Clinical trial results:
Does Ticagrelor inhibit growth of small abdominal aortic aneurysms? A randomised controlled trial (TicAAA)

Summary

EudraCT number	2013-002736-24
Trial protocol	SE
Global end of trial date	26 June 2017

Results information

Result version number	v1 (current)
This version publication date	27 October 2018
First version publication date	27 October 2018

Trial information

Trial identification

Sponsor protocol code	TicAAA-1.0

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Uppsala University Hospital
Sponsor organisation address	Akademiska sjukhuset ing 70, 1 tr, Uppsala, Sweden,
Public contact	Anders Wanhainen, Uppsala University Hospital, anders.wanhainen@surgsci.uu.se
Scientific contact	Anders Wanhainen, Uppsala University Hospital, anders.wanhainen@surgsci.uu.se

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	26 June 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 June 2017
Global end of trial reached?	Yes
Global end of trial date	26 June 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the efficacy of Ticagrelor on Abdominal aortic aneurysm (AAA)-expansion in a multi-centre, randomized, double-blinded for Ticagrelor and placebo.

Protection of trial subjects:

Patients were given full and adequate verbal and written information about the objectives, procedures and possible risks and benefits of the study, prior to enrolment. Study treatment was to be stopped in case of liver impairment, severe bleeding, elective aneurysm surgery, or the onset of any exclusion criteria. In the case of trauma during the study, the study drug was to be discontinued until the risk of bleeding ends.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 February 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 144
Worldwide total number of subjects	144
EEA total number of subjects	144

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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	6
From 65 to 84 years	138
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

158 patients were enrolled in the study. Of these, there were 14 enrolment failures due to 7 patients who did not satisfy inclusion criteria #4 (documented AAA 35-49mm), 4 patients failing various exclusion criteria, and 3 patients who left by choice.

Period 1

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

Blinding implementation details:

The active product and placebo were identical in appearance and packed in identical, non-transparent containers. Sealed envelopes with individual treatment codes showing allocated treatment for each randomised patient was kept by the PI, local pharmacy, and the Sponsor's safety department. The treatment code was not to be broken except in medical emergencies. Any breaking of the treatment code had to be documented.

Arms

Are arms mutually exclusive?	Yes
Arm title	Ticagrelor

Arm description:

Ticagrelor 90 mg tablet twice daily for 12 months

Arm type	Experimental
Investigational medicinal product name	Ticagrelor
Investigational medicinal product code	SUB30898
Other name	Brilique
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

90 mg tablet twice daily for 12 months

Arm title	Placebo

Arm description:

Ticagrelor placebo tablet twice daily for 12 months

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

Dosage and administration details:

Ticagrelor placebo tablet twice daily for 12 months

Number of subjects in period 1	Ticagrelor	Placebo
Started	72	72
Completed	67	67
Not completed	5	5
Adverse event, serious fatal	-	2
Physician decision	1	-
Elective aneurysm surgery	1	-
Adverse event, non-fatal	3	1
Protocol deviation	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Ticagrelor
Reporting group description:	
Ticagrelor 90 mg tablet twice daily for 12 months	
Reporting group title	Placebo
Reporting group description:	
Ticagrelor placebo tablet twice daily for 12 months	

Reporting group values	Ticagrelor	Placebo	Total
Number of subjects	72	72	144
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	69.5	68.3	
standard deviation	± 4.6	± 4.2	-
Gender categorical			
Units: Subjects			
Female	4	2	6
Male	68	70	138
Race			
Units: Subjects			
White	71	70	141
Other	1	2	3
Tobacco usage			
Smoking at enrollment was reported as never smoked, current smoker, or former smoker.			
Units: Subjects			
Current	22	26	48
Former	40	39	79
Never	10	7	17
Weight			
Units: kg			
arithmetic mean	86.3	88.1	
standard deviation	± 12.5	± 14.6	-
Height			
Units: cm			

arithmetic mean	177.6	179.4	
standard deviation	± 7.7	± 6.6	-
BMI Units: kg/m2			
arithmetic mean	27.39	27.31	
standard deviation	± 3.74	± 3.84	-

Subject analysis sets

Subject analysis set title	Ticagrelor (PPA)
Subject analysis set type	Per protocol

Subject analysis set description:

The PPA population was pre-defined in the study protocol as patients with at least 80% compliance with the intended use, no major protocol deviations and with measure of primary efficacy endpoint at 12 months after randomisation.

Subject analysis set title	Placebo (PPA)
Subject analysis set type	Per protocol

Subject analysis set description:

The PPA population was pre-defined in the study protocol as patients with at least 80% compliance with the intended use, no major protocol deviations and with measure of primary efficacy endpoint at 12 months after randomisation.

Subject analysis set title	Ticagrelor (ITT)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT population was pre-defined that patients with no post-dose observations for an efficacy endpoint should be removed from the ITT population.

Subject analysis set title	Placebo (ITT)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT population was pre-defined that patients with no post-dose observations for an efficacy endpoint should be removed from the ITT population.

Reporting group values	Ticagrelor (PPA)	Placebo (PPA)	Ticagrelor (ITT)
Number of subjects	55	63	69
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	69.4	68.7	69.5
standard deviation	± 4.5	± 4.2	± 4.5
Gender categorical Units: Subjects			
Female	2	2	4

Male	53	61	65

Race Units: Subjects			
White	54	62	68
Other	1	1	1
Tobacco usage			
Smoking at enrollment was reported as never smoked, current smoker, or former smoker.			
Units: Subjects			
Current	13	23	21
Former	32	34	38
Never	10	6	10
Weight Units: kg			
arithmetic mean	87.0	87.8	86.2
standard deviation	± 12.4	± 14.7	± 12.4
Height Units: cm			
arithmetic mean	177.9	179.1	177.6
standard deviation	± 7.8	± 6.7	± 7.8
BMI Units: kg/m2			
arithmetic mean	27.51	27.32	27.33
standard deviation	± 3.79	± 3.88	± 3.75

Reporting group values	Placebo (ITT)		
Number of subjects	70		
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	68.3		
standard deviation	± 4.2		
Gender categorical Units: Subjects			
Female	2		
Male	68		
Race Units: Subjects			
White	68		

Other	2		
Tobacco usage			
Smoking at enrollment was reported as never smoked, current smoker, or former smoker.			
Units: Subjects			
Current	25		
Former	39		
Never	6		
Weight			
Units: kg			
arithmetic mean	88.2		
standard deviation	± 14.8		
Height			
Units: cm			
arithmetic mean	179.3		
standard deviation	± 6.6		
BMI			
Units: kg/m2			
arithmetic mean	27.38		
standard deviation	± 3.88		

End points

End points reporting groups

Reporting group title	Ticagrelor
Reporting group description:	
Ticagrelor 90 mg tablet twice daily for 12 months	
Reporting group title	Placebo
Reporting group description:	
Ticagrelor placebo tablet twice daily for 12 months	
Subject analysis set title	Ticagrelor (PPA)
Subject analysis set type	Per protocol
Subject analysis set description:	
The PPA population was pre-defined in the study protocol as patients with at least 80% compliance with the intended use, no major protocol deviations and with measure of primary efficacy endpoint at 12 months after randomisation.	
Subject analysis set title	Placebo (PPA)
Subject analysis set type	Per protocol
Subject analysis set description:	
The PPA population was pre-defined in the study protocol as patients with at least 80% compliance with the intended use, no major protocol deviations and with measure of primary efficacy endpoint at 12 months after randomisation.	
Subject analysis set title	Ticagrelor (ITT)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT population was pre-defined that patients with no post-dose observations for an efficacy endpoint should be removed from the ITT population.	
Subject analysis set title	Placebo (ITT)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT population was pre-defined that patients with no post-dose observations for an efficacy endpoint should be removed from the ITT population.	

Primary: Difference in log-transformed volume of Abdominal Aortic Aneurysm (AAA) determined by magnetic resonance imaging (MRI) at 12 months

End point title	Difference in log-transformed volume of Abdominal Aortic Aneurysm (AAA) determined by magnetic resonance imaging (MRI) at 12 months
End point description:	
The analysis performed on the ITT population was an Analysis of Covariance (ANCOVA) model with difference in log-transformed AAA volume at 12 month - baseline as response variable. Treatment (Ticagrelor vs. Placebo) was included as a fixed factor in the ANCOVA model and log-transformed baseline AAA volume was included as a covariate. Missing outcomes were imputed using last-value-carried-forward (LVCF), excluding patients with no post-baseline measurement. The result were presented as the estimated geometric mean ratio Ticagrelor/Placebo, with 95% C.I. and two-sided p-value. AAA volume increase was similar in both arms, and there was no indication of a systemic difference between the treatments. The results of the secondary outcomes were in line with the primary variable.	
End point type	Primary
End point timeframe:	
Mean 12 months AAA volume increase from baseline (6 month values carried forward)	

End point values	Ticagrelor (ITT)	Placebo (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	67	69		
Units: cm3				
geometric mean (confidence interval 95%)	1.091 (1.074 to 1.109)	1.075 (1.061 to 1.090)		

Statistical analyses

Statistical analysis title	Analysis of difference in AAA volume by MRI

Statistical analysis description:

The primary outcome was baseline-adjusted AAA volume at 12 months in the ITT population analysed using an ANCOVA model with difference in log-transformed AAA volume at 12 month - baseline as response variable. Treatment (Ticagrelor vs. Placebo) was included as a fixed factor in the ANCOVA model and log-transformed baseline AAA volume was included as a covariate.

Comparison groups	Placebo (ITT) v Ticagrelor (ITT)
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.205
Method	ANCOVA

Notes:

[1] - Missing outcomes were imputed using last-value-carried-forward (LVCF), excluding patients with no post-baseline measurement.

Secondary: Difference in AAA diameter determined by MRI at 12 months vs at baseline

End point title	Difference in AAA diameter determined by MRI at 12 months vs at baseline

End point description:

67 Ticagrelor patients and 69 placebo patients were included in the ITT analysis, of which data for 2 Ticagrelor and 3 placebo patients were imputed using the 6-months value. Mean 12 months AAA diameter increase from baseline was 0.24 cm in the Ticagrelor treatment group and 0.18 cm in the placebo group, not affected by imputation.

End point type	Secondary

End point timeframe:

Mean 12 months AAA diameter increase from baseline (6 month values carried forward) determined by magnetic resonance imaging (MRI)

End point values	Ticagrelor (ITT)	Placebo (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	67[2]	69[3]		
Units: cm				
arithmetic mean (confidence interval 95%)	0.244 (0.190 to 0.298)	0.185 (0.142 to 0.227)		

Notes:

[2] - 67 Ticagrelor patients were included, of which data for 2 were imputed using the 6-months value.

[3] - 69 Placebo patients were included, of which data for 3 were imputed using the 6-months value.

Statistical analyses

No statistical analyses for this end point

Secondary: Difference in AAA diameter determined by ultrasound (US) at 12 months vs at baseline

End point title	Difference in AAA diameter determined by ultrasound (US) at 12 months vs at baseline

End point description:

69 Ticagrelor patients and 70 placebo patients were included in the ITT analysis, of which data for 2 Ticagrelor and 3 placebo patients were imputed using the 6-months value. Mean 12 months AAA diameter increase from baseline was 2.3 mm in the Ticagrelor treatment group and 2.2 mm in the placebo group, not affected by imputation.

End point type	Secondary

End point timeframe:

Mean 12 months AAA diameter increase from baseline (6 month values carried forward) determined by ultrasound (US)

End point values	Ticagrelor (ITT)	Placebo (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	69[4]	70[5]		
Units: mm				
arithmetic mean (confidence interval 95%)	2.29 (1.68 to 2.90)	2.17 (1.65 to 2.70)		

Notes:

[4] - 69 Ticagrelor patients were included, of which 2 patients were imputed using the 6-months value.

[5] - 70 Placebo patients were included, of which 3 patients were imputed using the 6-months value.

Statistical analyses

No statistical analyses for this end point

Secondary: Difference in thrombus volume determined by MRI at 12 months vs at baseline

End point title	Difference in thrombus volume determined by MRI at 12 months vs at baseline

End point description:

67 Ticagrelor patients and 69 placebo patients were included in the ITT analysis, of which data for 2 Ticagrelor and 3 placebo patients were imputed using the 6-months value.

End point type	Secondary

End point timeframe:

Mean 12 months thrombus volume increase from baseline (6 month values carried forward) determined by MRI

End point values	Ticagrelor (ITT)	Placebo (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	67[6]	69[7]		
Units: cm3				
geometric mean (confidence interval 95%)	1.130 (1.075 to 1.187)	1.109 (1.066 to 1.155)		

Notes:

[6] - 67 Ticagrelor patients were included, of which 2 patients were imputed using the 6-months value.

[7] - 69 Placebo patients were included, of which 3 patients were imputed using the 6-months value.

Statistical analyses

No statistical analyses for this end point

Secondary: Difference in need for surgery (≥ 55 mm) after 12 months

End point title	Difference in need for surgery (≥ 55 mm) after 12 months

End point description:

Need for surgery defined as aortic diameter 55 mm or larger, or reported need for surgery at 6 or 12 months ultrasound, or withdrawal from study due to need for surgery is presented for the ITT and PPA populations at 12 months.

End point type	Secondary

End point timeframe:

Difference in need for surgery (≥ 55 mm) after 12 months

End point values	Ticagrelor (PPA)	Placebo (PPA)	Ticagrelor (ITT)	Placebo (ITT)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	55	63	69	70
Units: Number of subjects	2	0	4	0

Statistical analyses

No statistical analyses for this end point

Secondary: Difference in aneurysm rupture after 12 months

End point title	Difference in aneurysm rupture after 12 months

End point description:

Aneurysm rupture was recorded in the US CRF. In case an aneurysm rupture was detected as an AE it was added to the CRF-reported events. Patients that withdrew from follow-up without having an event were counted as no event. There were no aneurysm ruptures recorded in the study.

End point type	Secondary

End point timeframe:

Difference in aneurysm rupture after 12 months

End point values	Ticagrelor (PPA)	Placebo (PPA)	Ticagrelor (ITT)	Placebo (ITT)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	55	63	69	70
Units: Number of subjects	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

SAEs were recorded from the enrolment visit (visit 1) and SAEs/AEs were recorded from the baseline visit (visit 2) until the last visit (12 months after the baseline visit).

Adverse event reporting additional description:

SAEs were continuously recorded in the eCRF from visit 1 and SAE+AE were recorded from visit 2. All included patients were informed to contact the site if they experienced any more than normal bleeding and/or any liver impairment during the study.

Assessment type	Systematic

Dictionary used

Dictionary name	ICD-10
Dictionary version	2016

Reporting groups

Reporting group title	Ticagrelor

Reporting group description:

Ticagrelor 90 mg tablet twice daily for 12 months

Reporting group title	Placebo

Reporting group description:

Ticagrelor placebo tablet twice daily

Serious adverse events	Ticagrelor	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 72 (6.94%)	7 / 72 (9.72%)	
number of deaths (all causes)	0	2	
number of deaths resulting from adverse events	0	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm			
subjects affected / exposed	1 / 72 (1.39%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fracture of clavicle			
subjects affected / exposed	1 / 72 (1.39%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture of other parts of lower leg			

subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Acute vascular disorders of intestine			
subjects affected / exposed	1 / 72 (1.39%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest, unspecified			
subjects affected / exposed	0 / 72 (0.00%)	2 / 72 (2.78%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Atrial fibrillation and atrial flutter, unspecified			
subjects affected / exposed	1 / 72 (1.39%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia, unspecified			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Other and unspecified medical devices associated with adverse incidents			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Haemorrhage, not elsewhere classified			
subjects affected / exposed	2 / 72 (2.78%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			

subjects affected / exposed	1 / 72 (1.39%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain, not elsewhere classified			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope and collapse			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock, unspecified			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Other specified disorders of male genital organs			
subjects affected / exposed	1 / 72 (1.39%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Paraesthesia of skin			

subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depressive episode, unspecified			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Retention of urine			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Ticagrelor	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	57 / 72 (79.17%)	38 / 72 (52.78%)	
General disorders and administration site conditions			
Haemorrhage, not elsewhere classified			
subjects affected / exposed	22 / 72 (30.56%)	8 / 72 (11.11%)	
occurrences (all)	33	11	
Dyspnoea			
subjects affected / exposed	19 / 72 (26.39%)	4 / 72 (5.56%)	
occurrences (all)	19	4	
Respiratory, thoracic and mediastinal disorders			
Acute nasopharyngitis			
subjects affected / exposed	4 / 72 (5.56%)	2 / 72 (2.78%)	
occurrences (all)	4	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported