



## Clinical trial results:

**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**

### Summary

EudraCT number	2014-001006-18
Trial protocol	GB IT
Global end of trial date	27 February 2017

### Results information

Result version number	v1 (current)
This version publication date	29 July 2017
First version publication date	29 July 2017

### Trial information

#### Trial identification

Sponsor protocol code	D5136C00007
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02214121
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	Pepparedsleden 1, Mölndal, Sweden, 431 50
Public contact	Brilinta Global Clinical Lead, AstraZeneca, +46 31 776 1000,
Scientific contact	Brilinta Global Clinical Lead, AstraZeneca, +46 31 776 1000,

Notes:

### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-000480-PIP01-08
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 February 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 February 2017
Global end of trial reached?	Yes
Global end of trial date	27 February 2017
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To characterise the relationship between ticagrelor dose and inhibition of platelet aggregation in paediatric patients with Sickle Cell Disease (SCD), using PK-PD modelling, to support dose selection for Phase III.

Protection of trial subjects:

For safety reasons, the dosing schedule had the potential to be modified for individual patients based on their PRU at Visit 2, 3 and 4. If the response in PRU was higher than expected, subsequent doses for that patient was lowered.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 September 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	United Kingdom: 15
Country: Number of subjects enrolled	Kenya: 8
Country: Number of subjects enrolled	Lebanon: 21
Country: Number of subjects enrolled	United States: 19
Country: Number of subjects enrolled	South Africa: 8
Worldwide total number of subjects	73
EEA total number of subjects	15

Notes:

### Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	43

Adolescents (12-17 years)	30
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted at 24 centres, in 6 countries. The first patient was enrolled to Part A of the study on 11 Sep 2014, and the last patient completed Part B of the study on 27 Feb 2017. Recruitment was stopped due to protocol amendment between 8 September 2015 and 1 June 2016.

### Pre-assignment

Screening details:

A total of 73 patients were enrolled to the study, 46 of which were randomised to Part A of the study (open label). Of the patients completing Part A, 25 was randomised to Part B of the study (double blind).

### Period 1

Period 1 title	Part A
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

### Arms

Arm title	Part A - Ticagrelor
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Arm description:

Actual treatment group for Part A of the study. Relevant for the Part A period.

Arm type	Experimental
Investigational medicinal product name	Ticagrelor 10 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Granules for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Granules for oral suspension 10 mg

Investigational medicinal product name	Ticagrelor 45 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Granules for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Granules for oral suspension 45 mg

Number of subjects in period 1 <sup>[1]</sup>	Part A - Ticagrelor
Started	45
Completed	39
Not completed	6
Patient decision	1
Dev. of study-specific withdrawal crit.	4
Other	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The number of patients in "Trial Information" is the number of enrolled subjects, whereas the subjects displayed here is the number actually part of Part A. There were a number of patients that were not randomised or taking IP that are not included in the arm.

## Period 2

Period 2 title	Part B
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

## Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Part B - Ticagrelor

Arm description:

Randomised treatment group for Part B of the study. Relevant for the Part B period.

Arm type	Experimental
Investigational medicinal product name	Ticagrelor 45 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Granules for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Granules for oral suspension 45 mg

Investigational medicinal product name	Ticagrelor 10 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Granules for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Granules for oral suspension 10 mg

<b>Arm title</b>	Part B - Placebo
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Arm description:

Randomised treatment group for Part B of the study. Relevant for the Part B period.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Granules for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Matching placebo for ticagrelor

<b>Number of subjects in period 2<sup>[2]</sup></b>	Part B - Ticagrelor	Part B - Placebo
Started	17	8
Completed	14	7
Not completed	3	1
Patient decision	1	-
Dev. of study-specific withdrawal crit.	2	-
Lost to follow-up	-	1

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Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Part B period was optional, therefore the number of patients completing Part A period is not the same as the number of patients starting Part B period.

## Baseline characteristics

### Reporting groups

Reporting group title	Part A - Ticagrelor
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Reporting group description:

Actual treatment group for Part A of the study. Relevant for the Part A period.

Reporting group values	Part A - Ticagrelor	Total	
Number of subjects	45	45	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	24	24	
Adolescents (12-17 years)	21	21	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age Continuous			
Relevant for the Part A period of the study.			
Units: Years			
arithmetic mean	11.2		
standard deviation	± 3.34	-	
Gender, Male/Female			
Relevant for the Part A period of the study			
Units: Subjects			
Male	21	21	
Female	24	24	
Race/Ethnicity, Customized			
Relevant for the Part A period of the study			
Units: Subjects			
White	10	10	
Black or African American	35	35	
Asian	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
American Indian or Alaska Native	0	0	
Other	0	0	
Ethnicity (NIH/OMB)			
Relevant for the Part A period			
Units: Subjects			
Hispanic or Latino	1	1	
Not Hispanic or Latino	44	44	
Unknown or Not Reported	0	0	

## Subject analysis sets

Subject analysis set title	Ticagrelor 0.125 mg/kg
Subject analysis set type	Safety analysis
Subject analysis set description: Single dose received at Visit 2.	
Subject analysis set title	Ticagrelor 0.75 mg/kg
Subject analysis set type	Safety analysis
Subject analysis set description: Single dose received at Visit 2.	
Subject analysis set title	Ticagrelor 0.375 mg/kg
Subject analysis set type	Safety analysis
Subject analysis set description: Single dose received at Visit 3.	
Subject analysis set title	Ticagrelor 0.563 mg/kg
Subject analysis set type	Safety analysis
Subject analysis set description: Single dose received at Visit 3	
Subject analysis set title	Ticagrelor 1.125 mg/kg
Subject analysis set type	Safety analysis
Subject analysis set description: Single dose received at Visit 3.	
Subject analysis set title	Ticagrelor 2.25 mg/kg
Subject analysis set type	Safety analysis
Subject analysis set description: Single dose received at Visit 3.	
Subject analysis set title	Ticagrelor 0.125 mg/kg bid
Subject analysis set type	Safety analysis
Subject analysis set description: Repeated bid treatment between Visit 3 and Visit 4.	
Subject analysis set title	Ticagrelor 0.563 mg/kg bid
Subject analysis set type	Safety analysis
Subject analysis set description: Repeated bid treatment between Visit 3 and Visit 4.	
Subject analysis set title	Ticagrelor 0.75 mg/kg bid
Subject analysis set type	Safety analysis
Subject analysis set description: Repeated bid treatment between Visit 3 and Visit 4.	
Subject analysis set title	Part B - Ticagrelor 0.125 mg/kg bid
Subject analysis set type	Safety analysis
Subject analysis set description: Repeated bid treatment during Part B.	
Subject analysis set title	Part B - Placebo
Subject analysis set type	Safety analysis
Subject analysis set description: Repeated bid treatment during Part B.	
Subject analysis set title	Part A - Overall
Subject analysis set type	Safety analysis
Subject analysis set description: All ticagrelor-treated patients in Part A	



Reporting group values	Ticagrelor 0.125 mg/kg	Ticagrelor 0.75 mg/kg	Ticagrelor 0.375 mg/kg
Number of subjects	14	31	7
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	11	13	6
Adolescents (12-17 years)	3	18	1
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous			
Relevant for the Part A period of the study.			
Units: Years			
arithmetic mean	9.4	12	8.9
standard deviation	± 3.73	± 2.83	± 4.22
Gender, Male/Female			
Relevant for the Part A period of the study			
Units: Subjects			
Male	8	13	3
Female	6	18	4
Race/Ethnicity, Customized			
Relevant for the Part A period of the study			
Units: Subjects			
White	2	8	2
Black or African American	12	23	5
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
American Indian or Alaska Native	0	0	0
Other	0	0	0
Ethnicity (NIH/OMB)			
Relevant for the Part A period			
Units: Subjects			
Hispanic or Latino	1	0	1
Not Hispanic or Latino	13	31	6
Unknown or Not Reported	0	0	0

Reporting group values	Ticagrelor 0.563 mg/kg	Ticagrelor 1.125 mg/kg	Ticagrelor 2.25 mg/kg
Number of subjects	18	10	9
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0

Children (2-11 years)	10	4	4
Adolescents (12-17 years)	8	6	5
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous			
Relevant for the Part A period of the study.			
Units: Years			
arithmetic mean	11.2	11.9	12.2
standard deviation	± 3.17	± 2.96	± 3.19
Gender, Male/Female			
Relevant for the Part A period of the study			
Units: Subjects			
Male	11	3	4
Female	7	7	5
Race/Ethnicity, Customized			
Relevant for the Part A period of the study			
Units: Subjects			
White	2	2	3
Black or African American	16	8	6
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
American Indian or Alaska Native	0	0	0
Other	0	0	0
Ethnicity (NIH/OMB)			
Relevant for the Part A period			
Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	18	10	9
Unknown or Not Reported	0	0	0

<b>Reporting group values</b>	Ticagrelor 0.125 mg/kg bid	Ticagrelor 0.563 mg/kg bid	Ticagrelor 0.75 mg/kg bid
Number of subjects	14	9	17
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	11	4	8
Adolescents (12-17 years)	3	5	9
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous			
Relevant for the Part A period of the study.			
Units: Years			
arithmetic mean	9.4	12.4	11.8
standard deviation	± 3.73	± 2.55	± 3.03

Gender, Male/Female			
Relevant for the Part A period of the study			
Units: Subjects			
Male	8	4	6
Female	6	5	11
Race/Ethnicity, Customized			
Relevant for the Part A period of the study			
Units: Subjects			
White	2	1	4
Black or African American	12	8	13
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
American Indian or Alaska Native	0	0	0
Other	0	0	0
Ethnicity (NIH/OMB)			
Relevant for the Part A period			
Units: Subjects			
Hispanic or Latino	1	0	0
Not Hispanic or Latino	13	9	17
Unknown or Not Reported	0	0	0

Reporting group values	Part B - Ticagrelor 0.125 mg/kg bid	Part B - Placebo	Part A - Overall
Number of subjects	9	3	45
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	7	2	24
Adolescents (12-17 years)	2	1	21
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous			
Relevant for the Part A period of the study.			
Units: Years			
arithmetic mean	9.4	9.7	11.2
standard deviation	± 3.91	± 5.13	± 3.34
Gender, Male/Female			
Relevant for the Part A period of the study			
Units: Subjects			
Male	5	2	21
Female	4	1	24
Race/Ethnicity, Customized			
Relevant for the Part A period of the study			
Units: Subjects			
White	1	0	10
Black or African American	8	3	35

Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
American Indian or Alaska Native	0	0	0
Other	0	0	0
Ethnicity (NIH/OMB)			
Relevant for the Part A period			
Units: Subjects			
Hispanic or Latino	1	0	1
Not Hispanic or Latino	8	3	44
Unknown or Not Reported	0	0	0

## End points

### End points reporting groups

Reporting group title	Part A - Ticagrelor
Reporting group description:	
Actual treatment group for Part A of the study. Relevant for the Part A period.	
Reporting group title	Part B - Ticagrelor
Reporting group description:	
Randomised treatment group for Part B of the study. Relevant for the Part B period.	
Reporting group title	Part B - Placebo
Reporting group description:	
Randomised treatment group for Part B of the study. Relevant for the Part B period.	
Subject analysis set title	Ticagrelor 0.125 mg/kg
Subject analysis set type	Safety analysis
Subject analysis set description:	
Single dose received at Visit 2.	
Subject analysis set title	Ticagrelor 0.75 mg/kg
Subject analysis set type	Safety analysis
Subject analysis set description:	
Single dose received at Visit 2.	
Subject analysis set title	Ticagrelor 0.375 mg/kg
Subject analysis set type	Safety analysis
Subject analysis set description:	
Single dose received at Visit 3.	
Subject analysis set title	Ticagrelor 0.563 mg/kg
Subject analysis set type	Safety analysis
Subject analysis set description:	
Single dose received at Visit 3.	
Subject analysis set title	Ticagrelor 1.125 mg/kg
Subject analysis set type	Safety analysis
Subject analysis set description:	
Single dose received at Visit 3.	
Subject analysis set title	Ticagrelor 2.25 mg/kg
Subject analysis set type	Safety analysis
Subject analysis set description:	
Single dose received at Visit 3.	
Subject analysis set title	Ticagrelor 0.125 mg/kg bid
Subject analysis set type	Safety analysis
Subject analysis set description:	
Repeated bid treatment between Visit 3 and Visit 4.	
Subject analysis set title	Ticagrelor 0.563 mg/kg bid
Subject analysis set type	Safety analysis
Subject analysis set description:	
Repeated bid treatment between Visit 3 and Visit 4.	
Subject analysis set title	Ticagrelor 0.75 mg/kg bid
Subject analysis set type	Safety analysis
Subject analysis set description:	
Repeated bid treatment between Visit 3 and Visit 4.	
Subject analysis set title	Part B - Ticagrelor 0.125 mg/kg bid
Subject analysis set type	Safety analysis

Subject analysis set description:

Repeated bid treatment during Part B.

Subject analysis set title	Part B - Placebo
Subject analysis set type	Safety analysis

Subject analysis set description:

Repeated bid treatment during Part B.

Subject analysis set title	Part A - Overall
Subject analysis set type	Safety analysis

Subject analysis set description:

All ticagrelor-treated patients in Part A

### Primary: P2Y12 reaction units (PRU) - Part A

End point title	P2Y12 reaction units (PRU) - Part A <sup>[1]</sup>
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End point description:

End point type	Primary
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End point timeframe:

PRU measurements are taken in conjunction with single doses at Visit 2 (Day 0) and Visit 3 (Day 7) and after repeated dosing at Visit 4 (Day 14).

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: All of the above: No statistical tests were planned or conducted, only descriptive statistics were used.

End point values	Ticagrelor 0.125 mg/kg	Ticagrelor 0.75 mg/kg	Ticagrelor 0.375 mg/kg	Ticagrelor 0.563 mg/kg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	14	31	7	18
Units: Unit				
arithmetic mean (standard deviation)				
Pre-dose	301.6 (± 46.55)	268 (± 35.95)	295.4 (± 42.3)	287.7 (± 34.35)
2 hours post-dose	278.2 (± 47.2)	138.4 (± 70.68)	229 (± 64.22)	176.2 (± 79.53)
6 hours post-dose	276 (± 75.43)	189 (± 69.84)	266 (± 57.98)	190.4 (± 47.78)
8 hours post-dose	343 (± 38.13)	99999999 (± 99999999)	318.3 (± 66.43)	318 (± 99999999)

End point values	Ticagrelor 1.125 mg/kg	Ticagrelor 2.25 mg/kg	Ticagrelor 0.125 mg/kg bid	Ticagrelor 0.563 mg/kg bid
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	10	9	14	9
Units: Unit				
arithmetic mean (standard deviation)				
Pre-dose	283.7 (± 36.88)	277.7 (± 39.36)	320 (± 99999999)	205.4 (± 53.22)
2 hours post-dose	128.9 (± 37.68)	79.9 (± 47.74)	271.2 (± 70.35)	102 (± 72.53)
6 hours post-dose	191.2 (± 57.59)	141.7 (± 69.58)	99999999 (± 99999999)	99999999 (± 99999999)

8 hours post-dose	99999999 (± 99999999)	99999999 (± 99999999)	99999999 (± 99999999)	99999999 (± 99999999)
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<b>End point values</b>	Ticagrelor 0.75 mg/kg bid			
Subject group type	Subject analysis set			
Number of subjects analysed	17			
Units: Unit				
arithmetic mean (standard deviation)				
Pre-dose	214.7 (± 48.71)			
2 hours post-dose	152 (± 72.35)			
6 hours post-dose	99999999 (± 99999999)			
8 hours post-dose	99999999 (± 99999999)			

## Statistical analyses

No statistical analyses for this end point

## Primary: P2Y12 reaction units (PRU) - Part B

End point title	P2Y12 reaction units (PRU) - Part B <sup>[2]</sup>
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End point description:

End point type	Primary
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End point timeframe:

PRU measurements are taken after 4 weeks of double blind treatment at the end of Part B.

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: All of the above: No statistical tests were planned or conducted, only descriptive statistics were used.

<b>End point values</b>	Part B - Ticagrelor 0.125 mg/kg bid	Part B - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	3		
Units: Unit				
arithmetic mean (standard deviation)				
Pre-dose	282.8 (± 19.26)	313.3 (± 20.13)		
2 hours post-dose	259.6 (± 61.95)	217.3 (± 78.34)		

## Statistical analyses

No statistical analyses for this end point

### Primary: Maximum plasma concentration (Cmax) - Part A

End point title	Maximum plasma concentration (Cmax) - Part A <sup>[3]</sup>
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End point description:

End point type	Primary
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End point timeframe:

PK measurements are taken in conjunction with single doses at Visit 2 (Day 0) and Visit 3 (Day 7) and after repeated dosing at Visit 4 (Day 14).

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: All of the above: No statistical tests were planned or conducted, only descriptive statistics were used.

End point values	Ticagrelor 0.125 mg/kg	Ticagrelor 0.75 mg/kg	Ticagrelor 0.375 mg/kg	Ticagrelor 0.563 mg/kg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	14	31	7	18
Units: ng/mL				
geometric mean (standard deviation)	15.24 (± 15.2709)	162.961 (± 84.923)	52.069 (± 34.4115)	96.031 (± 51.4902)

End point values	Ticagrelor 1.125 mg/kg	Ticagrelor 2.25 mg/kg	Ticagrelor 0.125 mg/kg bid	Ticagrelor 0.563 mg/kg bid
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	10	9	14	9
Units: ng/mL				
geometric mean (standard deviation)	269.174 (± 162.2147)	566.55 (± 225.9447)	13.973 (± 15.3652)	111.367 (± 81.1597)

End point values	Ticagrelor 0.75 mg/kg bid			
Subject group type	Subject analysis set			
Number of subjects analysed	17			
Units: ng/mL				
geometric mean (standard deviation)	157.216 (± 114.8138)			

## Statistical analyses

No statistical analyses for this end point



**Primary: Maximum plasma concentration (Cmax) - Part B**

End point title	Maximum plasma concentration (Cmax) - Part B <sup>[4]</sup>
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End point description:

End point type	Primary
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End point timeframe:

PK measurements are taken after 4 weeks of double blind treatment at the end of Part B.

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: All of the above: No statistical tests were planned or conducted, only descriptive statistics were used.

End point values	Part B - Ticagrelor 0.125 mg/kg bid			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: ng/mL				
geometric mean (standard deviation)	16.394 (± 13.3671)			

**Statistical analyses**

No statistical analyses for this end point

**Primary: Area under the plasma concentration time curve (AUC) - Part A**

End point title	Area under the plasma concentration time curve (AUC) - Part
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End point description:

The PK parameter presented was derived using a model based analysis and not from a non-compartmental (NCA) analysis.

End point type	Primary
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End point timeframe:

PK measurements are taken in conjunction with single doses at Visit 2 (Day 0) and Visit 3 (Day 7) and after repeated dosing at Visit 4 (Day 14).

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: All of the above: No statistical tests were planned or conducted, only descriptive statistics were used.

End point values	Ticagrelor 0.125 mg/kg	Ticagrelor 0.75 mg/kg	Ticagrelor 0.375 mg/kg	Ticagrelor 0.563 mg/kg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	14	31	7	18
Units: ng*h/mL				
geometric mean (standard deviation)	161.9 (± 72.24)	1151.9 (± 308.39)	437.5 (± 262.24)	879.3 (± 236.12)

End point values	Ticagrelor 1.125 mg/kg	Ticagrelor 2.25 mg/kg	Ticagrelor 0.125 mg/kg bid	Ticagrelor 0.563 mg/kg bid
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	10	9	14	9
Units: ng*h/mL				
geometric mean (standard deviation)	1638.7 ( $\pm$ 521.8)	2850.9 ( $\pm$ 1277.39)	161.9 ( $\pm$ 72.24)	913.5 ( $\pm$ 208.82)

End point values	Ticagrelor 0.75 mg/kg bid			
Subject group type	Subject analysis set			
Number of subjects analysed	17			
Units: ng*h/mL				
geometric mean (standard deviation)	1022.4 ( $\pm$ 287.32)			

## Statistical analyses

No statistical analyses for this end point

## Primary: Area under the plasma concentration time curve (AUC) - Part B

End point title	Area under the plasma concentration time curve (AUC) - Part
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End point description:

The PK parameter presented was derived using a model based analysis and not from a non-compartmental (NCA) analysis.

End point type	Primary
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End point timeframe:

PK measurements are taken after 4 weeks of double blind treatment at the end of Part B.

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: All of the above: No statistical tests were planned or conducted, only descriptive statistics were used.

End point values	Part B - Ticagrelor 0.125 mg/kg bid			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: ng*h/mL				
geometric mean (standard deviation)	160.6 ( $\pm$ 88.58)			

## Statistical analyses

**Secondary: Assessment of Ticagrelor concentration - Part A**

End point title	Assessment of Ticagrelor concentration - Part A
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End point description:
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End point type	Secondary
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End point timeframe:
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PK measurements are taken in conjunction with single doses at Visit 2 (Day 0) and Visit 3 (Day 7) and after repeated dosing at Visit 4 (Day 14).
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End point values	Ticagrelor 0.125 mg/kg	Ticagrelor 0.75 mg/kg	Ticagrelor 0.375 mg/kg	Ticagrelor 0.563 mg/kg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	14	31	7	18
Units: ng/mL				
geometric mean (standard deviation)				
Pre-dose	99999999 (± 99999999)	99999999 (± 99999999)	99999999 (± 99999999)	99999999 (± 99999999)
1 hour post-dose	12.713 (± 16.0627)	104.243 (± 103.1502)	34.069 (± 42.3746)	33.294 (± 55.4258)
2 hours post-dose	11.465 (± 8.7427)	107.729 (± 62.8343)	37.782 (± 31.689)	74.626 (± 50.7053)
4 hours post-dose	6.647 (± 4.4533)	75.907 (± 31.2786)	20.122 (± 9.9383)	51.005 (± 24.6435)
6 hours post-dose	3.663 (± 3.4061)	52.966 (± 29.0297)	19.435 (± 15.7259)	45.502 (± 17.895)
8 hours post-dose	3.88 (± 3.3171)	99999999 (± 99999999)	15.699 (± 20.7596)	15.691 (± 15.1392)

End point values	Ticagrelor 1.125 mg/kg	Ticagrelor 2.25 mg/kg	Ticagrelor 0.125 mg/kg bid	Ticagrelor 0.563 mg/kg bid
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	10	9	14	9
Units: ng/mL				
geometric mean (standard deviation)				
Pre-dose	99999999 (± 99999999)	99999999 (± 99999999)	2.17 (± 99999999)	31.937 (± 48.6501)
1 hour post-dose	182.558 (± 188.4254)	390.568 (± 294.2189)	99999999 (± 99999999)	80.414 (± 75.9675)
2 hours post-dose	162.435 (± 161.8489)	426.804 (± 212.5385)	13.973 (± 15.3652)	102.166 (± 78.0785)
4 hours post-dose	118.217 (± 42.0873)	188.383 (± 111.9267)	99999999 (± 99999999)	99999999 (± 99999999)
6 hours post-dose	69.708 (± 44.3168)	125.279 (± 89.0005)	99999999 (± 99999999)	99999999 (± 99999999)
8 hours post-dose	99999999 (± 99999999)	99999999 (± 99999999)	99999999 (± 99999999)	99999999 (± 99999999)

<b>End point values</b>	Ticagrelor 0.75 mg/kg bid			
Subject group type	Subject analysis set			
Number of subjects analysed	17			
Units: ng/mL				
geometric mean (standard deviation)				
Pre-dose	28.066 ( $\pm$ 27.1344)			
1 hour post-dose	151.52 ( $\pm$ 116.0079)			
2 hours post-dose	101.618 ( $\pm$ 65.2415)			
4 hours post-dose	99999999 ( $\pm$ 99999999)			
6 hours post-dose	99999999 ( $\pm$ 99999999)			
8 hours post-dose	99999999 ( $\pm$ 99999999)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Assessment of Ticagrelor concentration - Part B

End point title	Assessment of Ticagrelor concentration - Part B
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End point description:

End point type	Secondary
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End point timeframe:

PK measurements are taken after 4 weeks of double blind treatment at the end of Part B.

<b>End point values</b>	Part B - Ticagrelor 0.125 mg/kg bid			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: ng/mL				
geometric mean (standard deviation)				
Pre-dose	2.478 ( $\pm$ 3.958)			
1 hour post-dose	9.677 ( $\pm$ 9.4275)			
2 hours post-dose	14.144 ( $\pm$ 12.4711)			
4 hours post-dose	9.605 ( $\pm$ 14.4979)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Assessment of AR-C124910XX concentration - Part A

End point title	Assessment of AR-C124910XX concentration - Part A
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End point description:

End point type	Secondary
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End point timeframe:

PK measurements are taken in conjunction with single doses at Visit 2 (Day 0) and Visit 3 (Day 7) and after repeated dosing at Visit 4 (Day 14).

End point values	Ticagrelor 0.125 mg/kg	Ticagrelor 0.75 mg/kg	Ticagrelor 0.375 mg/kg	Ticagrelor 0.563 mg/kg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	14	31	7	18
Units: ng/mL				
geometric mean (standard deviation)				
Pre-dose	99999999 (± 99999999)	99999999 (± 99999999)	99999999 (± 99999999)	99999999 (± 99999999)
1 hour post-dose	1.782 (± 1.6604)	16.302 (± 22.4614)	4.577 (± 7.861)	3.708 (± 13.3332)
2 hours post-dose	2.681 (± 2.0733)	33.256 (± 25.3854)	11.757 (± 13.3322)	15.918 (± 17.4849)
4 hours post-dose	2.071 (± 1.277)	29.86 (± 13.8726)	7.63 (± 6.373)	17.015 (± 7.9272)
6 hours post-dose	1.646 (± 1.0427)	25.276 (± 10.8318)	9.762 (± 2.3304)	16.703 (± 5.8115)
8 hours post-dose	1.715 (± 1.0226)	99999999 (± 99999999)	6.176 (± 6.3168)	9.232 (± 2.5385)

End point values	Ticagrelor 1.125 mg/kg	Ticagrelor 2.25 mg/kg	Ticagrelor 0.125 mg/kg bid	Ticagrelor 0.563 mg/kg bid
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	10	9	14	9
Units: ng/mL				
geometric mean (standard deviation)				
Pre-dose	99999999 (± 99999999)	99999999 (± 99999999)	1.25 (± 99999999)	17.38 (± 10.0399)
1 hour post-dose	30.07 (± 44.295)	63.088 (± 84.2091)	99999999 (± 99999999)	24.945 (± 15.6547)

2 hours post-dose	52.932 (± 69.1056)	149.772 (± 71.3624)	4.026 (± 4.7624)	37.013 (± 32.765)
4 hours post-dose	50.887 (± 25.6964)	101.37 (± 44.6207)	99999999 (± 99999999)	99999999 (± 99999999)
6 hours post-dose	35.716 (± 22.3351)	76.941 (± 39.9167)	99999999 (± 99999999)	99999999 (± 99999999)
8 hours post-dose	99999999 (± 99999999)	99999999 (± 99999999)	99999999 (± 99999999)	99999999 (± 99999999)

<b>End point values</b>	Ticagrelor 0.75 mg/kg bid			
Subject group type	Subject analysis set			
Number of subjects analysed	17			
Units: ng/mL				
geometric mean (standard deviation)				
Pre-dose	20.359 (± 15.0788)			
1 hour post-dose	43.986 (± 29.8127)			
2 hours post-dose	44.69 (± 31.6577)			
4 hours post-dose	99999999 (± 99999999)			
6 hours post-dose	99999999 (± 99999999)			
8 hours post-dose	99999999 (± 99999999)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Assessment of AR-C124910XX concentration - Part B

End point title Assessment of AR-C124910XX concentration - Part B

End point description:

End point type Secondary

End point timeframe:

PK measurements are taken after 4 weeks of double blind treatment at the end of Part B.

<b>End point values</b>	Part B - Ticagrelor 0.125 mg/kg bid			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: ng/mL				
geometric mean (standard deviation)				

Pre-dose	1.81 ( $\pm$ 1.1213)			
1 hour post-dose	2.865 ( $\pm$ 1.6443)			
2 hours post-dose	4.16 ( $\pm$ 3.1503)			
4 hours post-dose	3.953 ( $\pm$ 4.1179)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Oral Clearance (CL/F) - Part A

End point title	Oral Clearance (CL/F) - Part A
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End point description:

The PK parameter presented were derived using a model based analysis and not from a non-compartmental (NCA) analysis.

End point type	Secondary
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End point timeframe:

PK measurements are taken in conjunction with single doses at Visit 2 (Day 0) and Visit 3 (Day 7) and after repeated dosing at Visit 4 (Day 14).

<b>End point values</b>	Part A - Overall			
Subject group type	Subject analysis set			
Number of subjects analysed	45			
Units: L/h				
geometric mean (standard deviation)	22.5 ( $\pm$ 7.531)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Oral Clearance (CL/F) - Part B

End point title	Oral Clearance (CL/F) - Part B
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End point description:

The PK parameter presented was derived using a model based analysis and not from a non-compartmental (NCA) analysis.

End point type	Secondary
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End point timeframe:

PK measurements are taken after 4 weeks of double blind treatment at the end of Part B.

<b>End point values</b>	Part B - Ticagrelor 0.125 mg/kg bid			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: L/h				
geometric mean (standard deviation)	19.15 ( $\pm$ 6.673)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of vaso-occlusive crises - Part B

End point title	Number of vaso-occlusive crises - Part B
End point description:	
End point type	Secondary
End point timeframe:	
During 4 weeks of study treatment starting from randomization in Part B (week 2) up to 4 weeks (week 6).	

<b>End point values</b>	Part B - Ticagrelor	Part B - Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	8		
Units: Number of events				
arithmetic mean (standard deviation)	1 ( $\pm$ 2)	0.6 ( $\pm$ 0.74)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of vaso-occlusive crises requiring hospitalization or emergency department visits - Part B

End point title	Number of vaso-occlusive crises requiring hospitalization or emergency department visits - Part B
End point description:	
End point type	Secondary
End point timeframe:	
During 4 weeks of study treatment starting from randomization in Part B (week 2) up to 4 weeks (week 6).	



<b>End point values</b>	Part B - Ticagrelor	Part B - Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	8		
Units: Number of events				
arithmetic mean (standard deviation)	0.2 (± 0.41)	0.1 (± 0.35)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of days hospitalized for vaso-occlusive crisis or other complications of sickle cell disease - Part B

End point title	Percentage of days hospitalized for vaso-occlusive crisis or other complications of sickle cell disease - Part B
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End point description:

End point type	Secondary
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End point timeframe:

During 4 weeks of study treatment starting from randomization in Part B (week 2) up to 4 weeks (week 6).

<b>End point values</b>	Part B - Ticagrelor	Part B - Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	8		
Units: Percentage of days				
arithmetic mean (standard deviation)	4.52 (± 11.816)	1.34 (± 3.788)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of days with pain (age ≥4) - Part B

End point title	Percentage of days with pain (age ≥4) - Part B
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End point description:

End point type	Secondary
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End point timeframe:

During 4 weeks of study treatment starting from randomization in Part B (week 2) up to 4 weeks (week 6).

End point values	Part B - Ticagrelor	Part B - Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	8		
Units: Percentage of days				
arithmetic mean (standard deviation)	27.01 (± 34.065)	31.78 (± 23.731)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Mean intensity of pain (age >=4) - Part B

End point title	Mean intensity of pain (age >=4) - Part B
End point description:	
End point type	Secondary
End point timeframe:	
During 4 weeks of study treatment starting from randomization in Part B (week 2) up to 4 weeks (week 6).	

End point values	Part B - Ticagrelor	Part B - Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	8		
Units: Mean intensity of pain				
arithmetic mean (standard deviation)				
Overall - Part B	1.4 (± 2.027)	0.87 (± 0.493)		
1st week	1.64 (± 2.603)	1.36 (± 0.827)		
2nd week	1.11 (± 2.236)	0.38 (± 0.525)		
3rd week	1.06 (± 1.881)	0.67 (± 1.116)		
4th week	1.46 (± 2.624)	0.83 (± 0.901)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of days of analgesic use (age >= 4) - Part B

End point title	Percentage of days of analgesic use (age >= 4) - Part B
End point description:	

End point type	Secondary
End point timeframe:	
During 4 weeks of study treatment starting from randomization in Part B (week 2) up to 4 weeks (week 6).	

End point values	Part B - Ticagrelor	Part B - Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	8		
Units: Percentage of days				
arithmetic mean (standard deviation)	16.79 (± 20.838)	18.56 (± 19.11)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of days of opioid analgesic use (age ≥4) - Part B

End point title	Percentage of days of opioid analgesic use (age ≥4) - Part B
End point description:	

End point type	Secondary
End point timeframe:	
During 4 weeks of study treatment starting from randomization in Part B (week 2) up to 4 weeks (week 6).	

End point values	Part B - Ticagrelor	Part B - Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	8		
Units: Percentage of days				
arithmetic mean (standard deviation)	12.46 (± 22.502)	0.54 (± 1.537)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of days of absence from school or work (age ≥6) - Part B

End point title	Percentage of days of absence from school or work (age ≥6) - Part B
End point description:	

End point type	Secondary
End point timeframe:	
During 4 weeks of study treatment starting from randomization in Part B (week 2) up to 4 weeks (week 6).	

End point values	Part B - Ticagrelor	Part B - Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	6		
Units: Percentage of days				
arithmetic mean (standard deviation)	4.87 (± 10.865)	5.95 (± 9.494)		

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Haemorrhagic events - Part A

End point title	Haemorrhagic events - Part A
End point description:	

End point type	Other pre-specified
End point timeframe:	
From randomisation to Part A (week 0) through Visit 4 (week 2)	

End point values	Part A - Ticagrelor			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: Number of events	0			

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Haemorrhagic events - Part B

End point title	Haemorrhagic events - Part B
End point description:	

End point type	Other pre-specified
End point timeframe:	
During 4 weeks of study treatment starting from randomization in Part B (week 2) up to 4 weeks (week 6)	

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<b>End point values</b>	Part B - Ticagrelor	Part B - Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	7		
Units: Number of events	0	0		

### **Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

SAEs were collected from Visit 1 and AEs from Visit 2. SAEs and Other AEs are presented by study period, where Part A consists of the time from randomization to Part A through Visit 4. Part B starts the day after Visit 4 and continues until Visit 8.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.1
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### Reporting groups

Reporting group title	Part A - Ticagrelor
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Reporting group description:

Randomised treatment group for Part A of the study. Relevant for the Part A period.

Reporting group title	Part B - Ticagrelor
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Reporting group description:

Randomised treatment group for Part B of the study. Relevant for the Part B period.

Reporting group title	Part B - Placebo
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Reporting group description:

Randomised treatment group for Part B of the study. Relevant for the Part B period.

<b>Serious adverse events</b>	Part A - Ticagrelor	Part B - Ticagrelor	Part B - Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 45 (11.11%)	4 / 16 (25.00%)	1 / 7 (14.29%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Blood and lymphatic system disorders			
Sickle cell anemia with crisis			
subjects affected / exposed	3 / 45 (6.67%)	3 / 16 (18.75%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute chest syndrome			
subjects affected / exposed	1 / 45 (2.22%)	1 / 16 (6.25%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Gastroenteritis viral			

subjects affected / exposed	1 / 45 (2.22%)	0 / 16 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

<b>Non-serious adverse events</b>	Part A - Ticagrelor	Part B - Ticagrelor	Part B - Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 45 (48.89%)	12 / 16 (75.00%)	5 / 7 (71.43%)
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 45 (2.22%)	1 / 16 (6.25%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Headache			
subjects affected / exposed	4 / 45 (8.89%)	0 / 16 (0.00%)	2 / 7 (28.57%)
occurrences (all)	7	0	2
Blood and lymphatic system disorders			
Sickle cell anemia with crisis			
subjects affected / exposed	6 / 45 (13.33%)	1 / 16 (6.25%)	1 / 7 (14.29%)
occurrences (all)	8	1	1
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	0 / 45 (0.00%)	1 / 16 (6.25%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Facial pain			
subjects affected / exposed	2 / 45 (4.44%)	1 / 16 (6.25%)	1 / 7 (14.29%)
occurrences (all)	4	1	2
Non-cardiac chest pain			
subjects affected / exposed	2 / 45 (4.44%)	1 / 16 (6.25%)	1 / 7 (14.29%)
occurrences (all)	2	2	1
Pain			
subjects affected / exposed	0 / 45 (0.00%)	1 / 16 (6.25%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Pyrexia			
subjects affected / exposed	1 / 45 (2.22%)	2 / 16 (12.50%)	0 / 7 (0.00%)
occurrences (all)	1	2	0

Ear and labyrinth disorders Tympanic membrane perforation subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0	1 / 16 (6.25%) 1	0 / 7 (0.00%) 0
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	6 / 45 (13.33%) 6	3 / 16 (18.75%) 6	2 / 7 (28.57%) 2
Abdominal pain upper subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0	2 / 16 (12.50%) 2	0 / 7 (0.00%) 0
Gastritis subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0	0 / 16 (0.00%) 0	1 / 7 (14.29%) 1
Nausea subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0	1 / 16 (6.25%) 1	0 / 7 (0.00%) 0
Vomiting subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0	3 / 16 (18.75%) 3	0 / 7 (0.00%) 0
Reproductive system and breast disorders Pelvic pain subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0	0 / 16 (0.00%) 0	1 / 7 (14.29%) 1
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1	2 / 16 (12.50%) 2	0 / 7 (0.00%) 0
Oropharyngeal pain subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1	3 / 16 (18.75%) 3	0 / 7 (0.00%) 0
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	5 / 45 (11.11%) 7	4 / 16 (25.00%) 4	2 / 7 (28.57%) 2
Back pain			



subjects affected / exposed occurrences (all)	3 / 45 (6.67%) 3	2 / 16 (12.50%) 2	1 / 7 (14.29%) 3
Musculoskeletal pain subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1	2 / 16 (12.50%) 2	1 / 7 (14.29%) 1
Neck pain subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0	1 / 16 (6.25%) 1	0 / 7 (0.00%) 0
Pain in extremity subjects affected / exposed occurrences (all)	5 / 45 (11.11%) 8	3 / 16 (18.75%) 4	2 / 7 (28.57%) 2
Infections and infestations			
Conjunctivitis subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0	0 / 16 (0.00%) 0	1 / 7 (14.29%) 1
Nasopharyngitis subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0	1 / 16 (6.25%) 1	0 / 7 (0.00%) 0
Otitis media subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0	1 / 16 (6.25%) 1	0 / 7 (0.00%) 0
Pharyngitis subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0	1 / 16 (6.25%) 1	0 / 7 (0.00%) 0
Tinea infection subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0	1 / 16 (6.25%) 1	0 / 7 (0.00%) 0

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 April 2014	<p>CSP Amendment 1: The purpose of this amendment was to address changes in the CSP related to the FDA's identified potential hold issues and non-hold comments for IND 120,366, dated 11 April 2014. An additional haematology and chemistry assessment was included at Visit 4. The stopping rules in Section 3.11 of the CSP were revised. Patients will be discontinued from study drug if any major bleeding should occur, not at the discretion of the PI. The time of the study follow-up visit (Visit 9) was changed to 30-35 days after last dose. Severity of AEs will be collected by maximum intensity. The intensity ratings are mild, moderate and severe. The Faces Pain Scale - Revised will be administered to patients aged <math>\geq 4</math> years instead of all patients. Inclusion criterion 2 was amended to read: "Experienced at least 2 vaso-occlusive crises requiring medical intervention during the past 12 months". The study was amended to a double-blind design. In addition clarifications on exclusion criterion 1, order of study procedures during study visits and recording of study drug intake in dosing diary have been made. First dose after each visit in the repeated dosing phase will be administered in the evening to simplify for the patients. Exclusion criterion 12; Males were deleted and 1 variable collected for AE was deleted due to error in writing. The time of the study enrolment visit (Visit 1) was changed, and is <math>\leq 30</math> days before Visit 2. TCD exams and ophthalmological exams were added as study procedures, for any patients who had not had the exams within the specified time periods, the new maximum time between Visit 1 and 2 allowed for these exams to be scheduled if needed.</p>
22 December 2014	<p>CSP Amendment 3: Analysis of the first 12 randomised patients showed that the exposure to ticagrelor was lower than predicted and the platelet inhibitory effect was also lower than intended. Protocol was therefore amended to increase to better characterise the PK-PD relationship for ticagrelor. The following is a description of changes: Initial doses of 0.125 mg/kg, followed 7 days later by 0.375 mg/kg or 0.563 mg/kg were amended to initial doses of 0.75 mg/kg, followed 7 days later by 1.125 mg/kg or 2.25 mg/kg. Inclusion criterion 2 concerning the history of VOC in the prior 12 months was removed. Inclusion criterion 4: The requirement for stable hydroxyurea dosing was changed from 3 months to 1 month. The amended protocol allowed for patients to opt out of participation in Part B to reduce study burden on patients/families. Since Part B was now optional, the PK-PD determinations previously scheduled for Visit 8 were moved to Visit 4 in order to assure that steady state PK-PD was obtained in all study patients. The pregnancy urine testing was moved from Visit 3 to Visit 2 to ensure that all patients were tested prior to first dose. A pregnancy test was added to Visit 4 for the patients only completing Part A to insure that all patients were tested following repeated dosing. If most of the remaining patients declined participation in Part B, the patients in the EAS were prone to selection bias. Results of statistical tests conducted under such circumstances were not generalisable and hence only descriptive statistics were used. The minimum number of days between Visit 1 and Visit 2 was increased from 7 days to 14 days to ensure that 30 days elapsed between Visit 1 and Visit 4. This ensured that the volume of blood to be drawn within 30 days was not higher than 3% of blood volume. The visit window between the treatment visits was shortened to better fit the visit schedule and to avoid requiring patients to take home large volumes of study drug.</p>

05 March 2015	CSP Amendment 2: AstraZeneca Study Team initiated the amendment to clarify wording, decrease patient burden, and to incorporate requests from the PDCO of the European Medicines Agency and the MHRA. The following is a description of notable changes: Updated the secondary objective to include the PK properties of the active metabolite of ticagrelor. Re-worded some inclusion/exclusion criteria for clarification and consistency with other parts of the CSP. Stated that randomisation would take place 7 to 30 days after enrolment. Changed collection of haematology and clinical chemistry sample at Visit 4 to 2 hours post-dose. Shortened the PK and PRU sampling time for Visit 2 and Visit 3 as last measurement occurred at 6 hours post-dose and corrected the volume of blood collection for patients with a weight of 16 to 21 kg. Confirmed that Visit 5 and Visit 7 could optionally be performed as telephone contacts rather than centre visits if the PI deemed this acceptable. Updated the criteria for interruption or discontinuation of study drug. Stated that laboratory testing performed prior to enrolment as part of usual clinical care did not need to be repeated as long as the values were obtained no more than 30 days prior to Visit 2. Added a new section specify ECG parameters collected for the study. Stated that NSAIDs could not be administered more frequently than 3 days per week during the study. Added a new section to clarify that any blood transfusion during the study will be recorded in the eCRF. Stated the maximum dose of ticagrelor in this study was 45 mg, regardless of the weight of a patient . Added pain assessment for SCD pain for children aged 2 to <4 years. FLACC form and instructions for completion of the form were added. This was studied as exploratory objectives. Added description of how PD (VerifyNow P2Y12) samples were collected and handled. Clarified that definition of VOC included medical intervention at short-stay unit.
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Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
08 September 2015	Analysis of the first 12 randomised patients showed that the exposure to ticagrelor was lower than predicted and the platelet inhibitory effect was also lower than intended. Protocol was therefore amended to increase to better characterise the PK-PD relationship for ticagrelor. Recruitment was halted as the CSP was amended.	01 June 2016

Notes:

## Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Whenever 99999999 is displayed in the End Point tables it indicates that data is missing for this cell. This is due to changes in protocol which modified the scheme for PRU measurements and concentration measurements of ticagrelor and AR-C124910XX.

Notes: