Clinical trial results:
A Phase 3, Double-Blind, Randomized, Efficacy and Safety Comparison of Prasugrel and Placebo in Pediatric Patients with Sickle Cell Disease.

Summary

EudraCT number	2012-003837-41
Trial protocol	GB BE NL IT
Global end of trial date	17 December 2015

Results information

Result version number	v1 (current)
This version publication date	01 July 2016
First version publication date	01 July 2016

Trial information

Trial identification

Sponsor protocol code	13038

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01794000
WHO universal trial number (UTN)	-
Other trial identifiers	Trial Alias: H7T-MC-TADO, Trial Number: 13038

Notes:

Sponsors

Sponsor organisation name	Eli Lilly and Company
Sponsor organisation address	Lilly Corporate Center, Indianapolis, IN, United States, 46285
Public contact	Available Mon - Fri 9 AM - 5 PM EST , Eli Lilly and Company, 1 877-CTLilly,
Scientific contact	Available Mon - Fri 9 AM - 5 PM EST, Eli Lilly and Company, 1 877-285-4559,

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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 December 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 December 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main purpose of the study is to evaluate the efficacy/safety of prasugrel as monotherapy for reduction of Vaso Occlusive Crisis in patients aged 2 to less than 18 years. The statistical analysis plan allowed for data cutoff on 17-Jul-2015. This was designated the submission data base lock which occurred Aug-2015 and patients continued study drug to garner more safety data (to inform labeling should the study have been positive). A review of the efficacy/safety by the Sponsors mid Sep-2015 confirmed a lack of efficacy with no new safety issues; patients were then contacted starting on 17-Sep-2015, and taken off of study drug. Almost all patients discontinued study drug by 1-Oct-2015, with follow up for study close out continuing until late 2015, and allowing for the 120 day safety assessment data lock in late Jan-2016.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonization (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 April 2013
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	United States: 48
Country: Number of subjects enrolled	Egypt: 45
Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	Ghana: 57
Country: Number of subjects enrolled	Kenya: 91
Country: Number of subjects enrolled	Oman: 6
Country: Number of subjects enrolled	Lebanon: 16
Country: Number of subjects enrolled	Saudi Arabia: 1
Country: Number of subjects enrolled	Canada: 8
Country: Number of subjects enrolled	Turkey: 42
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Brazil: 1
Country: Number of subjects enrolled	Italy: 14

Worldwide total number of subjects	341
EEA total number of subjects	26

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)	199
Adolescents (12-17 years)	142
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Text not entered

Period 1

Period 1 title	Double-Blind Phase (DBP)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Prasugrel

Arm description:

Participants will be titrated from initial daily dose of 0.08 milligram per kilogram (mg/kg) of orally administered prasugrel monotherapy at randomization to a dose that will achieve a P2Y12 reaction units (PRU) level of 231 to 136, as measured by VerifyNow instrument. This corresponds to a range of platelet inhibition of approximately 30% to 60%. The maximum possible dose allowed is 0.12 mg/kg daily, not to exceed 10 mg daily.

Arm type	Experimental
Investigational medicinal product name	Prasugrel
Investigational medicinal product code	
Other name	LY640315, Effient, Efient
Pharmaceutical forms	Chewable tablet
Routes of administration	Oral use

Dosage and administration details:

Participants will be titrated from initial daily dose of 0.08 milligram per kilogram (mg/kg) of orally administered prasugrel monotherapy at randomization to a dose that will achieve a P2Y12 reaction units (PRU) level of 231 to 136, as measured by VerifyNow instrument. This corresponds to a range of platelet inhibition of approximately 30% to 60%. The maximum possible dose allowed is 0.12 mg/kg daily, not to exceed 10 mg daily.

Arm title	Placebo

Arm description:

Participants in this treatment group will receive daily orally administered placebo after being mock titrated in a fashion identical to the active treatment group.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Chewable tablet
Routes of administration	Oral use

Dosage and administration details:

Participants in this treatment group will receive daily orally administered placebo after being mock titrated in a fashion identical to the active treatment group.

Number of subjects in period 1	Prasugrel	Placebo
Started	171	170
Received at least one dose of drug	170	170
Discontinued During Double Blind Phase	169	166
Completed	2	4
Not completed	169	166
Adverse event, serious fatal	1	2
Parent/Caregiver Decision	5	2
Physician decision	2	-
Consent withdrawn by subject	6	11
Adverse event, non-fatal	5	2
Sponsor Decision	148	149
Entry Criteria Not Met	2	-

Period 2

Period 2 title	Open-Label Extension Phase (OLE)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Prasugrel (OLE)

Arm description:

Participants who continued to meet eligibility criteria, who were not permanently discontinued from study drug, and who concluded their participation in 24 months of double blind treatment were to be considered eligible to enter the open label phase.

Arm type	Experimental
Investigational medicinal product name	Prasugrel
Investigational medicinal product code	
Other name	LY640315, Effient, Efient
Pharmaceutical forms	Chewable tablet
Routes of administration	Oral use

Dosage and administration details:

Participants who were on placebo during the double-blind treatment period will begin the OLE titration with the 0.08-mg/kg dose. The participants who had been on prasugrel will start the OLE on their final double-blind dose, which may be titrated up or down as required. Similar to the double-blind treatment period, doses will be adjusted to reach the target level of platelet inhibition. The maximum level of platelet inhibition that will be allowed in this study will be approximately 60% (corresponding to a PRU of 136). Any patient with a PRU less than 136 during the titration period who cannot be titrated to a lower dose will be discontinued from the study.

Number of subjects in period 2[1]	Prasugrel (OLE)
Started	3
Completed	0
Not completed	3
Sponsor Decision	3

Notes:

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

Justification: Participants who had not permanently discontinued study drug, completed 24 months of treatment and met OLE criteria were eligible to enter OLE.

Baseline characteristics

Reporting groups	
Reporting group title	Prasugrel
Reporting group description:	
Participants will be titrated from initial daily dose of 0.08 milligram per kilogram (mg/kg) of orally administered prasugrel monotherapy at randomization to a dose that will achieve a P2Y12 reaction units (PRU) level of 231 to 136, as measured by VerifyNow instrument. This corresponds to a range of platelet inhibition of approximately 30% to 60%. The maximum possible dose allowed is 0.12 mg/kg daily, not to exceed 10 mg daily.	
Reporting group title	Placebo
Reporting group description:	
Participants in this treatment group will receive daily orally administered placebo after being mock titrated in a fashion identical to the active treatment group.	

Reporting group values	Prasugrel	Placebo	Total
Number of subjects	171	170	341
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)			0
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: years			
arithmetic mean	10.606	10.58	
standard deviation	± 4.334	± 4.349	-
Gender, Male/Female Units: participants			
Female	87	86	173
Male	84	84	168
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	2	1	3
Not Hispanic or Latino	94	98	192
Unknown or Not Reported	75	71	146
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	113	109	222
White	58	58	116

More than one race	0	2	2
Unknown or Not Reported	0	1	1
Region of Enrollment Units: Subjects			
United States	23	25	48
Egypt	23	22	45
United Kingdom	5	4	9
Ghana	29	28	57
Kenya	47	44	91
Oman	2	4	6
Lebanon	8	8	16
Saudi Arabia	1	0	1
Canada	4	4	8
Turkey	20	22	42
Belgium	1	2	3
Brazil	1	0	1
Italy	7	7	14
Hydroxyurea Use at Baseline Units: Subjects			
Yes	77	76	153
No	94	94	188

End points

End points reporting groups

Reporting group title	Prasugrel

Reporting group description:

Participants will be titrated from initial daily dose of 0.08 milligram per kilogram (mg/kg) of orally administered prasugrel monotherapy at randomization to a dose that will achieve a P2Y12 reaction units (PRU) level of 231 to 136, as measured by VerifyNow instrument. This corresponds to a range of platelet inhibition of approximately 30% to 60%. The maximum possible dose allowed is 0.12 mg/kg daily, not to exceed 10 mg daily.

Reporting group title	Placebo

Reporting group description:

Participants in this treatment group will receive daily orally administered placebo after being mock titrated in a fashion identical to the active treatment group.

Reporting group title	Prasugrel (OLE)

Reporting group description:

Participants who continued to meet eligibility criteria, who were not permanently discontinued from study drug, and who concluded their participation in 24 months of double blind treatment were to be considered eligible to enter the open label phase.

Subject analysis set title	Prasugrel - Validadated Faces Pain Scale-Revised Population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All randomized participants who are 7 years or older and have both baseline and at least one post-baseline monthly outcome measure in any month. This is the Sickle cell population in which content validity has been established for the Faces Pain Scale-Revised (FPS-R).

Subject analysis set title	Placebo - Validadated Faces Pain Scale-Revised Population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All randomized participants who are 7 years or older and have both baseline and at least one post-baseline monthly outcome measure in any month. This is the Sickle cell population in which content validity has been established for the FPS-R.

Primary: Number of Vaso-Occlusive Crisis (VOC) Events per Participant per Year (Rate of VOC)

End point title	Number of Vaso-Occlusive Crisis (VOC) Events per Participant per Year (Rate of VOC)

End point description:

The VOC is a composite endpoint of painful crisis or acute chest syndrome. Events that occurred within 7 days from the prior event onset date were not counted as a new episode. Data collected through the primary completion date reported below.

End point type	Primary

End point timeframe:

Randomization through 24 Months

End point values	Prasugrel	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171[1]	170[2]		
Units: Number of Events per Participant-Year				
number (not applicable)	2.295	2.767		

Notes:

[1] - All randomized participants.

[2] - All randomized participants.

Statistical analyses

Statistical analysis title	Rate of Vaso-Occlusive Crisis

Statistical analysis description:

The time to a recurrent episode of VOC was analyzed using Andersen-Gill model. A robust variance estimate was used, with treatment, hydroxyurea use at baseline and age group included as factors in the model.

Comparison groups	Prasugrel v Placebo
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.117
Method	Andersen-Gill model
Parameter estimate	Rate Ratio
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1.05

Notes:

[3] - The time to a recurrent episode of VOC was analyzed using Andersen-Gill model. A robust variance estimate was used, with treatment, hydroxyurea use at baseline and age group included as factors in the model.

The rate ratio and 2-sided 95% Confidence Interval (CI) were estimated from the Andersen-Gill model.

Secondary: Monthly Rate of Days with Pain

End point title	Monthly Rate of Days with Pain

End point description:

Monthly rate of days with pain was measured through participant diaries using a modified version of the FPS-R. Each day participants selected the face on the scale that reflected their worst pain related to sickle cell disease (SCD) on that day. This pain scale contains six faces corresponding to the pain intensity of 0, 2, 4, 6, 8 or 10, in which 0 denotes no pain and 10 denotes the worst pain possible. Any day the participant selected a face other than face 0 was considered a day with pain. Monthly rate of days with pain was calculated for each participant by summing the number of days reported with any pain divided by the number of non-missing diary entries completed in the month. A month was defined as 4 weeks (28 days).The monthly rate was set to missing if there were more than 14 missing entries for the FPS-R in a specific month. Data collected through the primary completion date are present below.

End point type	Secondary

End point timeframe:

Randomization through 9 Months

End point values	Prasugrel - Validadated Faces Pain Scale-Revised Population	Placebo - Validadated Faces Pain Scale-Revised Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	127	127		
Units: Percentage of Days in a Month				
least squares mean (standard error)	17.457 (± 1.558)	17.699 (± 1.551)		

Statistical analyses

Statistical analysis title	Monthly Rate of Days with Pains
Comparison groups	Prasugrel - Validadated Faces Pain Scale-Revised Population v Placebo - Validadated Faces Pain Scale-Revised Population
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.912
Method	Mixed models analysis
Parameter estimate	Least Square Mean Difference
Point estimate	-0.242
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.564
upper limit	4.079

Notes:

[4] - Mixed Model Repeated Measures (MMRM) included fixed effects of treatment, baseline value of the pain-diary outcome measure, hydroxyurea use, age group, time and treatment-by-time interaction.

The Least Square (LS) Mean difference of prasugrel minus placebo and the corresponding 2-sided 95% CI were estimated from the MMRM model.

Secondary: Monthly Mean in Faces Pain Scale-Revised Score

End point title	Monthly Mean in Faces Pain Scale-Revised Score

End point description:

Each day participants selected the face on the FPS-R scale that reflected their worst pain related to sickle cell disease (SCD) on that day. Monthly mean in FPS-R score was calculated for each participant by summing the FPS-R score divided by the number of non-missing diary entries completed in the month. This pain scale contains six faces corresponding to the pain intensity of 0, 2, 4, 6, 8 or 10, in which 0 denotes no pain and 10 denotes the worst pain possible. A month was defined as 4 weeks (28 days). The monthly mean in FPS-R score was set to missing if there were more than 14 missing entries for the FPS-R in a specific month. Data collected through the primary completion date are presented below.

End point type	Secondary

End point timeframe:

Randomization through 9 Months

End point values	Prasugrel - Validadated Faces Pain Scale-Revised Population	Placebo - Validadated Faces Pain Scale-Revised Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	127	127		
Units: Units on a Scale				
least squares mean (standard error)	0.7116 (± 0.0757)	0.6148 (± 0.0753)		

Statistical analyses

Statistical analysis title	Monthly Mean in Faces Pain Scale-Revised Score
Comparison groups	Prasugrel - Validadated Faces Pain Scale-Revised Population v Placebo - Validadated Faces Pain Scale-Revised Population
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.365
Method	Mixed models analysis
Parameter estimate	Least Square Mean Difference
Point estimate	0.0968
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1132
upper limit	0.3068

Notes:

[5] - MMRM model included fixed effects of treatment, baseline value of the pain-diary outcome measure, hydroxyurea use, age group, time and treatment-by-time interaction. The LS Mean difference of prasugrel minus placebo and the corresponding 2-sided 95% CI were estimated from the MMRM model.
The rate ratio and 2-sided 95% CI were estimated from the Andersen-Gill model.

Secondary: Number of Painful Crisis Events per Participant per Year (Rate of Painful Crisis)

End point title	Number of Painful Crisis Events per Participant per Year (Rate of Painful Crisis)

End point description:

A painful crisis is defined as an onset of moderate to severe 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, ketorolac, or other analgesics prescribed by a health care provider (HCP) in a medical setting such as a hospital, clinic, emergency room visit, or telephone management. The painful crisis that occurred within 7 days from the prior event onset date was not counted as a new episode. Data collected through the primary completion date are presented below.

End point type	Secondary

End point timeframe:

Randomization through 24 Months

End point values	Prasugrel	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171[6]	170[7]		
Units: Number of Events per Participant-Year				
number (not applicable)	2.239	2.72		

Notes:

[6] - All randomized participants.

[7] - All randomized participants.

Statistical analyses

Statistical analysis title	Rate of Painful Crisis

Statistical analysis description:

The time to a recurrent episode of painful crisis was analyzed using Andersen-Gill model.

A robust variance estimate was used, with treatment, hydroxyurea use at baseline and age group included as factors in the model.

Comparison groups	Prasugrel v Placebo
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.109
Method	Andersen-Gill Model
Parameter estimate	Rate Ratio
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	1.04

Secondary: Number of Hospitalizations for VOC per Participant per Year (Rate of Hospitalizations)

End point title	Number of Hospitalizations for VOC per Participant per Year (Rate of Hospitalizations)

End point description:

Hospitalization that occurred within 7 days of the prior event onset date were not counted as a new episode. Data collected through the primary completion date are presented below.

End point type	Secondary

End point timeframe:

Randomization through 24 Months

End point values	Prasugrel	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171[8]	170[9]		
Units: Number of Events per Participant-Year				
number (not applicable)	1.064	1.126		

Notes:

[8] - All randomized participants.

[9] - All randomized participants.

Statistical analyses

Statistical analysis title	Rate of Hospitalizations

Statistical analysis description:

The time to a recurrent episode of hospitalization was analyzed using Andersen-Gill model.
A robust variance estimate was used, with treatment, hydroxyurea use at baseline and age group included as factors in the model.
The rate ratio and 2-sided 95% CI were estimated from the Andersen-Gill model.

Comparison groups	Prasugrel v Placebo
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.759
Method	Andersen-Gill model
Parameter estimate	Rate Ratio
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	1.37

Secondary: Number of Acute Chest Syndrome per Participant per Year (Rate of Acute Chest Syndrome)

End point title	Number of Acute Chest Syndrome per Participant per Year (Rate of Acute Chest Syndrome)

End point description:

Acute chest syndrome was defined as an acute illness characterized by fever and/or respiratory symptoms, accompanied by a new pulmonary infiltrate on a chest X-ray. Acute chest syndrome that occurred within 7 days of the prior event onset date was not counted as a new episode. Data collected through the primary completion date are presented below.

End point type	Secondary

End point timeframe:

Randomization through 24 Months

End point values	Prasugrel	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171[10]	170[11]		
Units: Number of Events per Participant-Year				
number (not applicable)	0.112	0.115		

Notes:

[10] - All randomized participants.

[11] - All randomized participants.

Statistical analyses

Statistical analysis title	Rate of Acute Chest Syndrome

Statistical analysis description:

The time to a recurrent episode of acute chest syndrome was analyzed using Andersen-Gill model. A robust variance estimate was used, with treatment, hydroxyurea use at baseline and age group included as factors in the model.

Comparison groups	Prasugrel v Placebo
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	other[12]
P-value	= 0.916 [13]
Method	Andersen-Gill model
Parameter estimate	Rate Ratio
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	1.93

Notes:

[12] - The time to a recurrent episode of acute chest syndrome was analyzed using Andersen-Gill model.
A robust variance estimate was used, with treatment, hydroxyurea use at baseline and age group included as factors in the model.
The rate ratio and 2-sided 95% CI were estimated from the Andersen-Gill model.

[13] - The time to a recurrent episode of acute chest syndrome was analyzed using Andersen-Gill model.

Secondary: Number of Red Blood Cell (RBC) Transfusions due to Sickle Cell Disease (SCD) per Participant per Year (Rate of RBC Transfusions)

End point title	Number of Red Blood Cell (RBC) Transfusions due to Sickle Cell Disease (SCD) per Participant per Year (Rate of RBC Transfusions)

End point description:

RBC transfusions that occurred within 7 days of the prior event onset date were not counted as a new episode. Data collected through the primary completion date are presented below.

End point type	Secondary

End point timeframe:

Randomization through 24 Months

End point values	Prasugrel	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171[14]	170[15]		
Units: Number of Events per Participant-Year				
number (not applicable)	0.497	0.42		

Notes:

[14] - All randomized participants.

[15] - All randomized participants.

Statistical analyses

Statistical analysis title	Rate of RBC Transfusions
Comparison groups	Prasugrel v Placebo
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.544 [16]
Method	Andersen-Gill model
Parameter estimate	Rate Ratio
Point estimate	1.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	1.91

Notes:

[16] - The time to a recurrent episode of RBC transfusion was analyzed using Andersen-Gill model. The rate ratio and 2-sided 95% CI were estimated from the Andersen-Gill model.

Secondary: Monthly Rate of Days of Analgesic Use

End point title	Monthly Rate of Days of Analgesic Use

End point description:

Monthly rate of days of analgesic use was measured through participant diaries and was calculated for each participant by summing the number of days they reported analgesic use divided by the number of diary entries completed in the month. A month was defined as 4 weeks (28 days). The monthly rate was set to missing if there were more than 14 missing entries for analgesic use in a specific month. Data collected through the primary completion date are presented below.

Analysis Population: All randomized participants who are 4 years or older and have baseline and at least one post-baseline monthly outcome measure in any month. Diaries were only provided to participants 4 years and older.

End point type	Secondary

End point timeframe:

Randomization through 9 Months

End point values	Prasugrel	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153	153		
Units: Percentage of Days in a Month				
least squares mean (standard error)	24.27 (± 2.29)	22.757 (± 2.337)		

Statistical analyses

Statistical analysis title	Monthly Rate of Days of Analgesic Use
Comparison groups	Prasugrel v Placebo
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	other[17]
P-value	= 0.602 [18]
Method	Mixed models analysis
Parameter estimate	Least Square Mean Difference
Point estimate	1.513
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.186
upper limit	7.213

Notes:

[17] - The MMRM model included the fixed effects of treatment, the baseline value of the pain-diary measure, hydroxyurea use, age group, time and treatment-by-time interaction.

The Least Square Mean difference of prasugrel minus placebo and the corresponding 2-sided 95% CI were estimated from the MMRM model.

[18] - The MMRM model included the fixed effects of treatment, the baseline value of the pain-diary measure, hydroxyurea use, age group, time and treatment-by-time interaction.

Secondary: Quarterly Rate of School Absence due to Sickle Cell Pain

End point title	Quarterly Rate of School Absence due to Sickle Cell Pain

End point description:

Quarterly rate of school absence due to sickle cell pain was measured through participant diaries and was calculated for each participant by summing the number of days with school absence due to sickle cell pain divided by the number of school dates in the quarter. A quarter was defined as 12 weeks. The quarterly rate was set to missing if there were more than 6 weeks of missing diary entries during a specific quarter. Data collected through the primary completion date are presented below.

Analysis Population: All Randomized participants who are 4 years or older and have both baseline and at least one post-baseline quarterly outcome measure in any quarter. Diaries were only provided to participants 4 years and older.

End point type	Secondary

End point timeframe:

Randomization through 9 Months

End point values	Prasugrel	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	115		
Units: Percentage of Days in a Quarter				
least squares mean (standard error)	11.527 (± 1.525)	10.255 (± 1.466)		

Statistical analyses

Statistical analysis title	Rate of School Absence due to Sickle Cell Pain
Comparison groups	Prasugrel v Placebo
Number of subjects included in analysis	220
Analysis specification	Pre-specified
Analysis type	other[19]
P-value	= 0.459
Method	Mixed models analysis
Parameter estimate	Least Square Mean Difference
Point estimate	1.272
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.109
upper limit	4.652

Notes:

[19] - The MMRM model included the fixed effects of treatment, the baseline value of the pain-diary measure, hydroxyurea use, age group, time and treatment-by-time interaction.

The LS Mean difference of prasugrel minus placebo and the corresponding 2-sided 95% CI were estimated from the MMRM model.

Secondary: Time to First Transient Ischemic Attack (TIA)/Ischemic Stroke

End point title	Time to First Transient Ischemic Attack (TIA)/Ischemic Stroke

End point description:

End point type	Secondary

End point timeframe:

Randomization through 24 Months

End point values	Prasugrel	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[20]	0[21]		
Units: Percentage of Participants				
number (not applicable)				

Notes:

[20] - No participants had a TIA or ischemic stroke at time of analysis.

[21] - No participants had a TIA or ischemic stroke at time of analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Days Hospitalized for VOC

End point title	Number of Days Hospitalized for VOC

End point description:

The total length of hospitalization in days for VOC was calculated for each participant. Data collected through the primary completion date are presented below.

End point type	Secondary

End point timeframe:

Randomization through 24 Months

End point values	Prasugrel	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69[22]	76[23]		
Units: Days				
least squares mean (standard error)	12.9 (± 1.72)	12 (± 1.63)		

Notes:

[22] - All randomized participants who were hospitalized for VOC.

[23] - All randomized participants who were hospitalized for VOC.

Statistical analyses

Statistical analysis title	Number of Days Hospitalized for VOC
Comparison groups	Prasugrel v Placebo
Number of subjects included in analysis	145
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.662 [24]
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.31
upper limit	5.19

Notes:

[24] - The ANCOVA model included the factors of treatment, hydroxyurea use, age group, and length of follow-up.

The LS Mean difference of prasugrel minus placebo and 2-sided 95% CI were estimated from the ANCOVA model.

Secondary: Time from Randomization to First and Second VOC

End point title	Time from Randomization to First and Second VOC

End point description:

Data collected through the primary completion date are presented below.

99999999 = Data Not Available - Upper limit of 95% Confidence Interval could not be calculated due to

limited data

End point type	Secondary

End point timeframe:

Randomization to First VOC and Second VOC respectively (up to 24 Months)

End point values	Prasugrel	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171[25]	170[26]		
Units: Days				
median (confidence interval 95%)				
Time from Randomization to the First VOC	90 (71 to 151)	87 (65 to 106)		
Time from Randomization to the Second VOC	338 (240 to 99999999)	238 (177 to 300)		

Notes:

[25] - All randomized participants.

[26] - All randomized participants.

Statistical analyses

Statistical analysis title	Time from Randomization to the First VOC
Comparison groups	Prasugrel v Placebo
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	other[27]
P-value	= 0.317
Method	Logrank

Notes:

[27] - A stratified log-rank test were performed with hydroxyurea use and age group as the stratification factors.

Statistical analysis title	Time from Randomization to the Second VOC
Comparison groups	Prasugrel v Placebo
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	other[28]
P-value	= 0.133
Method	Logrank

Notes:

[28] - A stratified log-rank test were performed with hydroxyurea use and age group as the stratification factors.

Secondary: Percentage of Participants with Hemorrhagic Events Requiring Medical Intervention

End point title	Percentage of Participants with Hemorrhagic Events Requiring Medical Intervention

End point description:

Medical intervention was defined as any medical evaluation resulting in therapy or further investigation, as determined by a trained medical professional. Data collected from the first dose of study medication through 10 days after last dose of study medication during the double blind study period are presented

below.

End point type	Secondary

End point timeframe:

First Dose through 24 Months

End point values	Prasugrel	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170[29]	170[30]		
Units: Percentage of Participants				
number (not applicable)	6.5	4.7		

Notes:

[29] - All randomized participants who received at least one dose of drug.

[30] - All randomized participants who received at least one dose of drug.

Statistical analyses

Statistical analysis title	Percentage of Participants with Hemorrhagic Events
Comparison groups	Prasugrel v Placebo
Number of subjects included in analysis	340
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.638
Method	Fisher exact

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events reported below reflect the entire study safety information through the supplemental data base lock (the study completion date).

Adverse event reporting additional description:

All randomized participants who received at least one dose of drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Prasugrel - Double Blind Phase

Reporting group description:

Participants will be titrated from initial daily dose of 0.08 milligram per kilogram (mg/kg) of orally administered prasugrel monotherapy at randomization to a dose that will achieve a P2Y12 reaction units (PRU) level of 231 to 136, as measured by VerifyNow instrument. This corresponds to a range of platelet inhibition of approximately 30% to 60%. The maximum possible dose allowed is 0.12 mg/kg daily, not to exceed 10 mg daily.

Reporting group title	Placebo - Double Blind Phase

Reporting group description:

Participants in this treatment group will receive daily orally administered placebo and will follow visit schedule identical to that in the active treatment group.

Reporting group title	Prasugrel - Open Label Phase

Reporting group description:

Participants who continued to meet eligibility criteria, who were not permanently discontinued from study drug, and who concluded their participation in 24 months of double blind treatment were to be considered eligible to enter the open label phase.

Serious adverse events	Prasugrel - Double Blind Phase	Placebo - Double Blind Phase	Prasugrel - Open Label Phase
Total subjects affected by serious adverse events			
subjects affected / exposed	100 / 170 (58.82%)	106 / 170 (62.35%)	0 / 3 (0.00%)
number of deaths (all causes)	1	2	0
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
deep vein thrombosis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 170 (0.59%)	0 / 170 (0.00%)	0 / 3 (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
haematoma			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	2 / 170 (1.18%)	1 / 170 (0.59%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
nail operation			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 170 (0.59%)	0 / 170 (0.00%)	0 / 3 (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
selective abortion			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed[1]	1 / 87 (1.15%)	0 / 170 (0.00%)	0 / 3 (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
General disorders and administration site conditions			
chest pain			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 170 (0.59%)	0 / 170 (0.00%)	0 / 3 (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
multi-organ failure			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 170 (0.00%)	1 / 170 (0.59%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
non-cardiac chest pain			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 170 (0.59%)	0 / 170 (0.00%)	0 / 3 (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
pain			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	0 / 170 (0.00%)	1 / 170 (0.59%)	0 / 3 (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
pyrexia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	2 / 170 (1.18%)	5 / 170 (2.94%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
anaphylactic reaction			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 170 (0.59%)	0 / 170 (0.00%)	0 / 3 (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
Reproductive system and breast disorders			
amenorrhoea			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed[2]	1 / 87 (1.15%)	0 / 170 (0.00%)	0 / 3 (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
priapism			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed[3]	0 / 170 (0.00%)	2 / 84 (2.38%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
thrombosis corpora cavernosa			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed[4]	0 / 170 (0.00%)	1 / 84 (1.19%)	0 / 3 (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
Respiratory, thoracic and mediastinal disorders			
acute chest syndrome			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	15 / 170 (8.82%)	14 / 170 (8.24%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 16	0 / 16	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
asthma			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 170 (0.59%)	0 / 170 (0.00%)	0 / 3 (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
epistaxis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	2 / 170 (1.18%)	1 / 170 (0.59%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
lung disorder			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 170 (0.59%)	0 / 170 (0.00%)	0 / 3 (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
pleural effusion			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 170 (0.59%)	0 / 170 (0.00%)	0 / 3 (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
pneumothorax			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 170 (0.59%)	0 / 170 (0.00%)	0 / 3 (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
pulmonary hypertension			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 170 (0.59%)	0 / 170 (0.00%)	0 / 3 (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

Psychiatric disorders			
suicidal ideation			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 170 (0.00%)	1 / 170 (0.59%)	0 / 3 (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
Investigations			
haemoglobin decreased			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 170 (0.59%)	0 / 170 (0.00%)	0 / 3 (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
platelet count decreased			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 170 (0.59%)	0 / 170 (0.00%)	0 / 3 (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
platelet count increased			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 170 (0.00%)	1 / 170 (0.59%)	0 / 3 (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
serum ferritin increased			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 170 (0.59%)	0 / 170 (0.00%)	0 / 3 (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
Injury, poisoning and procedural complications			
contusion			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 170 (0.00%)	1 / 170 (0.59%)	0 / 3 (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
fall			

alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 170 (0.59%)	1 / 170 (0.59%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hand fracture			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 170 (0.59%)	0 / 170 (0.00%)	0 / 3 (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
humerus fracture			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 170 (0.00%)	1 / 170 (0.59%)	0 / 3 (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
lower limb fracture			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 170 (0.00%)	1 / 170 (0.59%)	0 / 3 (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
thermal burn			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 170 (0.00%)	1 / 170 (0.59%)	0 / 3 (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
Cardiac disorders			
cardiac failure			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 170 (0.59%)	0 / 170 (0.00%)	0 / 3 (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
tachycardia			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	1 / 170 (0.59%)	0 / 170 (0.00%)	0 / 3 (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			
haemorrhage intracranial			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 170 (0.59%)	0 / 170 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
headache			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 170 (0.59%)	1 / 170 (0.59%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ruptured cerebral aneurysm			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 170 (0.59%)	0 / 170 (0.00%)	0 / 3 (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
Blood and lymphatic system disorders			
anaemia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	17 / 170 (10.00%)	20 / 170 (11.76%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 34	0 / 23	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
haemolysis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	3 / 170 (1.76%)	3 / 170 (1.76%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hypersplenism			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	3 / 170 (1.76%)	1 / 170 (0.59%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
intravascular haemolysis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 170 (0.59%)	2 / 170 (1.18%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
sickle cell anaemia with crisis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	75 / 170 (44.12%)	83 / 170 (48.82%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	2 / 187	0 / 202	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
splenic infarction			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 170 (0.59%)	0 / 170 (0.00%)	0 / 3 (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
thrombocytopenia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 170 (0.59%)	0 / 170 (0.00%)	0 / 3 (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
thrombotic thrombocytopenic purpura			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 170 (0.00%)	1 / 170 (0.59%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
vertigo			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	1 / 170 (0.59%)	0 / 170 (0.00%)	0 / 3 (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
Eye disorders			
disorder of orbit			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 170 (0.00%)	1 / 170 (0.59%)	0 / 3 (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
Gastrointestinal disorders			
abdominal pain			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 170 (0.00%)	1 / 170 (0.59%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
abdominal pain upper			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 170 (0.59%)	0 / 170 (0.00%)	0 / 3 (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
constipation			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 170 (0.59%)	1 / 170 (0.59%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
diarrhoea			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 170 (0.59%)	0 / 170 (0.00%)	0 / 3 (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
enteritis			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	0 / 170 (0.00%)	1 / 170 (0.59%)	0 / 3 (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
gastritis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 170 (0.59%)	2 / 170 (1.18%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
gingival bleeding			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 170 (0.59%)	0 / 170 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
vomiting			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 170 (0.00%)	1 / 170 (0.59%)	0 / 3 (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
Hepatobiliary disorders			
cholelithiasis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 170 (0.00%)	1 / 170 (0.59%)	0 / 3 (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
hepatic sequestration			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 170 (0.00%)	1 / 170 (0.59%)	0 / 3 (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
hyperbilirubinaemia			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	1 / 170 (0.59%)	0 / 170 (0.00%)	0 / 3 (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
Skin and subcutaneous tissue disorders			
ecchymosis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 170 (0.59%)	0 / 170 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
purpura			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 170 (0.59%)	0 / 170 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
acute kidney injury			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 170 (0.00%)	1 / 170 (0.59%)	0 / 3 (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
renal papillary necrosis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 170 (0.59%)	0 / 170 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
inappropriate antidiuretic hormone secretion			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 170 (0.00%)	1 / 170 (0.59%)	0 / 3 (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
Musculoskeletal and connective tissue disorders			
back pain			

alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 170 (0.00%)	1 / 170 (0.59%)	0 / 3 (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
dactylitis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 170 (0.00%)	1 / 170 (0.59%)	0 / 3 (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
musculoskeletal chest pain			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 170 (0.59%)	0 / 170 (0.00%)	0 / 3 (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
pain in extremity			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 170 (0.00%)	1 / 170 (0.59%)	0 / 3 (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
Infections and infestations			
abscess limb			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 170 (0.00%)	1 / 170 (0.59%)	0 / 3 (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
acinetobacter bacteraemia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 170 (0.59%)	0 / 170 (0.00%)	0 / 3 (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
acute sinusitis			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	0 / 170 (0.00%)	1 / 170 (0.59%)	0 / 3 (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
adenovirus infection			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 170 (0.00%)	1 / 170 (0.59%)	0 / 3 (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
arthritis bacterial			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 170 (0.00%)	1 / 170 (0.59%)	0 / 3 (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
atypical pneumonia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 170 (0.00%)	1 / 170 (0.59%)	0 / 3 (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
bacterial infection			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 170 (0.59%)	1 / 170 (0.59%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
bronchitis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 170 (0.59%)	0 / 170 (0.00%)	0 / 3 (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
cellulitis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 170 (0.59%)	0 / 170 (0.00%)	0 / 3 (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

cellulitis orbital alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 170 (0.59%)	0 / 170 (0.00%)	0 / 3 (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
corona virus infection alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 170 (0.00%)	1 / 170 (0.59%)	0 / 3 (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
enterovirus infection alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 170 (0.59%)	0 / 170 (0.00%)	0 / 3 (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 alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 170 (0.00%)	1 / 170 (0.59%)	0 / 3 (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
hepatitis a alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 170 (0.00%)	1 / 170 (0.59%)	0 / 3 (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
hepatitis c alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 170 (0.59%)	0 / 170 (0.00%)	0 / 3 (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
influenza alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	0 / 170 (0.00%)	3 / 170 (1.76%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
lower respiratory tract infection			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 170 (0.00%)	1 / 170 (0.59%)	0 / 3 (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
malaria			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	11 / 170 (6.47%)	11 / 170 (6.47%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 12	0 / 14	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
mastoiditis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 170 (0.00%)	1 / 170 (0.59%)	0 / 3 (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
nasopharyngitis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 170 (0.00%)	1 / 170 (0.59%)	0 / 3 (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
osteomyelitis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 170 (0.59%)	2 / 170 (1.18%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
osteomyelitis acute			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	2 / 170 (1.18%)	0 / 170 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

osteomyelitis chronic			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 170 (0.00%)	1 / 170 (0.59%)	0 / 3 (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
otitis media			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 170 (0.00%)	1 / 170 (0.59%)	0 / 3 (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
parvovirus b19 infection			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 170 (0.59%)	0 / 170 (0.00%)	0 / 3 (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
pharyngitis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 170 (0.59%)	0 / 170 (0.00%)	0 / 3 (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
pharyngitis streptococcal			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 170 (0.00%)	1 / 170 (0.59%)	0 / 3 (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
pilonidal cyst			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 170 (0.00%)	1 / 170 (0.59%)	0 / 3 (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
plasmodium falciparum infection			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	6 / 170 (3.53%)	4 / 170 (2.35%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 7	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pneumonia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	6 / 170 (3.53%)	7 / 170 (4.12%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 7	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pneumonia streptococcal			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 170 (0.59%)	0 / 170 (0.00%)	0 / 3 (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
pyomyositis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 170 (0.00%)	1 / 170 (0.59%)	0 / 3 (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
respiratory syncytial virus bronchiolitis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 170 (0.00%)	1 / 170 (0.59%)	0 / 3 (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
respiratory syncytial virus infection			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 170 (0.59%)	0 / 170 (0.00%)	0 / 3 (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 tract infection			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	2 / 170 (1.18%)	0 / 170 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
sepsis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 170 (0.59%)	4 / 170 (2.35%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
septic shock			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 170 (0.59%)	0 / 170 (0.00%)	0 / 3 (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
sinusitis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 170 (0.00%)	1 / 170 (0.59%)	0 / 3 (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
staphylococcal sepsis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 170 (0.00%)	2 / 170 (1.18%)	0 / 3 (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
tonsillitis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	2 / 170 (1.18%)	4 / 170 (2.35%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
tooth abscess			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 170 (0.59%)	0 / 170 (0.00%)	0 / 3 (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

tooth infection			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 170 (0.00%)	1 / 170 (0.59%)	0 / 3 (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
upper respiratory tract infection			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 170 (0.00%)	1 / 170 (0.59%)	0 / 3 (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
urinary tract infection			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	2 / 170 (1.18%)	2 / 170 (1.18%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
viral infection			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 170 (0.59%)	2 / 170 (1.18%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
viral tonsillitis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 170 (0.00%)	1 / 170 (0.59%)	0 / 3 (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
viral upper respiratory tract infection			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 170 (0.00%)	2 / 170 (1.18%)	0 / 3 (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
Metabolism and nutrition disorders			
dehydration			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	0 / 170 (0.00%)	1 / 170 (0.59%)	0 / 3 (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
hypoglycaemia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 170 (0.00%)	1 / 170 (0.59%)	0 / 3 (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

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This event is gender specific, only occurring in male or female subjects. The number of subjects exposed has been adjusted accordingly.
[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This event is gender specific, only occurring in male or female subjects. The number of subjects exposed has been adjusted accordingly.
[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This event is gender specific, only occurring in male or female subjects. The number of subjects exposed has been adjusted accordingly.
[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This event is gender specific, only occurring in male or female subjects. The number of subjects exposed has been adjusted accordingly.

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

Non-serious adverse events	Prasugrel - Double Blind Phase	Placebo - Double Blind Phase	Prasugrel - Open Label Phase
Total subjects affected by non-serious adverse events			
subjects affected / exposed	148 / 170 (87.06%)	154 / 170 (90.59%)	1 / 3 (33.33%)
Nervous system disorders			
headache			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	25 / 170 (14.71%)	29 / 170 (17.06%)	0 / 3 (0.00%)
occurrences (all)	32	43	0
Blood and lymphatic system disorders			
anaemia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	6 / 170 (3.53%)	11 / 170 (6.47%)	0 / 3 (0.00%)
occurrences (all)	8	13	0
sickle cell anaemia with crisis			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	90 / 170 (52.94%)	102 / 170 (60.00%)	1 / 3 (33.33%)
occurrences (all)	223	272	1
General disorders and administration site conditions			
nodule			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 170 (0.00%)	0 / 170 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
pain			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	18 / 170 (10.59%)	19 / 170 (11.18%)	0 / 3 (0.00%)
occurrences (all)	31	30	0
pyrexia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	35 / 170 (20.59%)	43 / 170 (25.29%)	1 / 3 (33.33%)
occurrences (all)	54	69	1
Gastrointestinal disorders			
abdominal pain			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	17 / 170 (10.00%)	20 / 170 (11.76%)	0 / 3 (0.00%)
occurrences (all)	23	28	0
abdominal pain upper			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	3 / 170 (1.76%)	11 / 170 (6.47%)	0 / 3 (0.00%)
occurrences (all)	3	14	0
constipation			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	9 / 170 (5.29%)	12 / 170 (7.06%)	0 / 3 (0.00%)
occurrences (all)	10	16	0
diarrhoea			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	6 / 170 (3.53%)	11 / 170 (6.47%)	0 / 3 (0.00%)
occurrences (all)	8	12	0
gastritis			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	10 / 170 (5.88%)	10 / 170 (5.88%)	0 / 3 (0.00%)
occurrences (all)	13	19	0
vomiting			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	7 / 170 (4.12%)	12 / 170 (7.06%)	0 / 3 (0.00%)
occurrences (all)	11	19	0
Respiratory, thoracic and mediastinal disorders			
cough			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	14 / 170 (8.24%)	17 / 170 (10.00%)	1 / 3 (33.33%)
occurrences (all)	19	19	1
epistaxis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	23 / 170 (13.53%)	21 / 170 (12.35%)	0 / 3 (0.00%)
occurrences (all)	48	29	0
oropharyngeal pain			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	9 / 170 (5.29%)	8 / 170 (4.71%)	0 / 3 (0.00%)
occurrences (all)	13	8	0
Musculoskeletal and connective tissue disorders			
arthralgia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	8 / 170 (4.71%)	10 / 170 (5.88%)	0 / 3 (0.00%)
occurrences (all)	11	11	0
back pain			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	20 / 170 (11.76%)	29 / 170 (17.06%)	0 / 3 (0.00%)
occurrences (all)	32	54	0
pain in extremity			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	28 / 170 (16.47%)	47 / 170 (27.65%)	0 / 3 (0.00%)
occurrences (all)	45	84	0
Infections and infestations			

malaria			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	33 / 170 (19.41%)	33 / 170 (19.41%)	0 / 3 (0.00%)
occurrences (all)	62	53	0
nasopharyngitis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	15 / 170 (8.82%)	18 / 170 (10.59%)	0 / 3 (0.00%)
occurrences (all)	19	34	0
pharyngitis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	4 / 170 (2.35%)	10 / 170 (5.88%)	0 / 3 (0.00%)
occurrences (all)	4	11	0
rhinitis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	11 / 170 (6.47%)	7 / 170 (4.12%)	0 / 3 (0.00%)
occurrences (all)	12	10	0
tonsillitis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	20 / 170 (11.76%)	24 / 170 (14.12%)	0 / 3 (0.00%)
occurrences (all)	26	31	0
upper respiratory tract infection			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	44 / 170 (25.88%)	37 / 170 (21.76%)	0 / 3 (0.00%)
occurrences (all)	76	69	0
urinary tract infection			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	17 / 170 (10.00%)	17 / 170 (10.00%)	0 / 3 (0.00%)
occurrences (all)	26	17	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 February 2013	- Primary endpoint was updated to include a composite of painful crisis or acute chest syndrome and to include not only oral/parenteral opioids and ketorolac but other prescribed analgesics. -Rate of painful crisis added to major secondary efficacy objectives - Hemorrhagic stroke removed from efficacy endpoints. - Inclusion criterion changed to allow patients ≥ 19 kg - Number of participants expected to be enrolled was increased - Stopping rules added for the Data Monitoring Committee - Schedule of events updated to allow additional blood draw

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.

The pre-defined levels of platelet inhibition and prasugrel as monotherapy may have contributed to the failure to meet any primary/secondary endpoint.

Notes: