



Clinical trial results:

A multi-center, double-blind, randomized, placebo-controlled study to assess the pharmacodynamics, pharmacokinetics, tolerability, and safety of a single subcutaneous injection of ACT-246475 in adults with stable coronary artery disease

Summary

EudraCT number	2017-003332-36
Trial protocol	GB DK SE NL DE
Global end of trial date	18 September 2018

Results information

Result version number	v1 (current)
This version publication date	04 October 2019
First version publication date	04 October 2019

Trial information

Trial identification

Sponsor protocol code	ID-076A201
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03384966
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Idorsia Pharmaceuticals Ltd.
Sponsor organisation address	Hegenheimermattweg 91 , Allschwil, Switzerland, 4123
Public contact	Clinical Trial Disclosure Desk, Idorsia Pharmaceuticals Ltd., clinical-trials-disclosure@idorsia.com
Scientific contact	Clinical Trial Disclosure Desk, Idorsia Pharmaceuticals Ltd., clinical-trials-disclosure@idorsia.com

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 October 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 August 2018
Global end of trial reached?	Yes
Global end of trial date	18 September 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to characterize inhibition of ADP-mediated platelet aggregation relative to placebo after a single subcutaneous injection of selatogrel (ACT-246475) either in the thigh or in the abdomen at 2 different doses in subjects with stable coronary artery disease receiving conventional background oral anti-platelet therapy (e.g., acetylsalicylic acid, P2Y12 receptor antagonists).

Protection of trial subjects:

Prior to the start of the study, each study site consulted an independent ethics committee (IEC) or institutional review board (IRB), i.e., a review panel that was responsible for ensuring the protection of the rights, safety, and well-being of human subjects involved in a clinical investigation. The protocol and any material provided to the subject (such as a subject information sheet or description of the study used to obtain informed consent) were reviewed and approved by the appropriate Independent ethics committee or institutional review board before the study was started. Written informed consent was obtained from each individual participating in the study after adequate explanation of the aims, methods, objectives, and potential hazards of the study. An Independent Safety Event Committee (ISEC) had overall responsibility for safeguarding the interests of subjects by monitoring study safety data in an unblinded manner, with a specific focus on clinically relevant major bleeding events.

Background therapy:

The subject's standard of care was not affected by study participation. For this study, subjects received a single administration of study drug on top of their standard of care treatment. Unless medically necessary, subjects continued their standard treatment(s) (including oral P2Y12 receptor antagonists and acetylsalicylic acid) as prescribed (treatments and doses), from Visit 1 (screening) and up to the last PK or PD blood sample collection (whichever was latest) at Visit 3 (Day 2).

Evidence for comparator: -

Actual start date of recruitment	24 January 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 66
Country: Number of subjects enrolled	Sweden: 30
Country: Number of subjects enrolled	United Kingdom: 77
Country: Number of subjects enrolled	Denmark: 1
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	Singapore: 8
Country: Number of subjects enrolled	United States: 153

Worldwide total number of subjects	346
EEA total number of subjects	179

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)	151
From 65 to 84 years	195
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted between 24 Jan and 18 Sep 2018. Of the 362 subjects screened, 346 subjects were randomized and 345 subjects were treated. One subject randomized to the 8 mg selatogrel arm did not receive the treatment allocated by the investigator due to a myocardial infarction on the day of randomization.

Pre-assignment

Screening details:

The study had a 21 day screening period window before study randomization.

Period 1

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

Blinding implementation details:

The double-blind design applied only to the treatment allocation (i.e., Selatogrel [ACT-246475 versus placebo]). The dose was blinded to the subjects only (single blind), and the injection site was not blinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	Selatogrel 8 mg

Arm description:

A single 8 mg dose of selatogrel (ACT-246475) was administered via a single subcutaneous (s.c.) injection either in the abdomen or the thigh.

Arm type	Experimental
Investigational medicinal product name	Selatogrel
Investigational medicinal product code	ACT-246475
Other name	
Pharmaceutical forms	Powder for suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Selatogrel (ACT-246475) is a reversible P2Y₁₂ receptor antagonist for s.c. administration. It was supplied in sealed glass vials at a strength of 20 mg.

The vials contained 22 mg of lyophilized Selatogrel (ACT-246475A) for reconstitution with water for injection.

Selatogrel (ACT-246475) was given as a single s.c. dose of 8 mg administered in a volume of 0.8 mL. Administration was performed at the investigational site by qualified personnel.

Arm title	Selatogrel 16 mg
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Arm description:

A single 16 mg dose of selatogrel (ACT-246475) was administered via a single subcutaneous (s.c.) injection either in the abdomen or the thigh.

Arm type	Experimental
Investigational medicinal product name	Selatogrel
Investigational medicinal product code	ACT-246475
Other name	
Pharmaceutical forms	Powder for suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Selatogrel (ACT-246475) is a reversible P2Y12 receptor antagonist for s.c. administration. It was supplied in sealed glass vials at a strength of 20 mg.

The vials contained 22 mg of lyophilized Selatogrel (ACT-246475A) for reconstitution with water for injection.

Selatogrel (ACT-246475) was given as a single s.c. dose of 16 mg administered in a volume of 0.8 mL. Administration was performed at the investigational site by qualified personnel.

Arm title	Matching Placebo
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Arm description:

Matching placebo was administered via single subcutaneous (s.c.) administration either in the thigh or the abdomen.

Arm type	Placebo
Investigational medicinal product name	Matching Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo matching lyophilized Selatogrel (ACT-246475A) for s.c. administration was supplied in sealed glass vials for reconstitution with water for injection.

Placebo was given as a single s.c. dose matching 8 or 16 mg ACT-246475 administered in a volume of 0.8 mL.

Administration was performed at the investigational site by qualified personnel.

Number of subjects in period 1	Selatogrel 8 mg	Selatogrel 16 mg	Matching Placebo
Started	115	115	116
Completed	114	115	116
Not completed	1	0	0
Physician decision	1	-	-

Period 2

Period 2 title	Follow-up period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

This was a non-treatment period, the blinding of single-dose from the treatment period was maintained.

Arms

Are arms mutually exclusive?	Yes
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Arm title	Selatogrel 8 mg (Follow-up)
Arm description: During this time the subjects were continued to be observed following the treatment period. No interventions were performed. The follow-up period was planned to last 28 to 35 days. The period started on Day 3 and ended with the safety follow-up telephone call or visit.	
Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	Selatogrel 16 mg (Follow-up)
Arm description: During this time the subjects were continued to be observed following the treatment period. No interventions were performed. The follow-up period was planned to last 28 to 35 days. The period started on Day 3 and ended with the safety follow-up telephone call or visit.	
Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	Matching Placebo (Follow-up)
Arm description: During this time the subjects were continued to be observed following the treatment period. No interventions were performed. The follow-up period was planned to last 28 to 35 days. The period started on Day 3 and ended with the safety follow-up telephone call or visit.	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 2	Selatogrel 8 mg (Follow-up)	Selatogrel 16 mg (Follow-up)	Matching Placebo (Follow-up)
Started	114	115	116
Completed	113	115	116
Not completed	1	0	0
Adverse event, serious fatal	1	-	-

Baseline characteristics

Reporting groups

Reporting group title	Selatogrel 8 mg
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Reporting group description:

A single 8 mg dose of selatogrel (ACT-246475) was administered via a single subcutaneous (s.c.) injection either in the abdomen or the thigh.

Reporting group title	Selatogrel 16 mg
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Reporting group description:

A single 16 mg dose of selatogrel (ACT-246475) was administered via a single subcutaneous (s.c.) injection either in the abdomen or the thigh.

Reporting group title	Matching Placebo
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Reporting group description:

Matching placebo was administered via single subcutaneous (s.c.) administration either in the thigh or the abdomen.

Reporting group values	Selatogrel 8 mg	Selatogrel 16 mg	Matching Placebo
Number of subjects	115	115	116
Age categorical			
Units: Subjects			
Adults (18-64 years)	48	48	55
From 65-84 years	67	67	61
Age continuous			
Units: years			
median	67	67	65
full range (min-max)	41 to 80	41 to 82	36 to 83
Gender categorical			
Units: Subjects			
Female	20	26	23
Male	95	89	93
Race			
Units: Subjects			
Black or African American	10	13	9
Asian	7	6	4
White	98	96	103
Ethnicity			
Units: Subjects			
Hispanic or Latino	1	1	0
Not Hispanic or Latino	114	114	116
Body Mass Index			
Units: kg/m ²			
arithmetic mean	29.0	29.4	30.6
standard deviation	± 5.0	± 5.7	± 4.9

Reporting group values	Total		
Number of subjects	346		

Age categorical			
Units: Subjects			
Adults (18-64 years)	151		
From 65-84 years	195		
Age continuous			
Units: years			
median			
full range (min-max)	-		
Gender categorical			
Units: Subjects			
Female	69		
Male	277		
Race			
Units: Subjects			
Black or African American	32		
Asian	17		
White	297		
Ethnicity			
Units: Subjects			
Hispanic or Latino	2		
Not Hispanic or Latino	344		
Body Mass Index			
Units: kg/m ²			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Selatogrel 8 mg
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Reporting group description:

A single 8 mg dose of selatogrel (ACT-246475) was administered via a single subcutaneous (s.c.) injection either in the abdomen or the thigh.

Reporting group title	Selatogrel 16 mg
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Reporting group description:

A single 16 mg dose of selatogrel (ACT-246475) was administered via a single subcutaneous (s.c.) injection either in the abdomen or the thigh.

Reporting group title	Matching Placebo
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Reporting group description:

Matching placebo was administered via single subcutaneous (s.c.) administration either in the thigh or the abdomen.

Reporting group title	Selatogrel 8 mg (Follow-up)
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Reporting group description:

During this time the subjects were continued to be observed following the treatment period. No interventions were performed. The follow-up period was planned to last 28 to 35 days. The period started on Day 3 and ended with the safety follow-up telephone call or visit.

Reporting group title	Selatogrel 16 mg (Follow-up)
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Reporting group description:

During this time the subjects were continued to be observed following the treatment period. No interventions were performed. The follow-up period was planned to last 28 to 35 days. The period started on Day 3 and ended with the safety follow-up telephone call or visit.

Reporting group title	Matching Placebo (Follow-up)
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Reporting group description:

During this time the subjects were continued to be observed following the treatment period. No interventions were performed. The follow-up period was planned to last 28 to 35 days. The period started on Day 3 and ended with the safety follow-up telephone call or visit.

Subject analysis set title	Selatogrel 8 mg Pharmacokinetic Analysis Set
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Subject analysis set type	Full analysis
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Subject analysis set description:

The Pharmacokinetic Analysis Set includes all subjects who had at least one plasma concentration measurement after administration of study treatment.

One subject did not receive study drug and 3 subjects had no plasma concentration measurement after administration of study treatment.

Subject analysis set title	Selatogrel 16 mg Pharmacokinetic Analysis Set
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Subject analysis set type	Full analysis
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Subject analysis set description:

The Pharmacokinetic Analysis Set includes all subjects who had at least one plasma concentration measurement after administration of study treatment.

Primary: Primary Pharmacodynamic Response

End point title	Primary Pharmacodynamic Response
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End point description:

The primary pharmacodynamic endpoint was the pharmacodynamic response, which was defined for each subject as a P2Y₁₂ Reaction Units < 100 starting 30 minutes after injection and lasting for at least 3 hours, as measured via the VerifyNow® assay.

End point type	Primary
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End point timeframe:

30 minutes after study drug administration (injection) and lasting for at least 3 h (based on nominal time).

End point values	Selatogrel 8 mg	Selatogrel 16 mg	Matching Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	114 ^[1]	115 ^[2]	116 ^[3]	
Units: subjects				
Responder	102	103	18	

Notes:

[1] - Full Analysis Set

[2] - Full Analysis Set

[3] - Full Analysis Set

Statistical analyses

Statistical analysis title	Selatogrel 8 mg versus Matching Placebo
Statistical analysis description:	
The primary goal was to determine that the proportion of subjects receiving a dose of selatogrel, who achieved a pharmacodynamic response as measured by VerifyNow® is statistically greater than 70%.	
Comparison groups	Selatogrel 8 mg v Matching Placebo
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[4]
Method	Chi-squared
Parameter estimate	Odds ratio (OR)
Point estimate	58.9
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	22.4
upper limit	154.8

Notes:

[4] - P value significance level was set to 0.025, i.e. type I error (0.05) adjusted for multiplicity (2 comparisons) using a Bonferroni approach.

Statistical analysis title	Selatogrel 16 mg versus Matching Placebo
Statistical analysis description:	
The primary goal was to determine that the proportion of subjects receiving a dose of selatogrel, who achieved a pharmacodynamic response as measured by VerifyNow® is statistically greater than 70%.	
Comparison groups	Selatogrel 16 mg v Matching Placebo
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[5]
Method	Chi-squared
Parameter estimate	Odds ratio (OR)
Point estimate	61.2

Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	23.1
upper limit	162.3

Notes:

[5] - P value significance level was set to 0.025, i.e. type I error (0.05) adjusted for multiplicity (2 comparisons) using a Bonferroni approach.

Secondary: Maximum plasma concentration - cmax

End point title	Maximum plasma concentration - cmax
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End point description:

The plasma pharmacokinetic parameters of selatogrel (ACT-246475) were derived by non-compartmental analyses of the plasma concentration-time profiles.

End point type	Secondary
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End point timeframe:

Plasma concentrations at all scheduled sampling time points (pre-dose, 15 minutes, 30 minutes, and 1,2,4,8 and 24 hours post dose).

End point values	Selatogrel 8 mg Pharmacokinetic Analysis Set	Selatogrel 16 mg Pharmacokinetic Analysis Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	111	115		
Units: ng/mL				
geometric mean (full range (min-max))	298 (146 to 868)	484 (161 to 1030)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to reach maximum plasma concentration - Tmax

End point title	Time to reach maximum plasma concentration - Tmax
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End point description:

Tmax was derived by non-compartmental analysis of the plasma concentration time.

End point type	Secondary
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End point timeframe:

Plasma concentrations at all scheduled sampling time points (pre-dose, 15 minutes, 30 minutes, and 1,2,4,8 and 24 hours post dose).

End point values	Selatogrel 8 mg Pharmacokinetic Analysis Set	Selatogrel 16 mg Pharmacokinetic Analysis Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	111	115		
Units: hour				
median (full range (min-max))	0.52 (0.38 to 1.05)	0.53 (0.23 to 2.02)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the plasma concentration-time curve from time zero to 24 hour time point - AUC0-24

End point title	Area under the plasma concentration-time curve from time zero to 24 hour time point - AUC0-24
End point description: The plasma PK parameters of selatogrel (ACT-246475) were derived by non-compartmental analyses of the plasma concentration-time profiles.	
End point type	Secondary
End point timeframe: Plasma concentrations at all scheduled sampling time points (pre-dose, 15 minutes, 30 minutes, and 1,2,4,8 and 24 hours post dose).	

End point values	Selatogrel 8 mg Pharmacokinetic Analysis Set	Selatogrel 16 mg Pharmacokinetic Analysis Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	111	115		
Units: h*ng/mL				
geometric mean (full range (min-max))	716 (347 to 1425)	1358 (487 to 2758)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment emergent adverse events (TEAEs) were those adverse events with onset date/time after the date/time of study drug administration and up to 48 hours after the date/time of study treatment administration.

Adverse event reporting additional description:

Follow-up period: SAEs were reported (none of them as treatment related) between Day 12 and Day 31 in 5 subjects in selatogrel 8 mg group (atrial fibrillation, ventricular fibrillation and fatal cardiac arrest, syncope, non cardiac chest pain and angina pectoris); 1 in 16 mg group (costochondritis) and 1 in placebo group (myocardial infarction).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Selatogrel 8 mg
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Reporting group description:

Treatment emergent adverse events (TEAEs) were those adverse events with onset date/time after the date/time of study drug administration and up to 48 hours after the date/time of study treatment administration.

Reporting group title	Selatogrel 16 mg
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Reporting group description:

Treatment emergent adverse events (TEAEs) were those adverse events with onset date/time after the date/time of study drug administration and up to 48 hours after the date/time of study treatment administration.

Reporting group title	Matching Placebo
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Reporting group description:

Treatment emergent adverse events (TEAEs) were those adverse events with onset date/time after the date/time of study drug administration and up to 48 hours after the date/time of study treatment administration.

Serious adverse events	Selatogrel 8 mg	Selatogrel 16 mg	Matching Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 114 (0.00%)	0 / 115 (0.00%)	0 / 116 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

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

Non-serious adverse events	Selatogrel 8 mg	Selatogrel 16 mg	Matching Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 114 (31.58%)	26 / 115 (22.61%)	25 / 116 (21.55%)

Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 114 (0.00%)	1 / 115 (0.87%)	2 / 116 (1.72%)
occurrences (all)	0	1	2
Hypotension			
subjects affected / exposed	0 / 114 (0.00%)	1 / 115 (0.87%)	0 / 116 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Injection site bruising			
subjects affected / exposed	3 / 114 (2.63%)	2 / 115 (1.74%)	0 / 116 (0.00%)
occurrences (all)	3	2	0
Injection site erythema			
subjects affected / exposed	0 / 114 (0.00%)	2 / 115 (1.74%)	0 / 116 (0.00%)
occurrences (all)	0	2	0
Injection site pruritus			
subjects affected / exposed	0 / 114 (0.00%)	2 / 115 (1.74%)	0 / 116 (0.00%)
occurrences (all)	0	2	0
Injection site reaction			
subjects affected / exposed	0 / 114 (0.00%)	1 / 115 (0.87%)	0 / 116 (0.00%)
occurrences (all)	0	1	0
Medical device site bruise			
subjects affected / exposed	1 / 114 (0.88%)	0 / 115 (0.00%)	0 / 116 (0.00%)
occurrences (all)	1	0	0
Oedema peripheral			
subjects affected / exposed	0 / 114 (0.00%)	1 / 115 (0.87%)	0 / 116 (0.00%)
occurrences (all)	0	1	0
Peripheral swelling			
subjects affected / exposed	0 / 114 (0.00%)	0 / 115 (0.00%)	1 / 116 (0.86%)
occurrences (all)	0	0	1
Pyrexia			
subjects affected / exposed	0 / 114 (0.00%)	1 / 115 (0.87%)	0 / 116 (0.00%)
occurrences (all)	0	1	0
Vessel puncture site bruise			
subjects affected / exposed	4 / 114 (3.51%)	0 / 115 (0.00%)	3 / 116 (2.59%)
occurrences (all)	6	0	4
Vessel puncture site erythema			

subjects affected / exposed occurrences (all)	2 / 114 (1.75%) 2	0 / 115 (0.00%) 0	0 / 116 (0.00%) 0
Vessel puncture site haematoma subjects affected / exposed occurrences (all)	1 / 114 (0.88%) 1	0 / 115 (0.00%) 0	0 / 116 (0.00%) 0
Reproductive system and breast disorders Vaginal haemorrhage subjects affected / exposed occurrences (all)	0 / 114 (0.00%) 0	0 / 115 (0.00%) 0	1 / 116 (0.86%) 1
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all)	6 / 114 (5.26%) 6 1 / 114 (0.88%) 1	10 / 115 (8.70%) 10 0 / 115 (0.00%) 0	0 / 116 (0.00%) 0 0 / 116 (0.00%) 0
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	1 / 114 (0.88%) 1	0 / 115 (0.00%) 0	0 / 116 (0.00%) 0
Investigations Blood creatinine increased subjects affected / exposed occurrences (all) Blood potassium increased subjects affected / exposed occurrences (all) ECG P wave inverted subjects affected / exposed occurrences (all) White blood cell count increased subjects affected / exposed occurrences (all)	0 / 114 (0.00%) 0 1 / 114 (0.88%) 1 0 / 114 (0.00%) 0 0 / 114 (0.00%) 0	0 / 115 (0.00%) 0 0 / 115 (0.00%) 0 1 / 115 (0.87%) 1 0 / 115 (0.00%) 0	1 / 116 (0.86%) 1 0 / 116 (0.00%) 0 0 / 116 (0.00%) 0 1 / 116 (0.86%) 1
Injury, poisoning and procedural complications			

Contusion			
subjects affected / exposed	1 / 114 (0.88%)	1 / 115 (0.87%)	3 / 116 (2.59%)
occurrences (all)	1	1	3
Eye contusion			
subjects affected / exposed	0 / 114 (0.00%)	1 / 115 (0.87%)	0 / 116 (0.00%)
occurrences (all)	0	1	0
Procedural dizziness			
subjects affected / exposed	0 / 114 (0.00%)	1 / 115 (0.87%)	0 / 116 (0.00%)
occurrences (all)	0	1	0
Procedural nausea			
subjects affected / exposed	0 / 114 (0.00%)	1 / 115 (0.87%)	0 / 116 (0.00%)
occurrences (all)	0	1	0
Wound haemorrhage			
subjects affected / exposed	0 / 114 (0.00%)	0 / 115 (0.00%)	1 / 116 (0.86%)
occurrences (all)	0	0	1
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	1 / 114 (0.88%)	0 / 115 (0.00%)	0 / 116 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 114 (4.39%)	4 / 115 (3.48%)	1 / 116 (0.86%)
occurrences (all)	5	4	1
Dizziness postural			
subjects affected / exposed	1 / 114 (0.88%)	0 / 115 (0.00%)	1 / 116 (0.86%)
occurrences (all)	1	0	1
Headache			
subjects affected / exposed	3 / 114 (2.63%)	3 / 115 (2.61%)	5 / 116 (4.31%)
occurrences (all)	3	3	5
Lethargy			
subjects affected / exposed	0 / 114 (0.00%)	0 / 115 (0.00%)	1 / 116 (0.86%)
occurrences (all)	0	0	1
Presyncope			
subjects affected / exposed	2 / 114 (1.75%)	0 / 115 (0.00%)	0 / 116 (0.00%)
occurrences (all)	2	0	0
Ear and labyrinth disorders			

Vertigo subjects affected / exposed occurrences (all)	0 / 114 (0.00%) 0	1 / 115 (0.87%) 1	0 / 116 (0.00%) 0
Gastrointestinal disorders			
Abdominal discomfort subjects affected / exposed occurrences (all)	1 / 114 (0.88%) 1	0 / 115 (0.00%) 0	0 / 116 (0.00%) 0
Diarrhoea subjects affected / exposed occurrences (all)	4 / 114 (3.51%) 4	1 / 115 (0.87%) 1	0 / 116 (0.00%) 0
Flatulence subjects affected / exposed occurrences (all)	1 / 114 (0.88%) 1	0 / 115 (0.00%) 0	1 / 116 (0.86%) 1
Mouth haemorrhage subjects affected / exposed occurrences (all)	0 / 114 (0.00%) 0	1 / 115 (0.87%) 1	0 / 116 (0.00%) 0
Nausea subjects affected / exposed occurrences (all)	0 / 114 (0.00%) 0	1 / 115 (0.87%) 1	1 / 116 (0.86%) 1
Vomiting subjects affected / exposed occurrences (all)	0 / 114 (0.00%) 0	0 / 115 (0.00%) 0	1 / 116 (0.86%) 1
Skin and subcutaneous tissue disorders			
Dermatitis contact subjects affected / exposed occurrences (all)	1 / 114 (0.88%) 1	0 / 115 (0.00%) 0	1 / 116 (0.86%) 1
Ecchymosis subjects affected / exposed occurrences (all)	0 / 114 (0.00%) 0	1 / 115 (0.87%) 1	0 / 116 (0.00%) 0
Erythema subjects affected / exposed occurrences (all)	0 / 114 (0.00%) 0	0 / 115 (0.00%) 0	1 / 116 (0.86%) 1
Hyperhidrosis subjects affected / exposed occurrences (all)	0 / 114 (0.00%) 0	1 / 115 (0.87%) 1	0 / 116 (0.00%) 0
Petechiae			

subjects affected / exposed occurrences (all)	0 / 114 (0.00%) 0	0 / 115 (0.00%) 0	1 / 116 (0.86%) 1
Renal and urinary disorders Pollakiuria subjects affected / exposed occurrences (all)	0 / 114 (0.00%) 0	0 / 115 (0.00%) 0	1 / 116 (0.86%) 1
Renal impairment subjects affected / exposed occurrences (all)	0 / 114 (0.00%) 0	1 / 115 (0.87%) 1	0 / 116 (0.00%) 0
Musculoskeletal and connective tissue disorders Muscle spasms subjects affected / exposed occurrences (all)	0 / 114 (0.00%) 0	1 / 115 (0.87%) 1	0 / 116 (0.00%) 0
Musculoskeletal discomfort subjects affected / exposed occurrences (all)	1 / 114 (0.88%) 1	0 / 115 (0.00%) 0	0 / 116 (0.00%) 0
Metabolism and nutrition disorders Gout subjects affected / exposed occurrences (all)	1 / 114 (0.88%) 1	0 / 115 (0.00%) 0	0 / 116 (0.00%) 0
Hypoglycaemia subjects affected / exposed occurrences (all)	1 / 114 (0.88%) 1	1 / 115 (0.87%) 1	0 / 116 (0.00%) 0

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