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

Summary

EudraCT number	2017-002421-38
Trial protocol	GB ES BE GR IT
Global end of trial date	13 August 2020

Results information

Result version number	v2 (current)
This version publication date	09 May 2021
First version publication date	22 February 2021
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	D5136C00009

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03615924
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	Karlebyhusentren, B674 Astraallen, Södertälje, Sweden, SE-151 85
Public contact	Global Clinical Lead, AstraZeneca, +1 877-240-9479, information.center@astrazeneca.com
Scientific contact	Global Clinical Lead, AstraZeneca, +1 877-240-9479, information.center@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	23 September 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 August 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To compare the effect of ticagrelor versus (Vs) placebo for the reduction of vaso-occlusive crisis (VOC), which is the composite of painful crisis and/or acute chest syndrome (ACS), in paediatric participants with sickle cell disease (SCD).

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 (including those for conducting trials with paediatric populations) and the AstraZeneca policy on Bioethics. The data monitoring committee was responsible for safeguarding the interests of the participants in the study by assessing the safety of the intervention during the study, and for reviewing the overall conduct of the clinical study.

Background therapy:

Participants were to receive standard of care for SCD adjusted to the individual participant at the discretion of the Investigator. If a participant was treated with hydroxyurea, the weight-adjusted dose had to be stable for 3 months before enrolment.

Evidence for comparator: -

Actual start date of recruitment	26 September 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Kenya: 55
Country: Number of subjects enrolled	India: 30
Country: Number of subjects enrolled	Uganda: 26
Country: Number of subjects enrolled	Egypt: 18
Country: Number of subjects enrolled	Lebanon: 15
Country: Number of subjects enrolled	Ghana: 5
Country: Number of subjects enrolled	South Africa: 2
Country: Number of subjects enrolled	Tanzania, United Republic of: 1
Country: Number of subjects enrolled	United Kingdom: 7
Country: Number of subjects enrolled	Turkey: 6
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Greece: 1
Country: Number of subjects enrolled	Brazil: 8

Country: Number of subjects enrolled	United States: 8
Worldwide total number of subjects	193
EEA total number of subjects	12

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)	115
Adolescents (12-17 years)	78
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This Phase III study was conducted in paediatric participants with SCD at 53 sites in 16 countries between 26 September 2018 and 13 August 2020. Paediatric participants who experienced at least two VOC events in the past 12 months prior to screening and who fulfilled the eligibility criteria were enrolled.

Pre-assignment

Screening details:

Participants randomized to ticagrelor received doses based on weight band (at randomization): ≥12 to ≤24 kilogram (kg)=15 milligram (mg), >24 to ≤48 kg=30 mg, >48 kg=45 mg. A total of 193 participants were randomized in this study.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Monitor, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Ticagrelor 15/30/45 mg bd

Arm description:

Paediatric participants received ticagrelor 15 mg, or 30 mg, or 45 mg tablets orally twice daily (bd) for at least 12 months but no longer than 24 months. The dose of ticagrelor was determined based on body weight at randomization:
• Participants with a body weight ≥12 to ≤24 kg received 1 tablet of ticagrelor 15 mg (1x15 mg) bd.
• Participants with a body weight >24 to ≤48 kg received 2 tablets of ticagrelor 15 mg (2x15 mg) bd.
• Participants with a body weight >48 kg received 3 tablets of ticagrelor 15 mg (3x15 mg) bd.

Arm type	Experimental
Investigational medicinal product name	Ticagrelor
Investigational medicinal product code	
Other name	BRILINTA™, BRILIQUE™
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants with a body weight ≥12 to ≤24 kg: 1 tablet of ticagrelor 15 mg orally bd.
Participants with a body weight >24 to ≤48 kg: 2 tablets of ticagrelor 15 mg orally bd.
Participants with a body weight >48 kg: 3 tablets of ticagrelor 15 mg orally bd.

Arm title	Placebo

Arm description:

Paediatric participants received placebo matching with ticagrelor 15 mg, or 30 mg, or 45 mg tablets orally bd for at least 12 months but no longer than 24 months. The number of placebo tablets was determined based on body weight at randomization:
• Participants with a body weight ≥12 to ≤24 kg received 1 tablet of placebo matching with ticagrelor 15 mg bd.
• Participants with a body weight >24 to ≤48 kg received 2 tablets of placebo matching with ticagrelor 30 mg bd.
• Participants with a body weight >48 kg received 3 tablets of placebo matching with ticagrelor 45 mg bd.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants with a body weight ≥12 to ≤24 kg: 1 tablet of placebo matching with ticagrelor 15 mg orally bd.
Participants with a body weight >24 to ≤48 kg: 2 tablets of placebo matching with ticagrelor 30 mg orally bd.
Participants with a body weight >48 kg: 3 tablets of placebo matching with ticagrelor 45 mg orally bd.

Number of subjects in period 1	Ticagrelor 15/30/45 mg bd	Placebo
Started	101	92
Received treatment	101	92
Completed	0	0
Not completed	101	92
Adverse event, serious fatal	3	1
Randomized in error	1	-
Study termination by Sponsor	94	86
Consent withdrawn by subject	2	5
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Ticagrelor 15/30/45 mg bd

Reporting group description:

Paediatric participants received ticagrelor 15 mg, or 30 mg, or 45 mg tablets orally twice daily (bd) for at least 12 months but no longer than 24 months. The dose of ticagrelor was determined based on body weight at randomization:
• Participants with a body weight ≥12 to ≤24 kg received 1 tablet of ticagrelor 15 mg (1x15 mg) bd.
• Participants with a body weight >24 to ≤48 kg received 2 tablets of ticagrelor 15 mg (2x15 mg) bd.
• Participants with a body weight >48 kg received 3 tablets of ticagrelor 15 mg (3x15 mg) bd.

Reporting group title	Placebo

Reporting group description:

Paediatric participants received placebo matching with ticagrelor 15 mg, or 30 mg, or 45 mg tablets orally bd for at least 12 months but no longer than 24 months. The number of placebo tablets was determined based on body weight at randomization:
• Participants with a body weight ≥12 to ≤24 kg received 1 tablet of placebo matching with ticagrelor 15 mg bd.
• Participants with a body weight >24 to ≤48 kg received 2 tablets of placebo matching with ticagrelor 30 mg bd.
• Participants with a body weight >48 kg received 3 tablets of placebo matching with ticagrelor 45 mg bd.

Reporting group values	Ticagrelor 15/30/45 mg bd	Placebo	Total
Number of subjects	101	92	193
Age Categorical Units: participants			
≥2 to <12 years	61	54	115
>=12 to <18 years	40	38	78
Age Continuous Units: years			
arithmetic mean	10.40	10.12	
standard deviation	± 4.128	± 3.799	-
Sex: Female, Male Units: participants			
Female	48	43	91
Male	53	49	102
Race/Ethnicity, Customized Units: Subjects			
White	25	21	46
Black or African American	60	51	111
Asian	15	15	30
Other	1	5	6
Race/Ethnicity, Customized Units: Subjects			
Hispanic or Latino	7	5	12
Not Hispanic or Latino	94	87	181

End points

End points reporting groups

Reporting group title	Ticagrelor 15/30/45 mg bd

Reporting group description:

Paediatric participants received ticagrelor 15 mg, or 30 mg, or 45 mg tablets orally twice daily (bd) for at least 12 months but no longer than 24 months. The dose of ticagrelor was determined based on body weight at randomization:
• Participants with a body weight ≥12 to ≤24 kg received 1 tablet of ticagrelor 15 mg (1x15 mg) bd.
• Participants with a body weight >24 to ≤48 kg received 2 tablets of ticagrelor 15 mg (2x15 mg) bd.
• Participants with a body weight >48 kg received 3 tablets of ticagrelor 15 mg (3x15 mg) bd.

Reporting group title	Placebo

Reporting group description:

Paediatric participants received placebo matching with ticagrelor 15 mg, or 30 mg, or 45 mg tablets orally bd for at least 12 months but no longer than 24 months. The number of placebo tablets was determined based on body weight at randomization:
• Participants with a body weight ≥12 to ≤24 kg received 1 tablet of placebo matching with ticagrelor 15 mg bd.
• Participants with a body weight >24 to ≤48 kg received 2 tablets of placebo matching with ticagrelor 30 mg bd.
• Participants with a body weight >48 kg received 3 tablets of placebo matching with ticagrelor 45 mg bd.

Primary: Number of Vaso-Occlusive Crisis Events

End point title	Number of Vaso-Occlusive Crisis Events

End point description:

A VOC is the composite of a painful crisis and/or an acute chest syndrome (ACS) event. The number of VOC events is defined as the count of VOC events experienced by a participant throughout the treatment period. The FAS included all randomized participants regardless of treatment received.

End point type	Primary

End point timeframe:

From randomization (Day 0) up to end of study (EOS) visit or date of premature study discontinuation, up to approximately 20 months

End point values	Ticagrelor 15/30/45 mg bd	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101	92		
Units: VOC events	249	202		

Statistical analyses

Statistical analysis title	Treatment comparison: Ticagrelor Vs Placebo

Statistical analysis description:

Incidence rates, incidence rate ratios, and p-values are from a negative binomial model analysis, with treatment group and baseline hydroxyurea use included in the model as covariates.

Comparison groups	Ticagrelor 15/30/45 mg bd v Placebo

Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7597
Method	Negative binomial model
Parameter estimate	Incidence rate ratio
Point estimate	1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.5

Secondary: Number of Painful Crisis Events

End point title	Number of Painful Crisis Events

End point description:

A painful crisis is an onset or worsening of pain that lasts at least 2 hours, for which there is no explanation other than vaso-occlusion and which requires therapy with oral or parenteral opioids, parenteral non-steroidal anti-inflammatory drugs, or other analgesics prescribed by a healthcare provider in a medical setting (such as a hospital, clinic or emergency room visit) or at home. Events with an onset date <=7 days of the previous event onset date are not counted as new events. The FAS included all randomized participants regardless of treatment received.

End point type	Secondary

End point timeframe:

From randomization (Day 0) up to EOS visit or date of premature study discontinuation, up to approximately 20 months

End point values	Ticagrelor 15/30/45 mg bd	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101	92		
Units: painful crisis events	248	209		

Statistical analyses

Statistical analysis title	Treatment comparison: Ticagrelor Vs Placebo

Statistical analysis description:

Incidence rates, incidence rate ratios, and p-values are from a negative binomial model analysis, with treatment group and baseline hydroxyurea use included in the model as covariates.

Comparison groups	Ticagrelor 15/30/45 mg bd v Placebo

Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9037
Method	Negative binomial model
Parameter estimate	Incidence rate ratio
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	1.45

Secondary: Number of Acute Chest Syndrome Events

End point title	Number of Acute Chest Syndrome Events

End point description:

The ACS is an acute illness characterized by fever and/or respiratory symptoms, accompanied by a new pulmonary infiltrate on a chest X-ray. Events with an onset date <=7 days of the previous event onset date are not counted as new events. The FAS included all randomized participants regardless of treatment received.

End point type	Secondary

End point timeframe:

From randomization (Day 0) up to EOS visit or date of premature study discontinuation, up to approximately 20 months

End point values	Ticagrelor 15/30/45 mg bd	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101	92		
Units: ACS events	6	6		

Statistical analyses

Statistical analysis title	Treatment comparison: Ticagrelor Vs Placebo

Statistical analysis description:

Incidence rates, incidence rate ratios, and p-values are from a negative binomial model analysis, with treatment group and baseline hydroxyurea use included in the model as covariates.

Comparison groups	Ticagrelor 15/30/45 mg bd v Placebo
Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7136
Method	Negative binomial model
Parameter estimate	Incidence rate ratio
Point estimate	0.76

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.17
upper limit	3.3

Secondary: Duration of Painful Crises

End point title	Duration of Painful Crises

End point description:

The duration of painful crises is defined as the sum of the duration of painful crises experienced by a participant over the defined treatment period. If two or more events have overlapping durations, the overlapping days were counted only once. The FAS included all randomized participants regardless of treatment received.

End point type	Secondary

End point timeframe:

From randomization (Day 0) up to EOS visit or date of premature study discontinuation, up to approximately 20 months

End point values	Ticagrelor 15/30/45 mg bd	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101	92		
Units: days	1476	1441		

Statistical analyses

Statistical analysis title	Treatment comparison: Ticagrelor Vs Placebo

Statistical analysis description:

Incidence rates, incidence rate ratios, and p-values are from a negative binomial model analysis, with treatment group and baseline hydroxyurea use included in the model as covariates.

Comparison groups	Ticagrelor 15/30/45 mg bd v Placebo
Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.497
Method	Negative binomial model
Parameter estimate	Incidence rate ratio
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	1.4

Secondary: Number of Vaso-Occlusive Crisis Events Requiring Hospitalization or Emergency Department Visits

End point title	Number of Vaso-Occlusive Crisis Events Requiring Hospitalization or Emergency Department Visits

End point description:

The number of VOC events requiring hospitalization or emergency department visits is defined as the count of VOC events experienced by a participant over the treatment period, for which the primary setting for VOC treatment was in-patient hospitalization or emergency department. Events with an onset date <=7 days of the previous event onset date are not counted as new events. The FAS included all randomized participants regardless of treatment received.

End point type	Secondary

End point timeframe:

From randomization (Day 0) up to EOS visit or date of premature study discontinuation, up to approximately 20 months

End point values	Ticagrelor 15/30/45 mg bd	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101	92		
Units: VOC events requiring hospitalization	87	51		

Statistical analyses

Statistical analysis title	Treatment comparison: Ticagrelor Vs Placebo

Statistical analysis description:

Incidence rates, incidence rate ratios, and p-values are from a negative binomial model analysis, with treatment group and baseline hydroxyurea use included in the model as covariates.

Comparison groups	Ticagrelor 15/30/45 mg bd v Placebo
Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1636
Method	Negative binomial model
Parameter estimate	Incidence rate ratio
Point estimate	1.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	2.36

Secondary: Number of Days Hospitalized for Vaso-Occlusive Crisis Events

End point title	Number of Days Hospitalized for Vaso-Occlusive Crisis Events

End point description:

The number of days hospitalized for all individual VOC events experienced by a participant during the treatment period is defined as the sum of the duration of all individual hospitalizations (taking into account potential overlapping hospitalization days of VOC components) during VOC events experienced by a participant over the treatment period for which the primary setting for VOC treatment was in-patient hospitalization. The FAS included all randomized participants regardless of treatment received.

End point type	Secondary

End point timeframe:

From randomization (Day 0) up to EOS visit or date of premature study discontinuation, up to approximately 20 months

End point values	Ticagrelor 15/30/45 mg bd	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101	92		
Units: days	526	256		

Statistical analyses

Statistical analysis title	Treatment comparison: Ticagrelor Vs Placebo

Statistical analysis description:

Incidence rates, incidence rate ratios, and p-values are from a negative binomial model analysis, with treatment group and baseline hydroxyurea use included in the model as covariates.

Comparison groups	Ticagrelor 15/30/45 mg bd v Placebo
Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2011
Method	Negative binomial model
Parameter estimate	Incidence rate ratio
Point estimate	1.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	3.75

Secondary: Number of Acute Sickle Cell Disease Complications

End point title	Number of Acute Sickle Cell Disease Complications

End point description:

The number of acute SCD complications is defined as the count of all individual acute SCD complications experienced by a participant over the treatment period. Acute SCD complications are defined as any one or more of the following individual complications: Transient ischaemic attack/ischaemic stroke, hepatic sequestration, splenic sequestration, priapism, and dactylitis. The FAS included all randomized

participants regardless of treatment received.

End point type	Secondary

End point timeframe:

From randomization (Day 0) up to EOS visit or date of premature study discontinuation, up to approximately 20 months

End point values	Ticagrelor 15/30/45 mg bd	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101	92		
Units: acute SCD complications	6	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Days Hospitalized for Acute Sickle Cell Disease Complications

End point title	Number of Days Hospitalized for Acute Sickle Cell Disease Complications

End point description:

The number of days hospitalized for acute SCD complications is defined as the sum of the duration of all individual hospitalizations (taking into account potential overlapping hospitalization days) due to acute SCD complications experienced by a participant over the treatment period, for which hospitalization was reported. The FAS included all randomized participants regardless of treatment received. Here, 9999 = Upper limit of confidence interval was not calculable due to 0 events in Ticagrelor 15/30/45 mg bd reporting group.

End point type	Secondary

End point timeframe:

From randomization (Day 0) up to EOS visit or date of premature study discontinuation, up to approximately 20 months

End point values	Ticagrelor 15/30/45 mg bd	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101	92		
Units: days	0	6		

Statistical analyses

Statistical analysis title	Treatment comparison: Ticagrelor Vs Placebo

Statistical analysis description:

Incidence rates, incidence rate ratios, and p-values are from a negative binomial model analysis, with treatment group and baseline hydroxyurea use included in the model as covariates.

Comparison groups	Ticagrelor 15/30/45 mg bd v Placebo
Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.994
Method	Negative binomial model
Parameter estimate	Incidence rate ratio
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	9999

Secondary: Number of Sickle Cell-Related Red Blood Cell (RBC) Transfusions

End point title	Number of Sickle Cell-Related Red Blood Cell (RBC) Transfusions

End point description:

The number of participants with at least one sickle cell-related RBC transfusion reported. Adverse events resulting in the need for RBC transfusions were captured prior to database lock to determine if the transfusion was sickle cell-related or not. The FAS included all randomized participants regardless of treatment received.

End point type	Secondary

End point timeframe:

From randomization (Day 0) up to EOS visit or date of premature study discontinuation, up to approximately 20 months

End point values	Ticagrelor 15/30/45 mg bd	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101	92		
Units: RBC transfusions	39	49		

Statistical analyses

Statistical analysis title	Treatment comparison: Ticagrelor Vs Placebo

Statistical analysis description:

Incidence rates, incidence rate ratios, and p-values are from a negative binomial model analysis, with treatment group and baseline hydroxyurea use included in the model as covariates.

Comparison groups	Ticagrelor 15/30/45 mg bd v Placebo

Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4822
Method	Negative binomial model
Parameter estimate	Incidence rate ratio
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.38
upper limit	1.58

Secondary: Health-Related Quality of Life Total Score Using the Paediatric Quality of Life Inventory (PedsQL) Sickle Cell Disease Module

End point title	Health-Related Quality of Life Total Score Using the Paediatric Quality of Life Inventory (PedsQL) Sickle Cell Disease Module

End point description:

The PedsQL SCD module instrument developed using a 5-point Likert scale (where 0= never and 4= almost always) for the participant self-report forms for ages ≥5 to <8 years, ≥8 to <13 years, and ≥13 to ≤18 years and the caregiver proxy-report form specific for ≥2 to <5 years was used. The PedsQL SCD module measures problems in the following categories:
• Pain: 3 sub-scales
• Worry: 2 sub-scales
• Emotions: 1 sub-scale
• Treatment: 1 sub-scale
• Communication: 2 sub-scales
• Total score
PedsQL SCD module items were reverse-scored and linearly transformed to a 0 to 100 scale (0= 100, 1= 75, 2= 50, 3= 25, 4= 0) so that higher scores indicate better quality of life. Baseline values are closest observation prior to and including randomization visit. The FAS population. Here, n= number of participants analyzed at specific time point; 9999= Standard deviation could not be calculated as only 1 participant had analyzable data; 99999= No participants were analyzed at that specific time point.

End point type	Secondary

End point timeframe:

For ages ≥2 to <5 years and ≥5 to <8 years: Baseline (observation prior to and including the randomization visit) and Months 6, and 12;
For ages ≥8 to <13 years and ≥13 to ≤18 years: Baseline and Months 6, 12, and 18

End point values	Ticagrelor 15/30/45 mg bd	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101	92		
Units: score on a scale				
arithmetic mean (standard deviation)				
>=2 to <5 years: Baseline (n=5,10)	88.81 (± 14.107)	67.02 (± 20.041)		
>=2 to <5 years: Month 6 (n=6,10)	80.75 (± 20.779)	81.37 (± 14.125)		
>=2 to <5 years: Month 12 (n=0,1)	99999 (± 99999)	88.10 (± 9999)		

>=5 to <8 years: Baseline (n=24,14)	75.05 (± 20.147)	74.04 (± 21.646)		
>=5 to <8 years: Month 6 (n=23,14)	83.04 (± 15.332)	84.91 (± 18.117)		
>=5 to <8 years: Month 12 (n=2,1)	65.63 (± 48.614)	97.50 (± 9999)		
>=8 to <13 years: Baseline (n=31,46)	62.35 (± 24.725)	67.98 (± 24.338)		
>=8 to <13 years: Month 6 (n=28,43)	76.52 (± 17.189)	75.76 (± 21.749)		
>=8 to <13 years: Month 12 (n=6,7)	83.20 (± 13.479)	64.12 (± 27.253)		
>=8 to <13 years: Month 18 (n=1,0)	86.05 (± 9999)	99999 (± 99999)		
>=13 to <=18 years: Baseline (n=37,22)	64.45 (± 18.746)	60.81 (± 24.979)		
>=13 to <=18 years: Month 6 (n=36,20)	68.13 (± 16.811)	74.42 (± 19.146)		
>=13 to <=18 years: Month 12 (n=9,5)	63.05 (± 19.810)	73.26 (± 22.589)		
>=13 to <=18 years: Month 18 (n=1,0)	65.12 (± 9999)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Fatigue Total Score Using Paediatric Quality of Life Inventory Multidimensional Fatigue Scale

End point title	Fatigue Total Score Using Paediatric Quality of Life Inventory Multidimensional Fatigue Scale

End point description:

The PedsQL multidimensional fatigue scale instrument developed using a 5-point Likert scale (where 0= never and 4= almost always) for participant self-report forms for ages ≥5 to <8 years, ≥8 to <13 years, and ≥13 to ≤18 years and caregiver proxy-report form specific for ≥2 to <5 years was used. PedsQL multidimensional fatigue scale measures problems in following categories:
• General (6 items)
• Sleep/rest (6 items)
• Cognitive fatigue (6 items)
• Total score (18 items)
PedsQL multidimensional fatigue scale items were reverse-scored and linearly transformed to a 0 to 100 scale (0= 100, 1= 75, 2= 50, 3= 25, 4= 0) so that higher scores indicate better quality of life. Baseline values are closest observation prior to and including randomization visit. FAS population. Here, n= number of participants analyzed at specific time point; 9999= Standard deviation could not be calculated as only 1 participant had analyzable data; 99999= No participants were analyzed at that specific time point.

End point type	Secondary

End point timeframe:

For ages ≥2 to <5 years and ≥5 to <8 years: Baseline (observation prior to and including the randomization visit) and Months 6, and 12;
For ages ≥8 to <13 years and ≥13 to ≤18 years: Baseline and Months 6, 12, and 18

End point values	Ticagrelor 15/30/45 mg bd	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101	92		
Units: score on a scale				
arithmetic mean (standard deviation)				
>=2 to <5 years: Baseline (n=5,10)	88.06 (± 16.304)	70.56 (± 23.220)		
>=2 to <5 years: Month 6 (n=5,10)	84.44 (± 15.541)	81.94 (± 22.775)		
>=2 to <5 years: Month 12 (n=0,1)	99999 (± 99999)	94.44 (± 9999)		
>=5 to <8 years: Baseline (n=25,14)	82.33 (± 11.450)	84.13 (± 16.139)		
>=5 to <8 years: Month 6 (n=22,14)	87.12 (± 10.553)	87.70 (± 16.076)		
>=5 to <8 years: Month 12 (n=2,1)	95.83 (± 5.893)	100.00 (± 9999)		
>=8 to <13 years: Baseline (n=30,44)	64.72 (± 26.779)	69.51 (± 25.261)		
>=8 to <13 years: Month 6 (n=28,43)	75.65 (± 18.571)	77.89 (± 22.283)		
>=8 to <13 years: Month 12 (n=6,7)	81.48 (± 17.866)	65.87 (± 25.495)		
>=8 to <13 years: Month 18 (n=1,0)	73.61 (± 9999)	99999 (± 99999)		
>=13 to <=18 years: Baseline (n=36,22)	68.06 (± 21.781)	67.17 (± 18.223)		
>=13 to <=18 years: Month 6 (n=35,20)	73.53 (± 19.138)	75.21 (± 14.913)		
>=13 to <=18 years: Month 12 (n=9,5)	67.13 (± 22.556)	60.28 (± 23.664)		
>=13 to <=18 years: Month 18 (n=1,0)	72.22 (± 9999)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Days of Absence From School or Work due to Sickle Cell Disease

End point title	Percentage of Days of Absence From School or Work due to Sickle Cell Disease

End point description:

For participants attending school/work at randomization, absence from school/work due to SCD was recorded weekly by the participant in the eDevice with the help of the caregiver if needed. The percentage of days absent from school/work due to SCD in the defined treatment period was calculated as follows:
Percentage of absent days = (total number of days reported)/(total number of questionnaires answered ×7). The FAS included all randomized participants regardless of treatment received. Only participants going to school or work at randomization are reported.

End point type	Secondary

End point timeframe:

From randomization (Day 0) up to EOS visit or date of premature study discontinuation, up to approximately 20 months

End point values	Ticagrelor 15/30/45 mg bd	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	82		
Units: percentage of days				
arithmetic mean (standard deviation)	5.24 (± 8.942)	4.24 (± 4.964)		

Statistical analyses

No statistical analyses for this end point

Secondary: Average Intensity of Worst Pain Daily During Vaso-Occlusive Crisis Events in Participants <5 years of Age

End point title	Average Intensity of Worst Pain Daily During Vaso-Occlusive Crisis Events in Participants <5 years of Age

End point description:

The Face, Legs, Activity, Cry, Consolability (FLACC) scale is caregiver-reported and used to assess pain daily during the VOC event for those participants <5 years of age as determined at randomization. Each of the 5 behaviours observed are assigned a score of 0, 1 or 2. The total FLACC score ranges between 0 and 10, with 0 representing "no pain" and 10 representing "very much pain". Lower score indicate better outcome. Worst pain ratings were collected once daily throughout the duration of the VOC event using an eDevice. The FAS included all randomized participants regardless of treatment received. Only participants <5 years of age who had experienced at least one individual VOC event and analyzed for pain assessment are reported.

End point type	Secondary

End point timeframe:

From randomization (Day 0) up to EOS visit or date of premature study discontinuation, up to approximately 20 months

End point values	Ticagrelor 15/30/45 mg bd	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	5		
Units: score on a scale				
arithmetic mean (standard deviation)	3.4 (± 2.51)	2.9 (± 1.99)		

Statistical analyses

No statistical analyses for this end point

Secondary: Average Intensity of Worst Pain Daily During Vaso-Occlusive Crisis Events in Participants ≥5 years of Age

End point title	Average Intensity of Worst Pain Daily During Vaso-Occlusive Crisis Events in Participants ≥5 years of Age

End point description:

The Faces Pain Scale-revised (FPS-R) was administered to assess pain daily during the VOC event by those participants aged ≥5 years as determined at randomization. The FPS-R consists of 6 faces and scoring ranges between 0 and 10 (with an increase in numeric value by 2), where 0 is "no pain" and 10 is "very much pain". Lower score indicate better outcome. Worst pain ratings were collected once daily throughout the duration of the VOC event using an eDevice. The FAS included all randomized participants regardless of treatment received. Only participants ≥5 years of age who had experienced at least one individual VOC event and analyzed for pain assessment are reported.

End point type	Secondary

End point timeframe:

From randomization (Day 0) up to EOS visit or date of premature study discontinuation, up to approximately 20 months

End point values	Ticagrelor 15/30/45 mg bd	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	40		
Units: score on a scale				
arithmetic mean (standard deviation)	4.5 (± 2.71)	4.1 (± 2.02)		

Statistical analyses

No statistical analyses for this end point

Secondary: Type of Analgesics Used by Participants During Vaso-Occlusive Crisis Events

End point title	Type of Analgesics Used by Participants During Vaso-Occlusive Crisis Events

End point description:

Analgesics use (opioid and non-opioid) during VOC events. The FAS included all randomized participants regardless of treatment received. Only participants who had at least one VOC and took an analgesic are reported.

End point type	Secondary

End point timeframe:

From randomization (Day 0) up to EOS visit or date of premature study discontinuation, up to approximately 20 months

End point values	Ticagrelor 15/30/45 mg bd	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	58		
Units: participants				
Opioids: Yes	46	22		
Opioids: No	57	50		

Non-opioids: Yes	69	57		
Non-opioids: No	14	7		

Statistical analyses

No statistical analyses for this end point

Secondary: Palatability of the Study Treatment Assessed by Study Medication Palatability Assessment (SMPA) in Participants ≤4 years of Age

End point title	Palatability of the Study Treatment Assessed by Study Medication Palatability Assessment (SMPA) in Participants ≤4 years of Age

End point description:

Response to palatability was assessed through the SMPA question "Was any behaviour observed when the study medication was given to this participant that would be indicative of a negative response to the palatability of the study medication?". This was presented as a binary outcome (that is, where "No" is no negative response and "Yes" is negative response). No negative response was considered as a positive outcome. Participants included in the Safety Analysis Set were analyzed for this endpoint. Here, n= number of participants ≤4 years of age who completed the assessment for study treatment palatability at the specific time point. NRP= Negative response to palatability.

End point type	Secondary

End point timeframe:

Baseline (randomization visit) and Month 6

End point values	Ticagrelor 15/30/45 mg bd	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	10		
Units: participants				
Baseline: Whole tablet; NRP - No (n=5,8)	5	8		
Baseline: Whole tablet; NRP - Yes (n=5,8)	0	0		
Baseline: Dispersed tablet; NRP - No (n=1,2)	1	2		
Baseline: Dispersed tablet; NRP - Yes (n=1,2)	0	0		
Month 6: Whole tablet; NRP - No (n=4,9)	4	9		
Month 6: Whole tablet; NRP - Yes (n=4,9)	0	0		
Month 6: Dispersed tablet; NRP - No (n=1,1)	1	1		
Month 6: Dispersed tablet; NRP - Yes (n=1,1)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Swallowability of the Study Treatment Assessed by Study Medication Palatability Assessment in Participants ≤4 years of Age

End point title	Swallowability of the Study Treatment Assessed by Study Medication Palatability Assessment in Participants ≤4 years of Age

End point description:

An observer's assessment of the participant's behaviour using the SMPA was performed for all participants taking the study treatment who are 2 to 4 years of age. Willingness to swallow was assessed and categorized as follows:
• Swallowed without a problem
• Some resistance but did swallow
• Spit out some/all of the medication
• Vomited up the medication.
The category "swallowed without a problem" was considered as positive outcome. The Safety Analysis Set included all participants who received at least 1 single dose of randomized study treatment, ticagrelor or placebo, and for whom any post-dose data were available. Here, n= number of participants ≤4 years of age who completed the assessment for study treatment swallowability at the specific time point. WT= Whole tablet and DT= Dispersed tablet.

End point type	Secondary

End point timeframe:

Baseline (randomization visit) and Month 6

End point values	Ticagrelor 15/30/45 mg bd	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	10		
Units: participants				
Baseline: WT; Swallow without problem (n=5,8)	5	8		
Baseline:WT;Some resistance but did swallow(n=5,8)	0	0		
Baseline: WT; Spit out some/all medication (n=5,8)	0	0		
Baseline: WT; Vomited up medication (n=5,8)	0	0		
Baseline: DT; Swallow without problem (n=1,2)	1	2		
Baseline:DT;Some resistance but did swallow(n=1,2)	0	0		
Baseline: DT; Spit out some/all medication (n=1,2)	0	0		
Baseline: DT; Vomited up medication (n=1,2)	0	0		
Month 6: WT; Swallow without problem (n=4,9)	4	9		
Month 6: WT;Some resistance but did swallow(n=4,9)	0	0		
Month 6: WT; Spit out some/all medication (n=4,9)	0	0		
Month 6: WT; Vomited up medication (n=4,9)	0	0		
Month 6: DT; Swallow without problem (n=1,1)	1	1		

Month 6: DT;Some resistance but did swallow(n=1,1)	0	0		
Month 6: DT; Spit out some/all medication (n=1,1)	0	0		
Month 6: DT; Vomited up medication (n=1,1)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Palatability of the Study Treatment Assessed by Facial Hedonic Scale (FHS) in Participants ≥5 years of Age

End point title	Palatability of the Study Treatment Assessed by Facial Hedonic Scale (FHS) in Participants ≥5 years of Age

End point description:

The FHS method was used for all participants taking the study treatment who are ≥5 years of age. The FHS consists of 5 faces with descriptions ranging from "Dislike very much" to "Like very much". The face with description "Like very much" was considered as positive outcome. The way in which the study treatment was taken, that is, whether the tablet is whole or dispersed, was captured. The Safety Analysis Set included all participants who received at least 1 single dose of randomized study treatment, ticagrelor or placebo, and for whom any post-dose data were available. Here, n= number of participants ≥5 years of age who completed the assessment for study treatment palatability at the specific time point.

End point type	Secondary

End point timeframe:

Baseline (randomization visit) and Month 6

End point values	Ticagrelor 15/30/45 mg bd	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	93	82		
Units: participants				
Baseline: Whole tablet; Dislike very much(n=92,80)	3	2		
Baseline: Whole tablet; Dislike a little (n=92,80)	4	2		
Baseline: Whole tablet; Not sure (n=92,80)	12	8		
Baseline: Whole tablet; Like a little (n=92,80)	25	23		
Baseline: Whole tablet; Like very much (n=92,80)	48	45		
Baseline:Dispersed tablet;Dislike very much(n=1,2)	0	0		
Baseline:Dispersed tablet; Dislike a little(n=1,2)	0	0		
Baseline: Dispersed tablet; Not sure (n=1,2)	1	0		
Baseline: Dispersed tablet; Like a little (n=1,2)	0	1		
Baseline: Dispersed tablet; Like very much (n=1,2)	0	1		

Month 6: Whole tablet; Dislike very much(n=83,74)	0	0		
Month 6: Whole tablet; Dislike a little (n=83,74)	5	3		
Month 6: Whole tablet; Not sure (n=83,74)	4	4		
Month 6: Whole tablet; Like a little (n=83,74)	30	20		
Month 6: Whole tablet; Like very much (n=83,74)	44	47		
Month 6: Dispersed tablet;Dislike very much(n=1,0)	0	0		
Month 6: Dispersed tablet; Dislike a little(n=1,0)	0	0		
Month 6: Dispersed tablet; Not sure (n=1,0)	1	0		
Month 6: Dispersed tablet; Like a little (n=1,0)	0	0		
Month 6: Dispersed tablet; Like very much (n=1,0)	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study treatment (Day 0) up to 7 days after last dose of study treatment, approximately 20 months.

Adverse event reporting additional description:

The Safety Analysis Set included all participants who received at least 1 single dose of randomized study treatment, ticagrelor or placebo, and for whom any post-dose data were available.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Ticagrelor 15/30/45 mg bd

Reporting group description:

Paediatric participants received ticagrelor 15 mg, or 30 mg, or 45 mg tablets orally bd for at least 12 months but no longer than 24 months. The dose of ticagrelor was determined based on body weight at randomization:
• Participants with a body weight ≥12 to ≤24 kg received 1 tablet of ticagrelor 15 mg (1x15 mg) bd.
• Participants with a body weight >24 to ≤48 kg received 2 tablets of ticagrelor 15 mg (2x15 mg) bd.
• Participants with a body weight >48 kg received 3 tablets of ticagrelor 15 mg (3x15 mg) bd.

Reporting group title	Placebo

Reporting group description:

Paediatric participants received placebo matching with ticagrelor 15 mg, or 30 mg, or 45 mg tablets orally bd for at least 12 months but no longer than 24 months. The number of placebo tablets was determined based on body weight at randomization:
• Participants with a body weight ≥12 to ≤24 kg received 1 tablet of placebo matching with ticagrelor 15 mg bd.
• Participants with a body weight >24 to ≤48 kg received 2 tablets of placebo matching with ticagrelor 30 mg bd.
• Participants with a body weight >48 kg received 3 tablets of placebo matching with ticagrelor 45 mg bd.

Serious adverse events	Ticagrelor 15/30/45 mg bd	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	44 / 100 (44.00%)	29 / 92 (31.52%)	
number of deaths (all causes)	3	1	
number of deaths resulting from adverse events	1	0	
Investigations			
Haemoglobin decreased			
subjects affected / exposed	0 / 100 (0.00%)	1 / 92 (1.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Jaw fracture			

subjects affected / exposed	1 / 100 (1.00%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post-traumatic pain			
subjects affected / exposed	1 / 100 (1.00%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	1 / 100 (1.00%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 100 (1.00%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 100 (6.00%)	7 / 92 (7.61%)	
occurrences causally related to treatment / all	0 / 7	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersplenism			
subjects affected / exposed	0 / 100 (0.00%)	3 / 92 (3.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 100 (0.00%)	1 / 92 (1.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sickle cell anaemia with crisis			
subjects affected / exposed	39 / 100 (39.00%)	24 / 92 (26.09%)	
occurrences causally related to treatment / all	0 / 75	0 / 41	
deaths causally related to treatment / all	0 / 0	0 / 1	
General disorders and administration			

site conditions			
Pyrexia			
subjects affected / exposed	2 / 100 (2.00%)	3 / 92 (3.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	1 / 100 (1.00%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 100 (0.00%)	1 / 92 (1.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	2 / 100 (2.00%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	1 / 100 (1.00%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchospasm			
subjects affected / exposed	1 / 100 (1.00%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Pemphigoid			
subjects affected / exposed	1 / 100 (1.00%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteonecrosis			

subjects affected / exposed	2 / 100 (2.00%)	1 / 92 (1.09%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Atypical pneumonia			
subjects affected / exposed	1 / 100 (1.00%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 100 (1.00%)	1 / 92 (1.09%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	3 / 100 (3.00%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 100 (0.00%)	1 / 92 (1.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 100 (0.00%)	2 / 92 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaria			
subjects affected / exposed	4 / 100 (4.00%)	1 / 92 (1.09%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis			
subjects affected / exposed	1 / 100 (1.00%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasopharyngitis			

subjects affected / exposed	1 / 100 (1.00%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngotonsillitis			
subjects affected / exposed	1 / 100 (1.00%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	4 / 100 (4.00%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 100 (0.00%)	1 / 92 (1.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection viral			
subjects affected / exposed	1 / 100 (1.00%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	6 / 100 (6.00%)	1 / 92 (1.09%)	
occurrences causally related to treatment / all	0 / 6	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 100 (1.00%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 100 (0.00%)	1 / 92 (1.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			

subjects affected / exposed	1 / 100 (1.00%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Ticagrelor 15/30/45 mg bd	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	82 / 100 (82.00%)	71 / 92 (77.17%)	
Nervous system disorders			
Headache			
subjects affected / exposed	24 / 100 (24.00%)	18 / 92 (19.57%)	
occurrences (all)	44	33	
Blood and lymphatic system disorders			
Leukocytosis			
subjects affected / exposed	6 / 100 (6.00%)	3 / 92 (3.26%)	
occurrences (all)	6	3	
Sickle cell anaemia with crisis			
subjects affected / exposed	60 / 100 (60.00%)	49 / 92 (53.26%)	
occurrences (all)	190	176	
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	7 / 100 (7.00%)	5 / 92 (5.43%)	
occurrences (all)	10	5	
Pain			
subjects affected / exposed	5 / 100 (5.00%)	8 / 92 (8.70%)	
occurrences (all)	18	9	
Pyrexia			
subjects affected / exposed	11 / 100 (11.00%)	10 / 92 (10.87%)	
occurrences (all)	15	12	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	15 / 100 (15.00%)	10 / 92 (10.87%)	
occurrences (all)	35	16	
Diarrhoea			

subjects affected / exposed	3 / 100 (3.00%)	5 / 92 (5.43%)	
occurrences (all)	5	5	
Vomiting			
subjects affected / exposed	6 / 100 (6.00%)	2 / 92 (2.17%)	
occurrences (all)	8	2	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	17 / 100 (17.00%)	7 / 92 (7.61%)	
occurrences (all)	22	11	
Epistaxis			
subjects affected / exposed	6 / 100 (6.00%)	8 / 92 (8.70%)	
occurrences (all)	9	13	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	14 / 100 (14.00%)	14 / 92 (15.22%)	
occurrences (all)	17	21	
Back pain			
subjects affected / exposed	21 / 100 (21.00%)	12 / 92 (13.04%)	
occurrences (all)	28	16	
Pain in extremity			
subjects affected / exposed	28 / 100 (28.00%)	23 / 92 (25.00%)	
occurrences (all)	58	39	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	6 / 100 (6.00%)	4 / 92 (4.35%)	
occurrences (all)	7	5	
Malaria			
subjects affected / exposed	12 / 100 (12.00%)	7 / 92 (7.61%)	
occurrences (all)	15	8	
Nasopharyngitis			
subjects affected / exposed	4 / 100 (4.00%)	6 / 92 (6.52%)	
occurrences (all)	7	7	
Upper respiratory tract infection			
subjects affected / exposed	19 / 100 (19.00%)	24 / 92 (26.09%)	
occurrences (all)	28	33	
Urinary tract infection			

subjects affected / exposed occurrences (all)	2 / 100 (2.00%) 3	5 / 92 (5.43%) 5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 April 2020	New subsection was added to allow modification of study conduct during COVID-19 pandemic including visits, Investigational Product administration, and procedures.

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.

AstraZeneca took the decision to terminate the study early, following a recommendation from the independent Data Monitoring Committee. This early termination was not considered to have had an impact on the robustness of the study results.

Notes: