Clinical trial results:
A Multi-centre, Phase I, Open-label, Single-dose Study to Investigate Pharmacokinetics (PK) of Ticagrelor in Infants and Toddlers, Aged 0 to less than 24 Months, with Sickle Cell Disease (HESTIA4)

Summary

EudraCT number	2017-003641-14
Trial protocol	BE ES GB IT
Global end of trial date	07 May 2019

Results information

Result version number	v1 (current)
This version publication date	06 November 2019
First version publication date	06 November 2019

Trial information

Trial identification

Sponsor protocol code	D5136C00010

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03492931
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	950 Wind River Ln, Gaithersburg, MD, United States, 20878
Public contact	Global Clinical Lead, AstraZeneca, +1 3028851180, ClinicalTrialTransparency@astrazeneca.com
Scientific contact	Global Clinical Lead, AstraZeneca, +1 3028851180, ClinicalTrialTransparency@astrazeneca.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 May 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 May 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

D5136C00010 is part of a paediatric development programme and is the first study with ticagrelor in paediatric patients aged 0 months to <24 months with sickle cell disease (SCD) to characterise pharmacokinetic (PK) properties after single doses.

Protection of trial subjects:

This study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Council for Harmonisation/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 March 2018
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	Belgium: 3
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Kenya: 7
Country: Number of subjects enrolled	Lebanon: 7
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	United Kingdom: 2
Worldwide total number of subjects	21
EEA total number of subjects	7

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)	21
Children (2-11 years)	0

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

Subject disposition

Recruitment

Recruitment details:

Paediatric patients aged 0 to <24 months with SCD were recruited to this Phase I open-label, single-dose study at 8 study centres in Belgium, Italy, Kenya, Lebanon, Spain and the United Kingdom. The first patient started in March 2018 and the last patient completed in May 2019.

Pre-assignment

Screening details:

Patients were diagnosed with homozygous sickle cell anaemia or sickle beta-zero-thalassaemia and had a body weight of at least 5 kilograms (kg) at screening. Patients participating in this study were not withheld from any other standard of care treatments that may be used in SCD.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Ticagrelor 0.1 mg/kg: <6 months old

Arm description:

Patients in the age group <6 months old received a single oral dose of 0.1 milligrams per kg (mg/kg) ticagrelor.

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

Dosage and administration details:

A single oral 0.1 mg/kg dose of ticagrelor. Before administration, ticagrelor granules were constituted with 10 millilitres (mL) of purified water to form a homogenous suspension of 1 mg/mL ticagrelor.

Arm title	Ticagrelor 0.2 mg/kg: 6 to <12 months old

Arm description:

Patients in the age group 6 to <12 months old received a single oral dose of 0.2 mg/kg ticagrelor.

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

Dosage and administration details:

A single oral 0.2 mg/kg dose of ticagrelor. Before administration, ticagrelor granules were constituted with 10 mL of purified water to form a homogenous suspension of 1 mg/mL ticagrelor.

Arm title	Ticagrelor 0.2 mg/kg: 12 to <24 months old

Arm description:

Patients in the age group 12 to <24 months old received a single oral dose of 0.2 mg/kg ticagrelor.

Arm type	Experimental

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

Dosage and administration details:

A single oral 0.2 mg/kg dose of ticagrelor. Before administration, ticagrelor granules were constituted with 10 mL of purified water to form a homogenous suspension of 1 mg/mL ticagrelor.

Number of subjects in period 1	Ticagrelor 0.1 mg/kg: <6 months old	Ticagrelor 0.2 mg/kg: 6 to <12 months old	Ticagrelor 0.2 mg/kg: 12 to <24 months old
Started	2	6	13
Received ticagrelor	2	6	13
Completed	2	6	13

Baseline characteristics

Reporting groups	
Reporting group title	Ticagrelor 0.1 mg/kg: <6 months old
Reporting group description:	
Patients in the age group <6 months old received a single oral dose of 0.1 milligrams per kg (mg/kg) ticagrelor.	
Reporting group title	Ticagrelor 0.2 mg/kg: 6 to <12 months old
Reporting group description:	
Patients in the age group 6 to <12 months old received a single oral dose of 0.2 mg/kg ticagrelor.	
Reporting group title	Ticagrelor 0.2 mg/kg: 12 to <24 months old
Reporting group description:	
Patients in the age group 12 to <24 months old received a single oral dose of 0.2 mg/kg ticagrelor.	

Reporting group values	Ticagrelor 0.1 mg/kg: <6 months old	Ticagrelor 0.2 mg/kg: 6 to <12 months old	Ticagrelor 0.2 mg/kg: 12 to <24 months old
Number of subjects	2	6	13
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)	2	6	13
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: Months			
arithmetic mean	3.5	9.0	16.2
standard deviation	± 0.71	± 1.26	± 3.00
Sex: Female, Male Units: Subjects			
Female	1	4	5
Male	1	2	8
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	6	8
White	2	0	5
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB) Units: Subjects			

Hispanic or Latino	0	0	0
Not Hispanic or Latino	2	6	13
Unknown or Not Reported	0	0	0

Reporting group values	Total		
Number of subjects	21		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	21		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age Continuous Units: Months			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: Subjects			
Female	10		
Male	11		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0		
Asian	0		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	14		
White	7		
More than one race	0		
Unknown or Not Reported	0		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0		
Not Hispanic or Latino	21		
Unknown or Not Reported	0		

End points

End points reporting groups

Reporting group title	Ticagrelor 0.1 mg/kg: <6 months old
Reporting group description:	
Patients in the age group <6 months old received a single oral dose of 0.1 milligrams per kg (mg/kg) ticagrelor.	
Reporting group title	Ticagrelor 0.2 mg/kg: 6 to <12 months old
Reporting group description:	
Patients in the age group 6 to <12 months old received a single oral dose of 0.2 mg/kg ticagrelor.	
Reporting group title	Ticagrelor 0.2 mg/kg: 12 to <24 months old
Reporting group description:	
Patients in the age group 12 to <24 months old received a single oral dose of 0.2 mg/kg ticagrelor.	
Subject analysis set title	Ticagrelor 0.2 mg/kg: 6 to <24 months old
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients in the age group 6 to <24 months old received a single oral dose of 0.2 mg/kg ticagrelor.	
Subject analysis set title	All Patients
Subject analysis set type	Full analysis
Subject analysis set description:	
Patients received single oral doses of 0.1 mg/kg ticagrelor (<6 months old) or 0.2 mg/kg ticagrelor (6 to <24 months old).	

Primary: Ticagrelor Mean Observed Plasma Concentrations

End point title	Ticagrelor Mean Observed Plasma Concentrations[1][2]
End point description:	
Blood samples were taken up to 6 hours post-dose so that the number and volume of blood samples were compliant with European Ethical Considerations in a Paediatric Population 2008. The geometric mean observed plasma concentration of ticagrelor is presented for each timepoint of sampling after patients had received a single oral dose of ticagrelor. Data is presented for each of the 2 doses of ticagrelor as well as for all patients. The lower limit of quantification (LLOQ) of ticagrelor was 1.00 nanograms per millilitre (ng/mL). Data is presented for the PK analysis set which included all patients who received at least 1 dose of ticagrelor and provided at least 1 post-dose analysable plasma sample without any important protocol deviations or events that would exclude the patient. '(n=x,y,z)' indicates the number of patients analysed at each timepoint.	
End point type	Primary
End point timeframe:	
Blood samples were collected on Day 1 at 1, 2, 4 and 6 hours post-dose.	

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: No formal statistical comparisons were carried out for this study. All endpoints were evaluated using standard summary descriptive statistics.
[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data is presented for all patients in the baseline period, with data for patients in the arms 'Ticagrelor 0.2 mg/kg: 6 to <12 months old' and 'Ticagrelor 0.2 mg/kg: 12 to <24 months old' represented within the analysis set 'Ticagrelor 0.2 mg/kg: 6 to <24 months old'.

End point values	Ticagrelor 0.1 mg/kg: <6 months old	Ticagrelor 0.2 mg/kg: 6 to <24 months old	All Patients	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	2[3]	19	21	
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
1 hour post-dose (n=1,19,20)	99999999 (± 99999999)	18.51 (± 154.70)	18.59 (± 147.75)	
2 hours post-dose (n=2,19,21)	99999999 (± 99999999)	21.82 (± 127.79)	21.86 (± 118.47)	
4 hours post-dose (n=2,19,21)	99999999 (± 99999999)	16.54 (± 61.78)	16.12 (± 59.75)	
6 hours post-dose (n=2,18,20)	99999999 (± 99999999)	10.39 (± 60.68)	10.25 (± 58.23)	

Notes:

[3] - '9999999' indicates the data was not calculated due to the sample size.

Statistical analyses

No statistical analyses for this end point

Primary: Ticagrelor Maximum Observed Plasma Concentrations (Cmax)

End point title	Ticagrelor Maximum Observed Plasma Concentrations

End point description:

Blood samples were taken up to 6 hours post-dose so that the number and volume of blood samples were compliant with European Ethical Considerations in a Paediatric Population 2008. The geometric mean Cmax for ticagrelor is presented for each of the 2 doses of ticagrelor and for all patients. Data is presented for the PK analysis set which included all patients who received at least 1 dose of ticagrelor and provided at least 1 post-dose analysable plasma sample without any important protocol deviations or events that would exclude the patient.

End point type	Primary

End point timeframe:

Blood samples were collected on Day 1 at 1, 2, 4 and 6 hours post-dose.

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: No formal statistical comparisons were carried out for this study. All endpoints were evaluated using standard summary descriptive statistics.
[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data is presented for all patients in the baseline period, with data for patients in the arms 'Ticagrelor 0.2 mg/kg: 6 to <12 months old' and 'Ticagrelor 0.2 mg/kg: 12 to <24 months old' represented within the analysis set 'Ticagrelor 0.2 mg/kg: 6 to <24 months old'.

End point values	Ticagrelor 0.1 mg/kg: <6 months old	Ticagrelor 0.2 mg/kg: 6 to <24 months old	All Patients	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	2	19	21	
Units: ng/mL				
geometric mean (geometric coefficient of variation)	23.80 (± 23.78)	34.44 (± 74.75)	33.25 (± 71.67)	

Statistical analyses

No statistical analyses for this end point

Primary: Ticagrelor Area Under the Plasma Concentration-Time Curve from Zero to 6 Hours (AUC[0-6])

End point title	Ticagrelor Area Under the Plasma Concentration-Time Curve from Zero to 6 Hours (AUC[0-6])[6][7]

End point description:

Blood samples were taken up to 6 hours post-dose so that the number and volume of blood samples were compliant with European Ethical Considerations in a Paediatric Population 2008. The geometric mean AUC(0-6) for ticagrelor is presented for each of the 2 doses of ticagrelor and for all patients. Data is presented for the PK analysis set which included all patients who received at least 1 dose of ticagrelor and provided at least 1 post-dose analysable plasma sample without any important protocol deviations or events that would exclude the patient.

End point type	Primary

End point timeframe:

Blood samples were collected on Day 1 at 1, 2, 4 and 6 hours post-dose.

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: No formal statistical comparisons were carried out for this study. All endpoints were evaluated using standard summary descriptive statistics.
[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data is presented for all patients in the baseline period, with data for patients in the arms 'Ticagrelor 0.2 mg/kg: 6 to <12 months old' and 'Ticagrelor 0.2 mg/kg: 12 to <24 months old' represented within the analysis set 'Ticagrelor 0.2 mg/kg: 6 to <24 months old'.

End point values	Ticagrelor 0.1 mg/kg: <6 months old	Ticagrelor 0.2 mg/kg: 6 to <24 months old	All Patients	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	2	19	21	
Units: ng*hours/mL (ng*h/mL)				
geometric mean (geometric coefficient of variation)	87.22 (± 32.72)	112.39 (± 52.21)	109.71 (± 50.59)	

Statistical analyses

No statistical analyses for this end point

Secondary: Active Metabolite (AR-C124910XX) Mean Observed Plasma Concentrations

End point title	Active Metabolite (AR-C124910XX) Mean Observed Plasma Concentrations[8]

End point description:

Blood samples were taken up to 6 hours post-dose so that the number and volume of blood samples were compliant with
European Ethical Considerations in a Paediatric Population 2008. The geometric mean observed plasma concentration of AR-C124910XX is presented for each timepoint of sampling after patients had received a single oral dose of ticagrelor. Data is presented for each of the 2 doses of ticagrelor as well as for all patients. The LLOQ of AR-C124910XX was 2.50 ng/mL. Data is presented for the PK analysis set which included all patients who received at least 1 dose of ticagrelor and provided at least 1 post-dose analysable plasma sample
without any important protocol deviations or events that would exclude the patient. '(n=x,y,z)' indicates the number of patients analysed at each timepoint.

End point type	Secondary

End point timeframe:

Blood samples were collected on Day 1 at 1, 2, 4 and 6 hours post-dose.

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data is presented for all patients in the baseline period, with data for patients in the arms 'Ticagrelor 0.2 mg/kg: 6 to <12 months old' and 'Ticagrelor 0.2 mg/kg: 12 to <24 months old' represented within the analysis set 'Ticagrelor 0.2 mg/kg: 6 to <24 months old'.

End point values	Ticagrelor 0.1 mg/kg: <6 months old	Ticagrelor 0.2 mg/kg: 6 to <24 months old	All Patients	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	2[9]	19	21	
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
1 hour post-dose (n=1,19, 20)	99999999 (± 99999999)	4.65 (± 88.79)	4.70 (± 85.91)	
2 hours post-dose (n=2,19,21)	99999999 (± 99999999)	7.40 (± 81.31)	7.35 (± 76.39)	
4 hours post-dose (n=2,19,21)	99999999 (± 99999999)	7.33 (± 53.57)	7.16 (± 52.08)	
6 hours post-dose (n=2,18,20)	99999999 (± 99999999)	5.89 (± 49.02)	5.77 (± 47.77)	

Notes:

[9] - '99999999' indicates the data was not calculated due to the sample size.

Statistical analyses

No statistical analyses for this end point

Secondary: Active Metabolite (AR-C124910XX) Cmax

End point title	Active Metabolite (AR-C124910XX) Cmax[10]

End point description:

Blood samples were taken up to 6 hours post-dose so that the number and volume of blood samples were compliant with European Ethical Considerations in a Paediatric Population 2008. The geometric mean Cmax for AR-C124910XX is presented for each of the 2 doses of ticagrelor and for all patients. Data is presented for the PK analysis set which included all patients who received at least 1 dose of ticagrelor and provided at least 1 post-dose analysable plasma sample without any important protocol deviations or events that would exclude the patient.

End point type	Secondary

End point timeframe:

Blood samples were collected on Day 1 at 1, 2, 4 and 6 hours post-dose.

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data is presented for all patients in the baseline period, with data for patients in the arms 'Ticagrelor 0.2 mg/kg: 6 to <12 months old' and 'Ticagrelor 0.2 mg/kg: 12 to <24 months old' represented within the analysis set 'Ticagrelor 0.2 mg/kg: 6 to <24 months old'.

End point values	Ticagrelor 0.1 mg/kg: <6 months old	Ticagrelor 0.2 mg/kg: 6 to <24 months old	All Patients	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	2	19	21	
Units: ng/mL				
geometric mean (geometric coefficient of variation)	6.89 (± 22.55)	9.17 (± 61.25)	8.93 (± 58.76)	

Statistical analyses

No statistical analyses for this end point

Secondary: Active Metabolite (AR-C124910XX) AUC(0-6)

End point title	Active Metabolite (AR-C124910XX) AUC(0-6)[11]

End point description:

Blood samples were taken up to 6 hours post-dose so that the number and volume of blood samples were compliant with European Ethical Considerations in a Paediatric Population 2008. The geometric mean AUC(0-6) for AR-C124910XX is presented for each of the 2 doses of ticagrelor and for all patients. Data is presented for the PK analysis set which included all patients who received at least 1 dose of ticagrelor and provided at least 1 post-dose analysable plasma sample without any important protocol deviations or events that would exclude the patient.

End point type	Secondary

End point timeframe:

Blood samples were collected on Day 1 at 1, 2, 4 and 6 hours post-dose.

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data is presented for all patients in the baseline period, with data for patients in the arms 'Ticagrelor 0.2 mg/kg: 6 to <12 months old' and 'Ticagrelor 0.2 mg/kg: 12 to <24 months old' represented within the analysis set 'Ticagrelor 0.2 mg/kg: 6 to <24 months old'.

End point values	Ticagrelor 0.1 mg/kg: <6 months old	Ticagrelor 0.2 mg/kg: 6 to <24 months old	All Patients	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	2	19	21	
Units: ng*h/mL				
geometric mean (geometric coefficient of variation)	29.76 (± 22.84)	34.97 (± 58.67)	34.44 (± 55.80)	

Statistical analyses

No statistical analyses for this end point

Secondary: Observer Assessment of Acceptability and Palatability of Ticagrelor

End point title	Observer Assessment of Acceptability and Palatability of Ticagrelor

End point description:

An observer's assessment of the patient's behaviour was performed directly as the patient was administered the single dose of ticagrelor on Day 1. The patient's willingness to swallow was recorded as one of the following: swallowed without a problem, some resistance but did swallow, spat out some/all of medication, vomited up the medication. The patient's negative response to palatability was assessed and the following outcomes were recorded: turned head to reject intake of the medication, twisted face or mouth in an expression of displeasure or other negative response. Data is presented for the safety analysis set which included all patients who received at least 1 single dose of ticagrelor, and for whom any post-dose data was available.

End point type	Secondary

End point timeframe:

Day 1 (directly after treatment administration)

End point values	Ticagrelor 0.1 mg/kg: <6 months old	Ticagrelor 0.2 mg/kg: 6 to <12 months old	Ticagrelor 0.2 mg/kg: 12 to <24 months old	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	6	13	
Units: Participants				
Swallowed without problem	2	5	10	
Some resistance but did swallow	0	0	3	
Spat out some/all	0	1	0	
Vomited up medication	0	0	0	
Turned head to reject intake	0	1	3	
Twisted face/mouth in displeasure	0	1	0	
Other negative response	0	0	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On-treatment adverse events (AEs) were collected from Day 1 up to Day 8 (approximately 1 week).

Adverse event reporting additional description:

AEs are presented for the safety analysis set which included all patients who received at least 1 single dose of ticagrelor, and for whom any post-dose data was available.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Ticagrelor 0.1 mg/kg: <6 months old

Reporting group description:

Patients in the age group <6 months old received a single oral dose of 0.1 mg/kg ticagrelor.

Reporting group title	Ticagrelor 0.2 mg/kg: 12 to <24 months old

Reporting group description:

Patients in the age group 12 to <24 months old received a single oral dose of 0.2 mg/kg ticagrelor.

Reporting group title	Ticagrelor 0.2 mg/kg: 6 to <12 months old

Reporting group description:

Patients in the age group 6 to <12 months old received a single oral dose of 0.2 mg/kg ticagrelor.

Serious adverse events	Ticagrelor 0.1 mg/kg: <6 months old	Ticagrelor 0.2 mg/kg: 12 to <24 months old	Ticagrelor 0.2 mg/kg: 6 to <12 months old
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 2 (0.00%)	1 / 13 (7.69%)	0 / 6 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Infections and infestations			
Bronchiolitis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 13 (7.69%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Ticagrelor 0.1 mg/kg: <6 months old	Ticagrelor 0.2 mg/kg: 12 to <24 months old	Ticagrelor 0.2 mg/kg: 6 to <12 months old
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 2 (0.00%)	3 / 13 (23.08%)	3 / 6 (50.00%)

Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 2 (0.00%)	1 / 13 (7.69%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Injury			
subjects affected / exposed	0 / 2 (0.00%)	1 / 13 (7.69%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Pallor			
subjects affected / exposed	0 / 2 (0.00%)	1 / 13 (7.69%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Blood and lymphatic system disorders			
Sickle cell anaemia with crisis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 13 (7.69%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Splenomegaly			
subjects affected / exposed	0 / 2 (0.00%)	1 / 13 (7.69%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Nasal congestion			
subjects affected / exposed	0 / 2 (0.00%)	1 / 13 (7.69%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 2 (0.00%)	1 / 13 (7.69%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 13 (7.69%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 2 (0.00%)	0 / 13 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 January 2018	- The synopsis (Investigational product, dosage and mode of administration) and sections of the protocol relating to the rationale for study design, doses, and control groups, and interim analysis were changed to declare that any dose adjustments would require a protocol amendment and regulatory approval. The prediction level of reduction in platelet reactivity unit text was amended. These updates reflected the Medicines and Healthcare products Regulatory Agency request.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

For the endpoint 'Ticagrelor Mean Plasma Concentrations', '9999999' indicates the data was not calculable for the sample size.

Notes: