Clinical trial results:
A randomised, double-blind, double-dummy, parallel-group, multicenter, phase IIb study to evaluate the effect of ticagrelor 10 mg and 45 mg bid versus placebo in reducing the number of days with pain in young adults with sickle cell disease.

Summary

EudraCT number	2014-005420-10
Trial protocol	GB
Global end of trial date	16 November 2016

Results information

Result version number	v1 (current)
This version publication date	14 October 2017
First version publication date	14 October 2017

Trial information

Trial identification

Sponsor protocol code	D5136C00008

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02482298
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	Pepparedsleden 1, S 431 83, Mölndal, Sweden,
Public contact	Brilinta Global Clinical Leader, AstraZeneca, +46 31 776 10 00,
Scientific contact	Brilinta Global Clinical Leader, AstraZeneca, +46 31 776 10 00,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
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	09 December 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 November 2016
Global end of trial reached?	Yes
Global end of trial date	16 November 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the efficacy of 2 different doses of ticagrelor versus placebo in reducing the number of days with pain due to sickle cell disease.

Protection of trial subjects:

A Study Steering Committee (SSC) and an Independent Expert Committee were used for this study. The SSC consisted of 4 active PIs who provided input in order to meet trial objectives. Monthly safety reports were provided in order to be aware of emerging safety results. The Independent Expert Committee consisted of 2 external members responsible for reviewing and commenting on the cumulative safety data.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 July 2015
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	Egypt: 21
Country: Number of subjects enrolled	Kenya: 33
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Lebanon: 7
Country: Number of subjects enrolled	United States: 6
Country: Number of subjects enrolled	Turkey: 13
Country: Number of subjects enrolled	United Kingdom: 6
Worldwide total number of subjects	87
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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	87
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 26 centers in 8 countries between 09 July 2015 and 16 November 2016.

Pre-assignment

Screening details:

The study duration was approximately 18 weeks, consisting of a screening period including a 4-week single-blind placebo treatment for baseline assessments, a 12-week double-blind randomised treatment period, and a 2-week follow-up period. A total of 194 patients were enrolled in the study. A total of 87 patients were randomized.

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

Arms

Are arms mutually exclusive?	Yes
Arm title	PLACEBO 10MG BID + PLACEBO 45MG BID

Arm description: -

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:

Matching placebo for ticagrelor 45 mg + matching placebo for ticagrelor 10 mg, 1 tablet bd given orally.

Arm title	TICAGRELOR 10MG BID + PLACEBO 45MG BID

Arm description: -

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

Dosage and administration details:

Ticagrelor 10 mg + matching placebo for ticagrelor 45 mg, 1 tablet bd given orally.

Arm title	TICAGRELOR 45MG BID + PLACEBO 10MG BID

Arm description: -

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

Dosage and administration details:

Ticagrelor 45 mg + matching placebo for ticagrelor 10 mg, 1 tablet bd given orally.

Number of subjects in period 1	PLACEBO 10MG BID + PLACEBO 45MG BID	TICAGRELOR 10MG BID + PLACEBO 45MG BID	TICAGRELOR 45MG BID + PLACEBO 10MG BID
Started	30	27	30
Completed	28	24	27
Not completed	2	3	3
Consent withdrawn by subject	2	1	2
Did Not Fulfill Randomization Criteria	-	1	-
Dev. of Study-Spec. Withdrawal Criteria	-	-	1
Lost to follow-up	-	1	-

Baseline characteristics

Reporting groups	
Reporting group title	PLACEBO 10MG BID + PLACEBO 45MG BID
Reporting group description: -	
Reporting group title	TICAGRELOR 10MG BID + PLACEBO 45MG BID
Reporting group description: -	
Reporting group title	TICAGRELOR 45MG BID + PLACEBO 10MG BID
Reporting group description: -	

Reporting group values	PLACEBO 10MG BID + PLACEBO 45MG BID	TICAGRELOR 10MG BID + PLACEBO 45MG BID	TICAGRELOR 45MG BID + PLACEBO 10MG BID
Number of subjects	30	27	30
Age categorical Units: Subjects			
Young adults (18-30 years)	30	27	30
Age Continuous Units: Years			
arithmetic mean	21.6	21.9	23.2
standard deviation	± 3.42	± 2.72	± 3.69
Gender, Male/Female Units: Subjects			
Female	16	15	16
Male	14	12	14
Race, Customized Units: Subjects			
Black Or African American	15	14	17
Other	0	1	0
White	15	12	13

Reporting group values	Total		
Number of subjects	87		
Age categorical Units: Subjects			
Young adults (18-30 years)	87		
Age Continuous Units: Years			
arithmetic mean			
standard deviation	-		
Gender, Male/Female Units: Subjects			
Female	47		
Male	40		
Race, Customized Units: Subjects			
Black Or African American	46		
Other	1		
White	40		

End points

End points reporting groups

Reporting group title	PLACEBO 10MG BID + PLACEBO 45MG BID
Reporting group description: -	
Reporting group title	TICAGRELOR 10MG BID + PLACEBO 45MG BID
Reporting group description: -	
Reporting group title	TICAGRELOR 45MG BID + PLACEBO 10MG BID
Reporting group description: -	

Primary: Change in proportion of days with pain due to sickle cell disease as measured by an eDiary

End point title	Change in proportion of days with pain due to sickle cell disease as measured by an eDiary
End point description:	
To investigate the efficacy of 2 different doses of ticagrelor versus placebo in reducing the number of days with pain due to sickle cell disease.	
End point type	Primary
End point timeframe:	
Baseline through Week 12	

End point values	PLACEBO 10MG BID + PLACEBO 45MG BID	TICAGRELOR 10MG BID + PLACEBO 45MG BID	TICAGRELOR 45MG BID + PLACEBO 10MG BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	30	27	30	
Units: Proportion of days with pain				
least squares mean (confidence interval 90%)	-0.1802 (-0.2673 to -0.0931)	-0.1352 (-0.226 to -0.0444)	-0.1001 (-0.1881 to -0.0121)	

Statistical analyses

Statistical analysis title	Change in proportion of days with pain
Comparison groups	PLACEBO 10MG BID + PLACEBO 45MG BID v TICAGRELOR 10MG BID + PLACEBO 45MG BID
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.045

Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.061
upper limit	0.151
Variability estimate	Standard error of the mean
Dispersion value	0.06367

Statistical analysis title	Change in proportion of days with pain
Comparison groups	PLACEBO 10MG BID + PLACEBO 45MG BID v TICAGRELOR 45MG BID + PLACEBO 10MG BID
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.0801
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.023
upper limit	0.1832
Variability estimate	Standard error of the mean
Dispersion value	0.06192

Secondary: Average of the daily worst pain values reported via eDiary	
End point title	Average of the daily worst pain values reported via eDiary
End point description:	
To determine the efficacy of 2 different doses of ticagrelor versus placebo in reducing the intensity of pain due to sickle cell disease.	
End point type	Secondary
End point timeframe:	
Baseline through Week 12	

End point values	PLACEBO 10MG BID + PLACEBO 45MG BID	TICAGRELOR 10MG BID + PLACEBO 45MG BID	TICAGRELOR 45MG BID + PLACEBO 10MG BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	30	27	30	
Units: Average daily worst pain rating				
arithmetic mean (standard deviation)	1.02 (± 1.106)	1.15 (± 1.547)	1.74 (± 2.277)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in proportion of days with analgesic use measured by an eDiary

End point title	Change in proportion of days with analgesic use measured by an eDiary

End point description:

To assess the efficacy of 2 different doses of ticagrelor versus placebo in reducing the use of analgesics by patients with sickle cell disease.

End point type	Secondary

End point timeframe:

Baseline through Week 12

End point values	PLACEBO 10MG BID + PLACEBO 45MG BID	TICAGRELOR 10MG BID + PLACEBO 45MG BID	TICAGRELOR 45MG BID + PLACEBO 10MG BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	30	27	30	
Units: Proportion of days with analgesic use				
least squares mean (confidence interval 90%)	-0.1991 (-0.2753 to -0.123)	-0.0799 (-0.159 to -0.0008)	-0.1016 (-0.1782 to -0.025)	

Statistical analyses

Statistical analysis title	Change in proportion of days of analgesic use
Comparison groups	PLACEBO 10MG BID + PLACEBO 45MG BID v TICAGRELOR 10MG BID + PLACEBO 45MG BID
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.1192
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.035
upper limit	0.2035

Variability estimate	Standard error of the mean
Dispersion value	0.05059

Statistical analysis title	Change in proportion of days of analgesic use
Comparison groups	PLACEBO 10MG BID + PLACEBO 45MG BID v TICAGRELOR 45MG BID + PLACEBO 10MG BID
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.0975
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.0155
upper limit	0.1795
Variability estimate	Standard error of the mean
Dispersion value	0.04923

Other pre-specified: Number of major bleeding or clinically relevant non-major bleeding events

End point title	Number of major bleeding or clinically relevant non-major bleeding events
End point description:	
To assess safety and tolerability of 2 different doses of ticagrelor versus placebo in patients with SCD	
End point type	Other pre-specified
End point timeframe:	
Baseline through Week 12	

End point values	PLACEBO 10MG BID + PLACEBO 45MG BID	TICAGRELOR 10MG BID + PLACEBO 45MG BID	TICAGRELOR 45MG BID + PLACEBO 10MG BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	30	26	30	
Units: Number of patients				
Total number of bleeding events	2	2	2	
Patients with any bleeding events	2	2	2	
Pts w/ any bleeding event requiring intervention	2	1	2	
Maximum severity of bleeding event: Minor	0	1	0	
Max sever. of bleed event: Clin-relevant nonmajor	2	1	2	

Maximum severity of bleeding event: Major	0	0	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Includes AEs with an onset date on or after the first dose of study medication during the treatment period and through the date of the last dose of study medication.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	PLACEBO 10MG BID + PLACEBO 45MG BID
Reporting group description: -	
Reporting group title	TICAGRELOR 10MG BID + PLACEBO 45MG BID
Reporting group description: -	
Reporting group title	TICAGRELOR 45MG BID + PLACEBO 10MG BID
Reporting group description: -	

Serious adverse events	PLACEBO 10MG BID + PLACEBO 45MG BID	TICAGRELOR 10MG BID + PLACEBO 45MG BID	TICAGRELOR 45MG BID + PLACEBO 10MG BID
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 30 (20.00%)	6 / 26 (23.08%)	5 / 30 (16.67%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Face injury			
subjects affected / exposed	1 / 30 (3.33%)	0 / 26 (0.00%)	0 / 30 (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
Vascular disorders			
Vascular occlusion			
subjects affected / exposed	1 / 30 (3.33%)	0 / 26 (0.00%)	0 / 30 (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
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 30 (0.00%)	1 / 26 (3.85%)	0 / 30 (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

Blood and lymphatic system disorders			
Reticulocytopenia			
subjects affected / exposed	0 / 30 (0.00%)	0 / 26 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sickle cell anaemia with crisis			
subjects affected / exposed	3 / 30 (10.00%)	5 / 26 (19.23%)	3 / 30 (10.00%)
occurrences causally related to treatment / all	0 / 7	0 / 6	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Local swelling			
subjects affected / exposed	1 / 30 (3.33%)	0 / 26 (0.00%)	0 / 30 (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
Hepatobiliary disorders			
Hepatic ischaemia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 26 (0.00%)	0 / 30 (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
Respiratory, thoracic and mediastinal disorders			
Acute chest syndrome			
subjects affected / exposed	0 / 30 (0.00%)	1 / 26 (3.85%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 26 (3.85%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	1 / 30 (3.33%)	0 / 26 (0.00%)	0 / 30 (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
Musculoskeletal chest pain			

subjects affected / exposed	1 / 30 (3.33%)	0 / 26 (0.00%)	0 / 30 (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
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 26 (0.00%)	0 / 30 (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
Gastroenteritis			
subjects affected / exposed	2 / 30 (6.67%)	0 / 26 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 30 (0.00%)	1 / 26 (3.85%)	0 / 30 (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: 5 %

Non-serious adverse events	PLACEBO 10MG BID + PLACEBO 45MG BID	TICAGRELOR 10MG BID + PLACEBO 45MG BID	TICAGRELOR 45MG BID + PLACEBO 10MG BID
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 30 (53.33%)	15 / 26 (57.69%)	20 / 30 (66.67%)
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 30 (26.67%)	11 / 26 (42.31%)	8 / 30 (26.67%)
occurrences (all)	23	25	28
Blood and lymphatic system disorders			
Sickle cell anaemia with crisis			
subjects affected / exposed	1 / 30 (3.33%)	1 / 26 (3.85%)	2 / 30 (6.67%)
occurrences (all)	3	1	3
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 30 (6.67%)	1 / 26 (3.85%)	2 / 30 (6.67%)
occurrences (all)	2	1	2
Non-cardiac chest pain			

subjects affected / exposed	3 / 30 (10.00%)	3 / 26 (11.54%)	4 / 30 (13.33%)
occurrences (all)	4	10	10
Pain			
subjects affected / exposed	1 / 30 (3.33%)	0 / 26 (0.00%)	2 / 30 (6.67%)
occurrences (all)	1	0	2
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 30 (10.00%)	5 / 26 (19.23%)	3 / 30 (10.00%)
occurrences (all)	4	11	3
Nausea			
subjects affected / exposed	1 / 30 (3.33%)	1 / 26 (3.85%)	3 / 30 (10.00%)
occurrences (all)	1	1	3
Toothache			
subjects affected / exposed	1 / 30 (3.33%)	2 / 26 (7.69%)	0 / 30 (0.00%)
occurrences (all)	1	2	0
Vomiting			
subjects affected / exposed	1 / 30 (3.33%)	2 / 26 (7.69%)	2 / 30 (6.67%)
occurrences (all)	1	3	2
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 30 (0.00%)	1 / 26 (3.85%)	2 / 30 (6.67%)
occurrences (all)	0	1	4
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 30 (0.00%)	2 / 26 (7.69%)	0 / 30 (0.00%)
occurrences (all)	0	2	0
Epistaxis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 26 (0.00%)	2 / 30 (6.67%)
occurrences (all)	1	0	2
Oropharyngeal pain			
subjects affected / exposed	2 / 30 (6.67%)	2 / 26 (7.69%)	1 / 30 (3.33%)
occurrences (all)	3	3	1
Musculoskeletal and connective tissue disorders			
Arthralgia			

subjects affected / exposed	6 / 30 (20.00%)	6 / 26 (23.08%)	9 / 30 (30.00%)
occurrences (all)	23	21	47
Back pain			
subjects affected / exposed	7 / 30 (23.33%)	4 / 26 (15.38%)	4 / 30 (13.33%)
occurrences (all)	20	10	12
Musculoskeletal chest pain			
subjects affected / exposed	0 / 30 (0.00%)	1 / 26 (3.85%)	2 / 30 (6.67%)
occurrences (all)	0	1	7
Musculoskeletal pain			
subjects affected / exposed	2 / 30 (6.67%)	3 / 26 (11.54%)	3 / 30 (10.00%)
occurrences (all)	2	5	9
Pain in extremity			
subjects affected / exposed	5 / 30 (16.67%)	4 / 26 (15.38%)	9 / 30 (30.00%)
occurrences (all)	11	12	22
Infections and infestations			
Pneumonia			
subjects affected / exposed	2 / 30 (6.67%)	2 / 26 (7.69%)	4 / 30 (13.33%)
occurrences (all)	4	2	4
Upper respiratory tract infection			
subjects affected / exposed	4 / 30 (13.33%)	1 / 26 (3.85%)	1 / 30 (3.33%)
occurrences (all)	5	1	1
Urinary tract infection			
subjects affected / exposed	4 / 30 (13.33%)	2 / 26 (7.69%)	2 / 30 (6.67%)
occurrences (all)	5	2	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 August 2015	Inclusion criterion of negative pregnancy test was moved from enrolment to at randomisation (Visit 2). Exclusion criteria related to liver function tests, known active or chronic infection, haemoglobin, and platelets moved from enrolment to randomisation (Visit 2). Exclusion criterion related to urine drug screen was removed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported