Electrocardiogram (ECG): Heart rate (beats/min), Heart Rhythm, QRS duration (ms), PR interval (ms), RR Interval (ms), QT interval (ms), QTc interval (unspecified) and any abnormalities.
- Physical Examination.
 1. General Appearance
 2. Skin
 3. Head and Neck
 4. Lymph Nodes
 5. Thyroid
 6. Musculoskeletal/spine and extremities

7. Cardiovascular
8. Respiratory
9. Abdomen and
10. Neurological

- Hy's Law (Part B only)
Assessed based on the below criteria:
Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) $\geq 3x$
Upper Limit of Normal (ULN) and Total Bilirubin (TBL) $\geq 2xULN$
- Hemorrhagic Events
- Transfusions

4. ANALYSIS METHODS

4.1 General principles

The statistical analysis will be performed using SAS[®] version 9.1.3 (SAS Institute, Inc.) or later.

Throughout patient data listings, figures and tables, treatment groups will be presented as ticagrelor for Part A, and ticagrelor and placebo for Part B. The disposition table and the number of patients per analysis set in Part A will however be presented by dose scheme. Unless otherwise specified, analyses will be performed for Part A and Part B separately.

Continuous variables will be summarised using the descriptive statistics number of patients (n), mean, standard deviation (SD), median, minimum (min) and maximum (max). The mean and median will be presented to 1 more decimal place (dp) than the raw data, SD two more and min and max to the same number of dps as the raw data. Percentages will be based on the number of patients in the respective analysis set and unless specified otherwise will include patients with non-missing values only. Categorical variables will be summarised by number and percentage of patients in each category n (%). Percentages will not be provided for a zero count and 100% will be provided to zero decimal places. Ratios will be presented to 2 decimal places.

Patient data listings will be based on all randomised patients, unless specified otherwise and will be sorted by Short patient identifier and timepoint. Dates will be presented in the format DDMMMYYYY. Unscheduled data will be presented in the listings, presented within scheduled visits in date order.

The baseline value will be defined as the last non missing assessment prior to the first dose of study treatment. Change from baseline will be calculated as the difference between post-baseline visit value minus the baseline value.

Part A is comprising time from randomisation date to date of Visit 4 or Part A termination date (whichever is earlier) and Part B is comprising time from date of Visit 4 plus 1 day to date of Visit 8 or Part B termination date (whichever is earlier).

No adjustment for multiplicity will be made.

4.2 Missing data handling considerations

There will be no imputation on AE data except AE dates. Missing AE dates will be imputed based on worst case scenario based on the following:

Start date for AEs (Onset day)

A: When start date is missing totally Start Date AE is set to start date of active treatment

B: When start date has information about year and month

a) Given month for Start Date AE > month for start date of active treatment,
Start Date AE = day 1 in given month

b) Given month for Start Date AE = month for start date of active treatment,
Start Date AE = start date of active treatment

c) Given month for Start Date AE < month for start date of active treatment,
Start Date AE = day 15 in given month

C: When start date has information about year

a) Given year for Start Date AE = year for start date of active treatment,
Start Date AE = start date of active treatment

b) Given year for Start Date AE < year for start date of active treatment,
Start Date AE = 1 July that year

c) Given year for Start Date AE > year for start date of active treatment,
Start Date AE = 1 January that year

Stop dates for AEs (Resolution date)

a) When stop date is missing completely but start date is known. The AE is considered ongoing for the length of the study.

- b) When both start and stop dates are missing completely, the AE is considered ongoing from start of active treatment and throughout the study.
- c) When stop date is missing day, the AE is considered ongoing until the end of the month, or until the end of the study, if the study ends in that month.
- d) When stop date is missing month and day, the AE is considered ongoing until 31 December or until the end of the study, if the study ends in that year.

For incomplete medication start and/or stop dates, where it is not possible to classify the medication as prior or concomitant, using available date information, it will be assumed that the medication is concomitant. For instance, if medication start date is partial but the medication end date is full and before the study drug start date, then it cannot be concomitant.

Other missing data will not be replaced.

4.3 Analysis methods

4.3.1 Patient Disposition

The number and percentage of patients by dosing schemes in Part A and treatment groups in Part B for each of the following will be provided

- Enrolled
- Randomised
- Received study treatment
- Completed the study.
- Discontinued from the study, overall and by reason

Listings will be provided for discontinued patients and patients completing the study. The summaries and listing will be based on All Enrolled patients.

4.3.2 Analysis Sets

The number of patients in each analysis set will be summarised by dosing schemes in Part A and treatment groups in Part B and overall. This will be based on All Enrolled patients.

4.3.3 Demographic Characteristics

Demographic characteristics (including age, sex, race, ethnic group, SCD genotype and occurrence of SCD complication) will be summarised using descriptive statistics. Summary statistics will be presented for all ticagrelor treated patients in Part A and treatment groups in

Part B (when applicable) for all patients in the SAF. A corresponding listing will also be provided.

4.3.4 Medical/Surgical/SCD/VOC History

Medical history as reported on the eCRF [2] will be summarised by system organ class (SOC) and preferred terms for all ticagrelor treated patients in Part A and by treatment groups in Part B using medical dictionary for regulatory activities (MedDRA version 19.1). The number of patients with relevant previous surgical procedures will be summarised by treatment group. Supporting listings will be provided. The same analyses will be performed for SCD characteristics and VOC history. The listings will be based on all randomised patients and the summaries will be based on SAF.

4.3.5 Concomitant Medications

A concomitant medication is defined as a medication that is started on or after the date of randomisation to Part A (Part A concomitant medication) or date of Visit 4 plus 1 day (Part B concomitant medication) or started prior to the respective date but is ongoing during the study treatment period.

Concomitant medication will be coded by utilising the AstraZeneca Drug Dictionary (version 16.2). Concomitant medications will be summarised for all ticagrelor treated patients in Part A and by treatment groups in Part B, by Anatomical Therapeutic Chemical (ATC) level 2 drug class and preferred term (PT) for the SAF. For the summary, patients will only be counted once within a drug class, and once for a medication.

A summary of the number and percentage of patients taking disallowed concomitant medications will also be presented. Disallowed medications will be identified prior to unblinding and will include anticoagulants or antiplatelet, NSAIDs, CYP3A4 inhibitors, and CYP3A4 substrates or inducers, where NSAIDs were allowed for up to 3 days within a week. The summaries will be based on SAF.

A listing will be provided for concomitant medications.

4.3.6 Compliance and Study Treatment Exposure

Study treatment compliance, study treatment exposure and exposure duration will be summarised for all ticagrelor treated patients in Part A and by treatment groups in Part B for the SAF.

The treatment exposure table will summarise for each treatment group the number of patients exposed and the mean dose exposition using descriptive statistics.

Exposure duration for Part A and Part B will be calculated as:

- (Date of last dose of Part A – Date of first dose Part A) + 1

- (Date of last dose of Part B – Date of first dose Part B) + 1

Study treatment exposure for Part A and Part B will be calculated as:

- Sum of number of days where dose was taken in Part A, which is the same as exposure duration minus the number of days where no study medication was taken.
- Sum of number of days where dose was taken in Part B, which is the same as exposure duration minus the number of days where no study medication was taken.

Study treatment compliance will be assessed separately for Part A and Part B based on the drug amount dispensed/returned and dispensed/return dates recorded in the Drug accountability page of the eCRF.

Compliance for Part A and Part B will be calculated as:

- $100 * [((\text{Sum of amount of drug dispensed single doses} + \text{Sum of amount of drug dispensed twice daily doses} / 2) \text{ in Part A} - (\text{Sum of amount of drug returned single doses} + \text{Sum of amount of drug returned twice daily doses} / 2) \text{ in Part A}) / (\text{Planned study treatment exposure for Part A})]$
- $100 * [((\text{Sum of amount of drug dispensed in Part B} - \text{Sum of amount of drug returned in Part B}) / 2) / (\text{Planned study treatment exposure for Part B})]$

Supportive listings will be provided. The summaries will be based on SAF.

4.3.7 Efficacy Analysis

4.3.7.1 Primary efficacy summary

The primary efficacy variables will be summarised using descriptive statistics using the PK/PD analysis sets for Part A and Part B.

Cmax and AUC will be summarised for each part by dose/ treatment group and visit/timepoint.

Summaries of Absolute Value and Change from Baseline of PRU by dose/ treatment group and visit/timepoint for Part A and Part B will be provided.

Plots for Individual PRU levels and PK values over time will be provided. Also, mean plots for PRU levels and PK values over time will be provided for Part A and Part B.

4.3.7.2 Secondary efficacy summary

An overall summary of CL/F will be provided. Summaries of Absolute Value of PK concentrations by dose/treatment group and visit/timepoint for Part A and Part B will be provided.

The secondary efficacy variables will be summarised by dose using descriptive statistics using the EAS or PK analysis sets.

Efficacy variables in Part A:

- Percentage of days with pain, presented for the age group “patients ≥ 4 years old” where pain means occurrence of any pain score > 0 .

These percentages are calculated as the ratio of the total number of days the patient reported pain for Part A divided by the total number of days the patient reported in diary on Part A multiplied by 100.

- Percentage of days of opioid analgesic use.

The ratio of the total number of days the patient had taken opioid analgesics for Part A divided by the number of days the patient reported on Part A in ePRO. A day with opioid analgesic use is defined as a day where the patient has reported taking analgesic in the ePRO and there is a corresponding entry of opioid analgesic as a concomitant medication.

- Percentage of days of analgesic use, presented for the age group “patients ≥ 4 years old”.

The ratio of the total number of days the patient had taken analgesics for Part A divided by the total number of days the patient reported on Part A in ePRO multiplied by 100.

- Percentage of days of absence from school or work, presented for the age group “patients ≥ 6 years old”.

The ratio of the total number of days the patient was absent from school or work for part A divided by 7*(number of weeks for which answer is reported in diary on Part A).

- Intensity of pain presented for the age group “patients ≥ 4 years old”.

These will be summarised descriptively using the SAF and actual treatment.

Regarding VOCs in Part A, a summary table will be provided with all VOCs along with a table with number of VOCs in prior 12 months for each patient and a table with Key patient information.

Palatability measures for Part A will also be summarised descriptively for all patients for whom the assessment is performed along with a listing.

Efficacy variables in Part B:

- Number of VOC,
- Number of VOC requiring hospitalisation or emergency department visits
- Days hospitalised for VOC or other complications of SCD
- Percentage of days with pain, presented for the age group “patients ≥ 4 years old”
- Percentage of days with pain, presented for the age group “patients < 4 years old” as exploratory objective.
- Percentage of days of opioid analgesic use
- Percentage of days of analgesic use, presented for the age group “patients ≥ 4 years old”
- Percentage of days of absence from school or work, presented for the age group “patients ≥ 6 years old”
- Intensity of pain, presented for the age group “patients ≥ 4 years old”
- Intensity of pain, presented for the age group “patients < 4 years old” as exploratory objective.

These will be summarised descriptively using the EAS and planned treatment.

4.3.7.3 Secondary efficacy analyses

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

- Percentage of days with pain, presented for the age group “patients ≥ 4 years old”.
The ratio of the total number of days the patient reported pain for Part B divided by the total number of days the patient reported on Part B in ePRO multiplied by 100.
- Percentage of days of opioid analgesic use.
The ratio of the total number of days the patient had taken opioid analgesics for Part B divided by the number of days the patient reported in ePRO. A day with opioid analgesic use is defined as a day where the patient has reported taking analgesic in the ePRO and there is a corresponding entry of opioid analgesic as a concomitant medication.
- Percentage of days of analgesic use, presented for the age group “patients ≥ 4 years old”.

The ratio of the total number of days the patient had taken analgesics for Part B divided by the total number of days the patient reported on Part B in ePRO multiplied by 100.

- Percentage of days hospitalised for VOC or other complications of SCD.
The ratio of the total number of days the patient was hospitalised for VOC or other complications for Part B divided by the total number of days the patient reported on Part B multiplied by 100.
- Percentage days of absence from school or work, presented for the age group “patients ≥ 6 years old”.
The ratio of the total number of days the patient was absent from school or work for part B divided by $7 \times$ (number of weeks for which answer is reported in diary on Part B).

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

Listings will be provided for VOC (Part B), Pain, Analgesic Use and Absence from School.

4.3.8 Safety Analysis

Safety data will not be formally analysed and will be evaluated using the SAF and actual treatment.

4.3.8.1 Adverse Events

Adverse events (AEs) will be listed by patient. All AEs will be coded using MedDRA dictionary (version 19.1). All AEs are reported on the eCRF from visit 2 except for serious adverse events (SAE) which will be reported on the eCRF from visit 1.

The following will be summarised for all ticagrelor treated patients in Part A and treatment groups in Part B:

- Overall summary, including
The number of patients with at least one AE, serious AE (SAE), AE leading to discontinuation of investigational product (IP) (DAE), AE leading to discontinuation from the study, and Deaths

- Summary of AE by MedDRA SOC and PT
- Summary of AE by MedDRA PT
- Summary of AEs caused by IP (according to investigator's assessment) by MedDRA SOC and PT
- Serious AEs by MedDRA SOC and PT
- AEs by maximum severity by MedDRA SOC and PT
- AEs leading to discontinuation of IP (DAE)
- AEs resulting in death

AEs starting between date of randomisation to Part A and date of Visit 4 plus 1 day will be counted into Part A, AEs starting after that up to and including date of Visit 8 will be counted into Part B. An AE that has started in part A and has changed into an SAE or a DAE in Part B will be handled as follows: AE counted in Part A and SAE/DAE is counted into Part B. An AE starting in Part A will not be counted in Part B, unless it changed into an SAE or a DAE in Part B. Each AE will be counted once per patient for the summary of patients. Missing severity will be left as missing and categorised as such. Missing causality will be considered as causality="yes".

A listing along with Key patient information will be provided separately for AEs, SAEs, and Deaths.

4.3.8.2 Laboratory Evaluations

Descriptive statistics of reported value and change from baseline for Clinical Chemistry and Haematology by visit for all ticagrelor treated patients in Part A and by treatment groups in Part B will be provided. Urinalysis and Coagulation parameters will be summarised by visit for all ticagrelor treated patients in Part A and by treatment groups in Part B using summary statistics for categorical data.

Clinical Chemistry and Haematology values will be categorised as normal, high, or low according to laboratory reference ranges. Shift tables for Haematology and Clinical Chemistry will display baseline value and last value during Part A and Part B, respectively. Results in SI units will be used for all summaries. The reference ranges will be supplied by the sites/CRAs and entered into the database along with the reference ranges.

Clinical Chemistry, Haematology, Urinalysis and Coagulation will be listed for Part A and Part B together. Out-of-range values will be flagged.

Unscheduled visits will not be included in the summaries but will be presented in the listings.

Hy's law assessment [7] will be summarised for liver risks and symptoms for treatment groups in Part A and Part B using summary statistics for categorical data along with a listing for Part A and B together.

4.3.8.3 Vital Signs

Descriptive statistics by visit for all ticagrelor treated patients in Part A and by treatment groups in Part B, will be provided for reported value and change from baseline for weight (kg), Sitting SBP (mmHg), Sitting DBP (mmHg) and Sitting Pulse (bpm). Weight will only be measured at visit 1, 2, 3 and 8, height will only be assessed at enrollment, hence no change from baseline is needed for height.

Vitals signs will be listed.

4.3.8.4 ECGs

Incidence of abnormalities for overall ECG evaluation will be summarised at Visit 1 (or within 6 months prior to enrolment) and at Visit 4 for all ticagrelor treated patients in Part A and by treatment groups in Part B.

Descriptive statistics for reported value will be provided for Heart rate and Heart Rhythm, PR interval, QRS duration, RR interval, QT interval, QTc interval (unspecified), and any abnormalities, by visit for each treatment group.

ECG parameters will be summarised using continuous descriptive statistics, except abnormal ECG values, that will be summarised using categorical descriptive statistics. Supportive listings will be provided.

4.3.8.5 Physical Examination

Incidence of physical examination abnormalities will be summarised for Enrollment and Follow-Up by clinical significance for treatment groups in Part B. Abnormal values will be summarised using categorical descriptive statistics. Supportive listing will be provided.

4.3.9 Randomisation scheme and codes

A listing will be provided for scheme and codes.

4.3.10 Haemorrhagic Events

A summary table will be presented for Haemorrhagic events, classified as “Major Bleeding, Clinically relevant non-major bleeding, and Minor Bleeding” [8], for all ticagrelor treated patients in Part A and by treatment groups in Part B using summary statistics for categorical data for the SAF.

Haemorrhagic events will be listed.

4.3.11 Transfusions

Transfusions will be analyzed for each Part by occurrence (Yes/ No) and by blood product type using summary statistics for categorical data for the SAF. A listing will be provided for Blood Product type, the Number of units transferred, Date of Transfusion and AE number.

5. CHANGES OF ANALYSIS FROM PROTOCOL

Not applicable

6. REFERENCES

[1] Protocol (D5136C00007) Revised Clinical Study Protocol Lebanon Republic, dated 18Mar2015

[2] eCRF (D5136C00007) version 2.0, dated 13Aug2014

[3] Diary Data (D5136C00007) version 1.0, dated 04Apr2014

[4] Hicks et al 2001

Hicks C, Baeyer C, Spafford P, Korlaar I, Goodenough B. The faces pain scale – revised: toward a common metric in pediatric pain measurement. *Pain* 2001;93(2):173-83

[5] Cohen et al 2008

Cohen L, Lemanek K, Blount R, Dahlquist L, Lim C, Palermo T et al. Evidence-based assessment of paediatric pain. *J Paediatric Psychology* 2008;33(9):939-55

[6] Clinical Study Protocol Appendix G version 1.0, dated 05Mar2014.

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

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[10] Protocol (D5136C00007) Revised Clinical Study Protocol Lebanon Republic, dated 22Dec2015

[11] Protocol (D5136C00007) Revised Clinical Study Protocol for Kenya, dated 03Feb2016