



Clinical trial results:

Multi-center, blinded, randomized, parallel-group, Phase 3 study with aprocitentan in subjects with Resistant Hypertension (RHT)

Summary

EudraCT number	2017-004393-33
Trial protocol	DE GB FR ES BE FI CZ HU NL PL DK GR LT IT
Global end of trial date	25 April 2022

Results information

Result version number	v1 (current)
This version publication date	05 April 2023
First version publication date	05 April 2023

Trial information

Trial identification

Sponsor protocol code	ID-080A301
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03541174
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Idorsia Pharmaceuticals Ltd
Sponsor organisation address	Hegenheimermattweg 91, Allschwil, Switzerland, 4123
Public contact	Idorsia Clinical Trial Information, Idorsia Pharmaceuticals Ltd, +41 58 844 1977, idorsiaclinicaltrials@idorsia.com
Scientific contact	Idorsia Clinical Trial Information, Idorsia Pharmaceuticals Ltd, +41 58 844 1977, idorsiaclinicaltrials@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	12 May 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 April 2022
Global end of trial reached?	Yes
Global end of trial date	25 April 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the blood pressure (BP) lowering effect of aprocitentan when added to standard of care in true resistant hypertension (RHT) subjects.

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 IEC or IRB before the study was started. Sponsor personnel and the investigators were required to conduct the study in full compliance with ICH-GCP Guidelines, the principles of the Declaration of Helsinki, and with the laws and regulations of the countries in which the study is conducted. Both the sponsor and the investigators had the right to terminate the study at any time, and in such a case, were responsible for protecting the subjects' interests. The investigators were responsible for maintaining the subjects' identities in strictest confidence. Written informed consent was required to be obtained from each individual participating in the study prior to any study procedure and after adequate explanation of the aims, methods, objectives, and potential hazards of the study. It was made clear to each subject that he or she was completely free to refuse to enter the study, or to withdraw from it at any time for any reason.

Background therapy:

At least 4 weeks before the start of the run-in period, the individualized background antihypertensive medications/therapies (except beta-blockers) of subjects with resistant hypertension and having a mean trough sitting systolic blood pressure of equal to or greater than 140 mmHg measured unattended by an automated office blood pressure measurement (AOBPM) was standardized by switching to a fixed combination of a calcium channel blocker (amlodipine), an angiotensin receptor blocker (valsartan) and a diuretic (hydrochlorothiazide), i.e., standardized background antihypertensive therapy (SBAT).

In case a beta-blocker was used as one of the background antihypertensive medications or for any other indication, this could be kept, with the provision that it had been initiated and the dose kept stable for at least 4 weeks prior to the screening visit and the dose kept stable until the end-of-treatment.

After randomization, SBAT continued to be taken every morning except on the morning of study visit days, where study treatment and SBAT was administered after the completion of the visit assessments and the measurement of blood pressure.

Evidence for comparator: -

Actual start date of recruitment	18 June 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 8
Country: Number of subjects enrolled	Poland: 51

Country: Number of subjects enrolled	Spain: 18
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Belgium: 8
Country: Number of subjects enrolled	Czechia: 28
Country: Number of subjects enrolled	Finland: 16
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Germany: 18
Country: Number of subjects enrolled	Greece: 8
Country: Number of subjects enrolled	Hungary: 6
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	Lithuania: 10
Country: Number of subjects enrolled	Australia: 23
Country: Number of subjects enrolled	Canada: 21
Country: Number of subjects enrolled	China: 27
Country: Number of subjects enrolled	Israel: 10
Country: Number of subjects enrolled	Russian Federation: 166
Country: Number of subjects enrolled	Ukraine: 86
Country: Number of subjects enrolled	United States: 211
Worldwide total number of subjects	730
EEA total number of subjects	183

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)	409
From 65 to 84 years	321
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was done from 18 June 2018 to 25 April 2022.

Pre-assignment

Screening details:

730 participants are considered to be enrolled in the study and were randomized to treatment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
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Arm title	Aprocitentan 12.5 mg in Part 1 (Double-blind)
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Arm description:

Subjects were randomized and received aprocitentan 12.5 mg, orally, once daily in the morning for 4 weeks.

Arm type	Experimental
Investigational medicinal product name	Aprocitentan
Investigational medicinal product code	ACT-132577
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received aprocitentan 12.5 mg, orally, once daily in the morning for 4 weeks.

Arm title	Aprocitentan 25 mg in Part 1 (Double-blind)
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Arm description:

Subjects were randomized and received aprocitentan 25 mg, orally, once daily in the morning for 4 weeks.

Arm type	Experimental
Investigational medicinal product name	Aprocitentan
Investigational medicinal product code	ACT-132577
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received aprocitentan 25 mg, orally, once daily in the morning for 4 weeks.

Arm title	Placebo in Part 1 (Double-blind)
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Arm description:

Subjects were randomized and received placebo (matching aprocitentan), orally, once daily in the morning for 4 weeks.

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

Dosage and administration details:

Subjects received placebo (matching aprocitentan), orally, once daily in the morning for 4 weeks.

Number of subjects in period 1	Aprocitentan 12.5 mg in Part 1 (Double-blind)	Aprocitentan 25 mg in Part 1 (Double-blind)	Placebo in Part 1 (Double-blind)
Started	243	243	244
Completed	232	234	238
Not completed	11	9	6
Adverse event, non-fatal	6	5	2
Other reasons	3	2	3
Withdrawal by subject	2	2	1

Period 2

Period 2 title	Single-blind single-arm Part 2
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Arms

Arm title	Aprocitentan 25 mg in Part 2 (single-blind, single arm)
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Arm description:

Participants that completed the double-blind part 1 received aprocitentan 25 mg, orally, once daily in the morning for 32 weeks.

Arm type	Experimental
Investigational medicinal product name	Aprocitentan
Investigational medicinal product code	ACT-132577
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received aprocitentan 25 mg, orally, once daily in the morning for 4 weeks.

Number of subjects in period 2	Aprocitentan 25 mg in Part 2 (single-blind, single arm)
Started	704
Completed	613
Not completed	91
Adverse event, serious fatal	5
Adverse event, non-fatal	25
Pregnancy	1
Other reasons	32
Lost to follow-up	8
Lack of efficacy	1
Withdrawal by subject	19

Period 3

Period 3 title	Double-blind Withdrawal Part 3
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Data analyst, Carer, Subject, Assessor

Arms

Are arms mutually exclusive?	No
Arm title	Aprocitentan 25 mg in Part 3 (double-blind withdrawal)

Arm description:

After the 32-week single-blind, single-arm aprocitentan 25 mg (Part 2), participants were re-randomized and received aprocitentan 25 mg, orally, once daily in the morning for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	Aprocitentan
Investigational medicinal product code	ACT-132577
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received aprocitentan 25 mg, orally, once daily in the morning for 12 weeks.

Arm title	Placebo in Part 3 (double-blind withdrawal)
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Arm description:

After the 32-week single-blind, single-arm aprocitentan 25 mg (Part 2), participants were re-randomized and received placebo (matching aprocitentan), orally, once daily in the morning for 12 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo in Part 3
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received placebo (matching aprocitentan), orally, once daily in the morning for 12 weeks.

Number of subjects in period 3	Aprocitentan 25 mg in Part 3 (double- blind withdrawal)	Placebo in Part 3 (double-blind withdrawal)
Started	307	307
Completed	288	289
Not completed	19	18
Re-randomized in part 3, however no drug dispensed	1	-
Adverse event, non-fatal	8	7
Other reasons	9	6
Lost to follow-up	-	1
Withdrawal by subject	1	4

Baseline characteristics

Reporting groups

Reporting group title	Aprocitentan 12.5 mg in Part 1 (Double-blind)
Reporting group description: Subjects were randomized and received aprocitentan 12.5 mg, orally, once daily in the morning for 4 weeks.	
Reporting group title	Aprocitentan 25 mg in Part 1 (Double-blind)
Reporting group description: Subjects were randomized and received aprocitentan 25 mg, orally, once daily in the morning for 4 weeks.	
Reporting group title	Placebo in Part 1 (Double-blind)
Reporting group description: Subjects were randomized and received placebo (matching aprocitentan), orally, once daily in the morning for 4 weeks.	

Reporting group values	Aprocitentan 12.5 mg in Part 1 (Double-blind)	Aprocitentan 25 mg in Part 1 (Double-blind)	Placebo in Part 1 (Double-blind)
Number of subjects	243	243	244
Age categorical Units: Subjects			
Adults (18-64 years)	143	136	130
From 65-84 years	100	107	114
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	61.2	61.7	62.2
standard deviation	± 10.3	± 10.4	± 11.2
Gender categorical Units: Subjects			
Female	99	98	99
Male	144	145	145
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	11	14	13
Native Hawaiian or Other Pacific Islander	1	0	0
Black or African American	28	28	26
White	203	200	202
More than one race	0	0	0
Unknown or Not Reported	0	1	3
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	28	22	23
Not Hispanic or Latino	213	219	218
Unknown or Not Reported	2	2	3
Body Mass Index at Screening Visit Units: kilogram(s)/square metre			
arithmetic mean	33.6	34.3	33.3

standard deviation	± 6.2	± 6.8	± 5.6
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Reporting group values	Total		
Number of subjects	730		
Age categorical Units: Subjects			
Adults (18-64 years)	409		
From 65-84 years	321		
85 years and over	0		
Age continuous Units: years arithmetic mean standard deviation	-		
Gender categorical Units: Subjects			
Female	296		
Male	434		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0		
Asian	38		
Native Hawaiian or Other Pacific Islander	1		
Black or African American	82		
White	605		
More than one race	0		
Unknown or Not Reported	4		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	73		
Not Hispanic or Latino	650		
Unknown or Not Reported	7		
Body Mass Index at Screening Visit Units: kilogram(s)/square metre arithmetic mean standard deviation	-		

End points

End points reporting groups

Reporting group title	Aprocitentan 12.5 mg in Part 1 (Double-blind)
Reporting group description: Subjects were randomized and received aprocitentan 12.5 mg, orally, once daily in the morning for 4 weeks.	
Reporting group title	Aprocitentan 25 mg in Part 1 (Double-blind)
Reporting group description: Subjects were randomized and received aprocitentan 25 mg, orally, once daily in the morning for 4 weeks.	
Reporting group title	Placebo in Part 1 (Double-blind)
Reporting group description: Subjects were randomized and received placebo (matching aprocitentan), orally, once daily in the morning for 4 weeks.	
Reporting group title	Aprocitentan 25 mg in Part 2 (single-blind, single arm)
Reporting group description: Participants that completed the double-blind part 1 received aprocitentan 25 mg, orally, once daily in the morning for 32 weeks.	
Reporting group title	Aprocitentan 25 mg in Part 3 (double-blind withdrawal)
Reporting group description: After the 32-week single-blind, single-arm aprocitentan 25 mg (Part 2), participants were re-randomized and received aprocitentan 25 mg, orally, once daily in the morning for 12 weeks.	
Reporting group title	Placebo in Part 3 (double-blind withdrawal)
Reporting group description: After the 32-week single-blind, single-arm aprocitentan 25 mg (Part 2), participants were re-randomized and received placebo (matching aprocitentan), orally, once daily in the morning for 12 weeks.	

Primary: Change From Baseline to Week 4 of Double-blind Treatment in Mean Trough Sitting Systolic Blood Pressure (SiSBP) Measured by Automated Office Blood Pressure Measurement

End point title	Change From Baseline to Week 4 of Double-blind Treatment in Mean Trough Sitting Systolic Blood Pressure (SiSBP) Measured by Automated Office Blood Pressure Measurement
End point description: Changes from baseline to Week 4 in mean trough SiSBP were analyzed using a mixed model. Participants had their blood pressure (BP) measured at the study site using the automated oscillometric sphygmomanometer (Microlife WatchBP® Office) which was provided to each site. BP was to be measured at trough (before taking the study treatment and SBAT). The BP assessment, participant preparation (e.g., arm selection, arm position, cuff size) was standardized and followed the American Heart Association guidelines / Canadian Education Program on Hypertension. The participant was resting undisturbed, alone (unattended) in a quiet place for 5 minutes at each visit. BP was measured at each visit with the same device, which recorded five sitting blood pressure readings (one per minute, the first value was excluded from the average). A negative change indicates a decrease in SiSBP from baseline.	
End point type	Primary
End point timeframe: Pre-dose Day 1 (Part 1 double-blind randomized baseline) up to Week 4 (End of double-blind randomized part 1).	

End point values	Aprocitentan 12.5 mg in Part 1 (Double-blind)	Aprocitentan 25 mg in Part 1 (Double-blind)	Placebo in Part 1 (Double-blind)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	243	243	244	
Units: mmHg				
least squares mean (confidence interval 97.5%)	-15.26 (-17.36 to -13.17)	-15.20 (-17.27 to -13.13)	-11.47 (-13.57 to -9.38)	

Statistical analyses

Statistical analysis title	SiSBP analysis Part 1: 12.5 mg vs placebo (AOBPM)
Statistical analysis description:	
The analysis was performed on the Full Analysis Set (FAS). The FAS included all participants who were randomized and had a baseline sitting systolic blood pressure, measured by automated office blood pressure measurement. Baseline was defined as the last measurement before randomization.	
Comparison groups	Aprocitentan 12.5 mg in Part 1 (Double-blind) v Placebo in Part 1 (Double-blind)
Number of subjects included in analysis	487
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0042 ^[1]
Method	Mixed models analysis
Parameter estimate	LS Mean difference to placebo
Point estimate	-3.79
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-6.76
upper limit	-0.82

Notes:

[1] - Mixed effects model for Repeated Measures: Change from baseline in SiSBP = baseline SiSBP + treatment + visit + treatment x visit + baseline x visit.

Statistical analysis title	SiSBP analysis Part 1: 25 mg vs placebo (AOBPM)
Statistical analysis description:	
The analysis was performed on the Full Analysis Set (FAS). The FAS included all participants who were randomized and had a baseline sitting systolic blood pressure, measured by automated office blood pressure measurement. Baseline was defined as the last measurement before randomization.	
Comparison groups	Aprocitentan 25 mg in Part 1 (Double-blind) v Placebo in Part 1 (Double-blind)
Number of subjects included in analysis	487
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0046 ^[2]
Method	Mixed models analysis
Parameter estimate	LS Mean difference to placebo
Point estimate	-3.73

Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-6.67
upper limit	-0.78

Notes:

[2] - Mixed effects model for Repeated Measures: Change from baseline in SiSBP = baseline SiSBP + treatment + visit + treatment x visit + baseline x visit.

Secondary: Change From Double-blind Withdrawal Baseline (Week 36) to Week 40 in Mean Trough Sitting Systolic Blood Pressure (SiSBP) Measured by Unattended Automated Office Blood Pressure Measurement

End point title	Change From Double-blind Withdrawal Baseline (Week 36) to Week 40 in Mean Trough Sitting Systolic Blood Pressure (SiSBP) Measured by Unattended Automated Office Blood Pressure Measurement
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End point description:

Changes from double-blind withdrawal baseline (Week 36) to Week 40 in mean trough SiSBP were analyzed using a mixed model. Participants had their blood pressure (BP) measured at the study site using the automated oscillometric sphygmomanometer (Microlife WatchBP® Office) which was provided to each site. BP was to be measured at trough (before taking the study treatment and SBAT). The BP assessment, participant preparation (e.g., arm selection, arm position, cuff size) was standardized and followed the American Heart Association guidelines / Canadian Education Program on Hypertension. The participant was resting undisturbed, alone (unattended) in a quiet place for 5 minutes at each visit. BP was measured at each visit with the same device, which recorded five sitting blood pressure readings (one per minute, the first value was excluded from the average). A negative change indicates a decrease in SiSBP from baseline.

End point type	Secondary
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End point timeframe:

Pre-dose Week 36 (Part 3 double-blind-withdrawal baseline) up to Week 40.

End point values	Aprocitentan 25 mg in Part 3 (double-blind withdrawal)	Placebo in Part 3 (double-blind withdrawal)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	307	307		
Units: mmHg				
least squares mean (confidence interval 95%)	-1.47 (-2.97 to 0.04)	4.36 (2.87 to 5.85)		

Statistical analyses

Statistical analysis title	SiSBP analysis in Part 3: 25 mg vs placebo (AOBPM)
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Statistical analysis description:

Mixed effects model for Repeated Measures: Change from DB-WD baseline in SiSBP = DB-WD baseline SiSBP + stratum (randomized treatment in DB part) + treatment + visit + treatment x visit + DB-WD baseline x visit.

Comparison groups	Aprocitentan 25 mg in Part 3 (double-blind withdrawal) v Placebo in Part 3 (double-blind withdrawal)
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Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LS mean difference to placebo
Point estimate	-5.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.94
upper limit	-3.71

Secondary: Change From Baseline to Week 4 of Double-blind Treatment in Mean Trough Sitting Diastolic Blood Pressure (SiDBP) Measured by Unattended Automated Office Blood Pressure Measurement

End point title	Change From Baseline to Week 4 of Double-blind Treatment in Mean Trough Sitting Diastolic Blood Pressure (SiDBP) Measured by Unattended Automated Office Blood Pressure Measurement
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End point description:

Changes from baseline to Week 4 in mean trough SiDBP were analyzed using a mixed model. Participants had their blood pressure (BP) measured at the study site using the automated oscillometric sphygmomanometer (Microlife WatchBP® Office) which was provided to each site. BP was to be measured at trough (before taking the study treatment and SBAT). The BP assessment, participant preparation (e.g., arm selection, arm position, cuff size) was standardized and followed the American Heart Association guidelines / Canadian Education Program on Hypertension. BP was measured at each visit with the same device, which recorded five sitting blood pressure readings (one per minute, the first value was excluded from the average). The participant was resting undisturbed, alone (unattended) in a quiet place for 5 minutes at each visit. A negative change indicates a decrease in SiDBP from baseline.

End point type	Secondary
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End point timeframe:

Pre-dose Day 1 (Part 1 double-blind randomized baseline) up to Week 4 (End of double-blind randomized part 1).

End point values	Aprocitentan 12.5 mg in Part 1 (Double- blind)	Aprocitentan 25 mg in Part 1 (Double-blind)	Placebo in Part 1 (Double- blind)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	243	243	244	
Units: mmHg				
least squares mean (confidence interval 95%)	-10.43 (-11.58 to -9.27)	-10.95 (-12.09 to -9.82)	-6.48 (-7.63 to -5.33)	

Statistical analyses

Statistical analysis title	SiDBP analysis Part 1: 12.5 mg vs placebo (AOBPM)
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Statistical analysis description:

Mixed effects model for Repeated Measures: Change from baseline in SiDBP = baseline SiDBP +

treatment + visit + treatment x visit + baseline x visit.

Comparison groups	Aprocitentan 12.5 mg in Part 1 (Double-blind) v Placebo in Part 1 (Double-blind)
Number of subjects included in analysis	487
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LS Mean difference to placebo
Point estimate	-3.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.57
upper limit	-2.31

Statistical analysis title	SiDBP analysis Part 1: 25 mg vs placebo (AOBPM)
Statistical analysis description:	
Mixed effects model for Repeated Measures: Change from baseline in SiDBP = baseline SiDBP + treatment + visit + treatment x visit + baseline x visit.	
Comparison groups	Aprocitentan 25 mg in Part 1 (Double-blind) v Placebo in Part 1 (Double-blind)
Number of subjects included in analysis	487
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LS mean difference to placebo
Point estimate	-4.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.09
upper limit	-2.85

Secondary: Changes From Baseline to Week 4 of Double-blind Treatment in 24-hour Mean Systolic (SBP) and Diastolic Blood Pressure (DBP) Measured by Ambulatory Blood Pressure Monitoring

End point title	Changes From Baseline to Week 4 of Double-blind Treatment in 24-hour Mean Systolic (SBP) and Diastolic Blood Pressure (DBP) Measured by Ambulatory Blood Pressure Monitoring
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End point description:

ABPM devices were provided to each site by the central blood pressure laboratory. On the first day after all visit assessments were performed, the ABPM device (Mobil-O-Graph NG) was fitted to the participant. The following day (i.e., second day), the participant came back to site to have the ABPM device removed. ABPM data collected over the 24-hours was electronically transferred to the central BP laboratory. Systolic blood pressure and diastolic blood pressure were measured at predetermined times every 20 minutes from 06:00 to 21:59, and every 30 minutes from 22:00 to 05:59. For each participant and at each visit (baseline and Week 4) the 24-hour mean SBP (or DBP) was calculated from the area under the SBP (or DBP) time curve and divided by the time span. A negative change indicates a

decrease in 24-hour mean systolic / diastolic blood pressure from baseline.

End point type	Secondary
End point timeframe:	
Pre-dose Day 1 (Part 1 double-blind randomized baseline) and Week 4 (End of double-blind randomized part 1).	

End point values	Aprocitentan 12.5 mg in Part 1 (Double- blind)	Aprocitentan 25 mg in Part 1 (Double-blind)	Placebo in Part 1 (Double- blind)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	206	207	220	
Units: mmHg				
least squares mean (confidence interval 95%)				
24-hour mean systolic blood pressure	-6.73 (-8.20 to -5.26)	-8.44 (-9.88 to -7.00)	-2.55 (-4.00 to -1.10)	
24-hour mean diastolic blood pressure	-6.25 (-7.20 to -5.29)	-7.74 (-8.67 to -6.80)	-1.92 (-2.87 to -0.98)	

Statistical analyses

Statistical analysis title	24-h mean SBP analysis Part 1: 12.5 mg vs placebo
Comparison groups	Aprocitentan 12.5 mg in Part 1 (Double-blind) v Placebo in Part 1 (Double-blind)
Number of subjects included in analysis	426
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS Means difference to placebo
Point estimate	-4.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.25
upper limit	-2.12

Statistical analysis title	24-h mean SBP analysis Part 1: 25 mg vs placebo
Comparison groups	Aprocitentan 25 mg in Part 1 (Double-blind) v Placebo in Part 1 (Double-blind)

Number of subjects included in analysis	427
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS Mean difference to placebo
Point estimate	-5.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.95
upper limit	-3.85

Statistical analysis title	24-h mean DBP analysis Part 1: 12.5 mg vs placebo
Comparison groups	Aprocitentan 12.5 mg in Part 1 (Double-blind) v Placebo in Part 1 (Double-blind)
Number of subjects included in analysis	426
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS Mean difference to placebo
Point estimate	-4.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.66
upper limit	-2.98

Statistical analysis title	24-h mean DBP analysis Part 1: 25 mg vs placebo
Comparison groups	Aprocitentan 25 mg in Part 1 (Double-blind) v Placebo in Part 1 (Double-blind)
Number of subjects included in analysis	427
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS Mean difference to placebo
Point estimate	-5.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.14
upper limit	-4.49

Secondary: Change From Double-blind Withdrawal Baseline (Week 36) to Week 40 of Double-blind-withdrawal (DB-WD) Treatment in Trough Sitting Diastolic Blood Pressure (SiDBP) Measured by Unattended Automated Office Blood Pressure

End point title	Change From Double-blind Withdrawal Baseline (Week 36) to Week 40 of Double-blind-withdrawal (DB-WD) Treatment in Trough Sitting Diastolic Blood Pressure (SiDBP) Measured by Unattended Automated Office Blood Pressure
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End point description:

Changes from double-blind withdrawal (Week 36) to Week 40 in mean trough SiDBP were analyzed using a mixed model. Participants had their blood pressure (BP) measured at the study site using the automated oscillometric sphygmomanometer (Microlife WatchBP® Office) which was provided to each site. BP was to be measured at trough (before taking the study treatment and SBAT). The BP assessment, participant preparation (e.g., arm selection, arm position, cuff size) was standardized and followed the American Heart Association guidelines / Canadian Education Program on Hypertension. The participant was resting undisturbed, alone (unattended) in a quiet place for 5 minutes at each visit. BP was measured at each visit with the same device, which recorded five sitting blood pressure readings (one per minute, the first value was excluded from the average). A negative change indicates a decrease in SiDBP from baseline.

End point type	Secondary
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End point timeframe:

Pre-dose Week 36 (Part 3 double-blind-withdrawal baseline) up to Week 40.

End point values	Aprocitentan 25 mg in Part 3 (double-blind withdrawal)	Placebo in Part 3 (double-blind withdrawal)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	307	307		
Units: mmHg				
least squares mean (confidence interval 95%)	-0.52 (-1.54 to 0.50)	4.67 (3.66 to 5.68)		

Statistical analyses

Statistical analysis title	SiDBP analysis in Part 3: 25 mg vs placebo (AOBPM)
Comparison groups	Aprocitentan 25 mg in Part 3 (double-blind withdrawal) v Placebo in Part 3 (double-blind withdrawal)
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LS Mean difference to placebo
Point estimate	-5.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.62
upper limit	-3.76

Secondary: Changes From Double-blind Withdrawal Baseline (Week 36) to Week 40 of Double-blind-withdrawal (DB-WD) Treatment in 24-hour Mean Systolic (SBP) and Diastolic Blood Pressure (DBP) Measured by Ambulatory Blood Pressure Monitoring

End point title	Changes From Double-blind Withdrawal Baseline (Week 36) to Week 40 of Double-blind-withdrawal (DB-WD) Treatment in 24-hour Mean Systolic (SBP) and Diastolic Blood Pressure (DBP) Measured by Ambulatory Blood Pressure Monitoring
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End point description:

ABPM devices were provided to each site by the central blood pressure laboratory. On the first day after all visit assessments were performed, the ABPM device (Mobil-O-Graph NG) was fitted to the participant. The following day (i.e., second day), the participant came back to site to have the ABPM device removed. ABPM data collected over the 24-hours was electronically transferred to the central BP laboratory. Systolic blood pressure and diastolic blood pressure were measured at predetermined times every 20 minutes from 06:00 to 21:59, and every 30 minutes from 22:00 to 05:59. For each participant and at each visit (the double-blind withdrawal baseline [Week 36] and the week 40) the 24-hour mean SBP (or DBP) was calculated from the area under the SBP (or DBP) time curve. A negative change indicates a decrease in 24-hour mean systolic / diastolic blood pressure from baseline.

End point type	Secondary
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End point timeframe:

From Week 36 (Part 3 double-blind-withdrawal baseline) and Week 40.

End point values	Aprocitentan 25 mg in Part 3 (double-blind withdrawal)	Placebo in Part 3 (double-blind withdrawal)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	237	241		
Units: mmHg				
least squares mean (confidence interval 95%)				
24-hour mean systolic blood pressure	-0.07 (-1.46 to 1.32)	6.46 (5.06 to 7.85)		
24-hour mean diastolic blood pressure	-0.47 (-1.34 to 0.40)	6.28 (5.40 to 7.15)		

Statistical analyses

Statistical analysis title	Part 3 analysis: 24-hour mean SiSBP (ABPM)
Comparison groups	Aprocitentan 25 mg in Part 3 (double-blind withdrawal) v Placebo in Part 3 (double-blind withdrawal)
Number of subjects included in analysis	478
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS Mean difference to placebo
Point estimate	-6.53

Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.5
upper limit	-4.56

Statistical analysis title	Part 3 analysis: 24-hour mean SiDBP (ABPM)
Comparison groups	Placebo in Part 3 (double-blind withdrawal) v Aprocitantan 25 mg in Part 3 (double-blind withdrawal)
Number of subjects included in analysis	478
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS Mean difference to placebo
Point estimate	-6.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.98
upper limit	-5.52

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AE were considered treatment-emergent, if the onset date is between the first intake of treatment up to 30 days after the stop of study treatment. Study treatment was up to 48 weeks. The length of treatment in each part is described in each treatment arm.

Adverse event reporting additional description:

Only participants entering the randomized treatment period were considered enrolled for the study and are included in the AE analysis. The Run-in period was designed to exclude potential placebo responders and is not part of the statistical analysis of the study.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.1
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Reporting groups

Reporting group title	Aprocitentan 12.5 mg in Part 1 (Double-blind)
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Reporting group description:

Subjects were randomized and received aprocitentan 12.5 mg, orally, once daily in the morning for 4 weeks.

Reporting group title	Aprocitentan 25 mg in Part 1 (Double-blind)
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Reporting group description:

Subjects were randomized and received aprocitentan 25 mg, orally, once daily in the morning for 4 weeks.

Reporting group title	Placebo in Part 1 (Double-blind)
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Reporting group description:

Subjects were randomized and received placebo (matching aprocitentan), orally, once daily in the morning for 4 weeks.

Reporting group title	Aprocitentan 25 mg in Part 2 (Single-blind, single arm)
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Reporting group description:

Participants that completed the double-blind part received aprocitentan 25 mg, orally, once daily in the morning for 32 weeks.

Reporting group title	Aprocitentan 25 mg in Part 3 (Double-blind withdrawal)
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Reporting group description:

After the 32-week single-blind, single-arm aprocitentan 25 mg (Part 2), participants were re-randomized and received aprocitentan 25 mg, orally, once daily in the morning for 12 weeks.

Reporting group title	Placebo in Part 3 (Double-blind withdrawal)
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Reporting group description:

After the 32-week single-blind, single-arm aprocitentan 25 mg (Part 2), participants were re-randomized and received placebo (matching aprocitentan), orally, once daily in the morning for 12 weeks.

Serious adverse events	Aprocitentan 12.5 mg in Part 1 (Double-blind)	Aprocitentan 25 mg in Part 1 (Double-blind)	Placebo in Part 1 (Double-blind)
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 243 (3.29%)	8 / 245 (3.27%)	3 / 242 (1.24%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Adenocarcinoma of colon			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive breast carcinoma			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastatic neoplasm			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cancer			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cell carcinoma			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mantle cell lymphoma			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			

subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Distributive shock			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic stenosis			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	1 / 243 (0.41%)	0 / 245 (0.00%)	0 / 242 (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
Hypotension			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive urgency			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intermittent claudication			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery stenosis			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Coronary artery bypass			

subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip arthroplasty			
subjects affected / exposed	1 / 243 (0.41%)	0 / 245 (0.00%)	0 / 242 (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
Peripheral artery bypass			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toe amputation			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 243 (0.00%)	1 / 245 (0.41%)	0 / 242 (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
Oedema peripheral			
subjects affected / exposed	0 / 243 (0.00%)	1 / 245 (0.41%)	0 / 242 (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
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden cardiac death			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			

subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Endometrial hyperplasia			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine polyp			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 243 (0.00%)	1 / 245 (0.41%)	0 / 242 (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 failure			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pulmonary embolism			
subjects affected / exposed	1 / 243 (0.41%)	0 / 245 (0.00%)	0 / 242 (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
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood pressure increased			
subjects affected / exposed	0 / 243 (0.00%)	1 / 245 (0.41%)	0 / 242 (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
Injury, poisoning and procedural complications			
Chest injury			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic intracranial haemorrhage			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haemorrhage			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Procedural intestinal perforation subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute left ventricular failure			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure chronic			
subjects affected / exposed	0 / 243 (0.00%)	1 / 245 (0.41%)	0 / 242 (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 failure acute			

subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 243 (0.00%)	1 / 245 (0.41%)	0 / 242 (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
Atrioventricular block second degree			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiogenic shock			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left ventricular dysfunction			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery dissection			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	1 / 243 (0.41%)	0 / 245 (0.00%)	0 / 242 (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			
Cerebrovascular accident			

subjects affected / exposed	0 / 243 (0.00%)	1 / 245 (0.41%)	0 / 242 (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
Cerebral infarction			
subjects affected / exposed	1 / 243 (0.41%)	0 / 245 (0.00%)	0 / 242 (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
Brain oedema			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial paresis			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	1 / 243 (0.41%)	0 / 245 (0.00%)	1 / 242 (0.41%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			

subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Meniere's disease			
subjects affected / exposed	0 / 243 (0.00%)	1 / 245 (0.41%)	0 / 242 (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
Vestibular ataxia			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Umbilical hernia, obstructive			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Rectal fissure			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis chronic			
subjects affected / exposed	0 / 243 (0.00%)	1 / 245 (0.41%)	0 / 242 (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			
Cholecystitis acute			
subjects affected / exposed	1 / 243 (0.41%)	0 / 245 (0.00%)	0 / 242 (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			
Skin ulcer			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angioedema			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dermatitis allergic			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Calculus urinary			

subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephropathy toxic			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureteric stenosis			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Rotator cuff syndrome			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteochondrosis			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 243 (0.00%)	2 / 245 (0.82%)	0 / 242 (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

COVID-19 pneumonia			
subjects affected / exposed	2 / 243 (0.82%)	0 / 245 (0.00%)	1 / 242 (0.41%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess jaw			
subjects affected / exposed	0 / 243 (0.00%)	1 / 245 (0.41%)	0 / 242 (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
Cholecystitis infective			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	1 / 242 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 243 (0.41%)	1 / 245 (0.41%)	0 / 242 (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
Sepsis			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	1 / 242 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			

subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic gangrene			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonsillar abscess			
subjects affected / exposed	0 / 243 (0.00%)	1 / 245 (0.41%)	0 / 242 (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
Wound infection			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureteritis			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			

subjects affected / exposed	0 / 243 (0.00%)	0 / 245 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Aprocitentan 25 mg in Part 2 (Single- blind, single arm)	Aprocitentan 25 mg in Part 3 (Double- blind withdrawal)	Placebo in Part 3 (Double-blind withdrawal)
Total subjects affected by serious adverse events			
subjects affected / exposed	82 / 704 (11.65%)	18 / 310 (5.81%)	9 / 303 (2.97%)
number of deaths (all causes)	9	1	0
number of deaths resulting from adverse events	9	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	1 / 704 (0.14%)	0 / 310 (0.00%)	0 / 303 (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
Invasive breast carcinoma			
subjects affected / exposed	1 / 704 (0.14%)	0 / 310 (0.00%)	0 / 303 (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
Metastatic neoplasm			
subjects affected / exposed	1 / 704 (0.14%)	0 / 310 (0.00%)	0 / 303 (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
Renal cancer			
subjects affected / exposed	1 / 704 (0.14%)	0 / 310 (0.00%)	0 / 303 (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
Renal cell carcinoma			
subjects affected / exposed	1 / 704 (0.14%)	0 / 310 (0.00%)	0 / 303 (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
Mantle cell lymphoma			

subjects affected / exposed	1 / 704 (0.14%)	0 / 310 (0.00%)	0 / 303 (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
Lung neoplasm malignant			
subjects affected / exposed	1 / 704 (0.14%)	0 / 310 (0.00%)	0 / 303 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	1 / 704 (0.14%)	0 / 310 (0.00%)	0 / 303 (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
Hypertension			
subjects affected / exposed	0 / 704 (0.00%)	1 / 310 (0.32%)	0 / 303 (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
Distributive shock			
subjects affected / exposed	1 / 704 (0.14%)	0 / 310 (0.00%)	0 / 303 (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
Aortic stenosis			
subjects affected / exposed	0 / 704 (0.00%)	1 / 310 (0.32%)	0 / 303 (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
Deep vein thrombosis			
subjects affected / exposed	1 / 704 (0.14%)	0 / 310 (0.00%)	0 / 303 (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
Hypotension			
subjects affected / exposed	1 / 704 (0.14%)	0 / 310 (0.00%)	0 / 303 (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
Hypertensive urgency			

subjects affected / exposed	1 / 704 (0.14%)	0 / 310 (0.00%)	0 / 303 (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
Intermittent claudication			
subjects affected / exposed	1 / 704 (0.14%)	0 / 310 (0.00%)	0 / 303 (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
Peripheral artery stenosis			
subjects affected / exposed	1 / 704 (0.14%)	0 / 310 (0.00%)	0 / 303 (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
Surgical and medical procedures			
Coronary artery bypass			
subjects affected / exposed	1 / 704 (0.14%)	0 / 310 (0.00%)	0 / 303 (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
Hip arthroplasty			
subjects affected / exposed	0 / 704 (0.00%)	0 / 310 (0.00%)	0 / 303 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery bypass			
subjects affected / exposed	1 / 704 (0.14%)	0 / 310 (0.00%)	0 / 303 (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
Toe amputation			
subjects affected / exposed	1 / 704 (0.14%)	0 / 310 (0.00%)	0 / 303 (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
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 704 (0.14%)	0 / 310 (0.00%)	0 / 303 (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

Oedema peripheral			
subjects affected / exposed	0 / 704 (0.00%)	0 / 310 (0.00%)	0 / 303 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 704 (0.00%)	1 / 310 (0.32%)	0 / 303 (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
Sudden cardiac death			
subjects affected / exposed	1 / 704 (0.14%)	0 / 310 (0.00%)	0 / 303 (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
Pyrexia			
subjects affected / exposed	1 / 704 (0.14%)	0 / 310 (0.00%)	0 / 303 (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
Death			
subjects affected / exposed	1 / 704 (0.14%)	0 / 310 (0.00%)	0 / 303 (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			
Endometrial hyperplasia			
subjects affected / exposed	0 / 704 (0.00%)	0 / 310 (0.00%)	1 / 303 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine polyp			
subjects affected / exposed	1 / 704 (0.14%)	0 / 310 (0.00%)	0 / 303 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			

subjects affected / exposed	1 / 704 (0.14%)	0 / 310 (0.00%)	0 / 303 (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
Dyspnoea			
subjects affected / exposed	1 / 704 (0.14%)	1 / 310 (0.32%)	0 / 303 (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
Pulmonary oedema			
subjects affected / exposed	1 / 704 (0.14%)	0 / 310 (0.00%)	0 / 303 (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 failure			
subjects affected / exposed	1 / 704 (0.14%)	0 / 310 (0.00%)	0 / 303 (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 embolism			
subjects affected / exposed	0 / 704 (0.00%)	0 / 310 (0.00%)	0 / 303 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 704 (0.14%)	0 / 310 (0.00%)	0 / 303 (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
Blood pressure increased			
subjects affected / exposed	0 / 704 (0.00%)	0 / 310 (0.00%)	0 / 303 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Chest injury			
subjects affected / exposed	1 / 704 (0.14%)	0 / 310 (0.00%)	0 / 303 (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

Traumatic intracranial haemorrhage			
subjects affected / exposed	1 / 704 (0.14%)	0 / 310 (0.00%)	0 / 303 (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
Tibia fracture			
subjects affected / exposed	1 / 704 (0.14%)	0 / 310 (0.00%)	0 / 303 (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
Subdural haemorrhage			
subjects affected / exposed	1 / 704 (0.14%)	0 / 310 (0.00%)	0 / 303 (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
Road traffic accident			
subjects affected / exposed	1 / 704 (0.14%)	0 / 310 (0.00%)	0 / 303 (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
Procedural intestinal perforation			
subjects affected / exposed	1 / 704 (0.14%)	0 / 310 (0.00%)	0 / 303 (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
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	3 / 704 (0.43%)	3 / 310 (0.97%)	0 / 303 (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
Angina unstable			
subjects affected / exposed	5 / 704 (0.71%)	1 / 310 (0.32%)	0 / 303 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	2 / 704 (0.28%)	0 / 310 (0.00%)	0 / 303 (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
Acute left ventricular failure			

subjects affected / exposed	0 / 704 (0.00%)	1 / 310 (0.32%)	0 / 303 (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
Atrioventricular block			
subjects affected / exposed	1 / 704 (0.14%)	0 / 310 (0.00%)	0 / 303 (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
Cardiac failure congestive			
subjects affected / exposed	3 / 704 (0.43%)	0 / 310 (0.00%)	0 / 303 (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
Cardiac failure chronic			
subjects affected / exposed	1 / 704 (0.14%)	0 / 310 (0.00%)	0 / 303 (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
Cardiac failure acute			
subjects affected / exposed	0 / 704 (0.00%)	0 / 310 (0.00%)	1 / 303 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	1 / 704 (0.14%)	0 / 310 (0.00%)	0 / 303 (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
Atrioventricular block second degree			
subjects affected / exposed	1 / 704 (0.14%)	0 / 310 (0.00%)	0 / 303 (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
Cardiogenic shock			
subjects affected / exposed	0 / 704 (0.00%)	1 / 310 (0.32%)	0 / 303 (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
Left ventricular dysfunction			

subjects affected / exposed	1 / 704 (0.14%)	0 / 310 (0.00%)	0 / 303 (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
Coronary artery dissection			
subjects affected / exposed	0 / 704 (0.00%)	0 / 310 (0.00%)	1 / 303 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	2 / 704 (0.28%)	0 / 310 (0.00%)	0 / 303 (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
Myocardial infarction			
subjects affected / exposed	2 / 704 (0.28%)	1 / 310 (0.32%)	0 / 303 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	2 / 704 (0.28%)	0 / 310 (0.00%)	0 / 303 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	0 / 704 (0.00%)	0 / 310 (0.00%)	0 / 303 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain oedema			
subjects affected / exposed	1 / 704 (0.14%)	0 / 310 (0.00%)	0 / 303 (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
Syncope			
subjects affected / exposed	2 / 704 (0.28%)	0 / 310 (0.00%)	0 / 303 (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
Transient ischaemic attack			

subjects affected / exposed	1 / 704 (0.14%)	1 / 310 (0.32%)	0 / 303 (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
Facial paresis			
subjects affected / exposed	0 / 704 (0.00%)	1 / 310 (0.32%)	0 / 303 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial			
subjects affected / exposed	0 / 704 (0.00%)	0 / 310 (0.00%)	1 / 303 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 704 (0.00%)	0 / 310 (0.00%)	1 / 303 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	1 / 704 (0.14%)	0 / 310 (0.00%)	0 / 303 (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			
subjects affected / exposed	1 / 704 (0.14%)	0 / 310 (0.00%)	0 / 303 (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
Ear and labyrinth disorders			
Meniere's disease			
subjects affected / exposed	0 / 704 (0.00%)	0 / 310 (0.00%)	0 / 303 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vestibular ataxia			
subjects affected / exposed	1 / 704 (0.14%)	0 / 310 (0.00%)	0 / 303 (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
Erysipelas			

subjects affected / exposed	1 / 704 (0.14%)	0 / 310 (0.00%)	0 / 303 (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
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 704 (0.14%)	0 / 310 (0.00%)	0 / 303 (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
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 704 (0.14%)	0 / 310 (0.00%)	0 / 303 (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
Umbilical hernia, obstructive			
subjects affected / exposed	1 / 704 (0.14%)	0 / 310 (0.00%)	0 / 303 (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
Rectal fissure			
subjects affected / exposed	1 / 704 (0.14%)	0 / 310 (0.00%)	0 / 303 (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
Pancreatitis chronic			
subjects affected / exposed	0 / 704 (0.00%)	1 / 310 (0.32%)	0 / 303 (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			
Cholecystitis acute			
subjects affected / exposed	0 / 704 (0.00%)	0 / 310 (0.00%)	0 / 303 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	0 / 704 (0.00%)	1 / 310 (0.32%)	0 / 303 (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

Angioedema			
subjects affected / exposed	0 / 704 (0.00%)	0 / 310 (0.00%)	1 / 303 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dermatitis allergic			
subjects affected / exposed	1 / 704 (0.14%)	0 / 310 (0.00%)	0 / 303 (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			
subjects affected / exposed	1 / 704 (0.14%)	0 / 310 (0.00%)	0 / 303 (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
Calculus urinary			
subjects affected / exposed	2 / 704 (0.28%)	0 / 310 (0.00%)	0 / 303 (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
Nephropathy toxic			
subjects affected / exposed	1 / 704 (0.14%)	0 / 310 (0.00%)	0 / 303 (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
Ureteric stenosis			
subjects affected / exposed	1 / 704 (0.14%)	0 / 310 (0.00%)	0 / 303 (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
Musculoskeletal and connective tissue disorders			
Rotator cuff syndrome			
subjects affected / exposed	1 / 704 (0.14%)	0 / 310 (0.00%)	0 / 303 (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
Osteochondrosis			
subjects affected / exposed	1 / 704 (0.14%)	0 / 310 (0.00%)	0 / 303 (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

Osteoarthritis			
subjects affected / exposed	1 / 704 (0.14%)	0 / 310 (0.00%)	0 / 303 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	1 / 704 (0.14%)	0 / 310 (0.00%)	0 / 303 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 704 (0.00%)	0 / 310 (0.00%)	0 / 303 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19 pneumonia			
subjects affected / exposed	14 / 704 (1.99%)	4 / 310 (1.29%)	2 / 303 (0.66%)
occurrences causally related to treatment / all	0 / 14	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 3	0 / 1	0 / 0
COVID-19			
subjects affected / exposed	0 / 704 (0.00%)	1 / 310 (0.32%)	0 / 303 (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
Abscess jaw			
subjects affected / exposed	0 / 704 (0.00%)	0 / 310 (0.00%)	0 / 303 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis infective			
subjects affected / exposed	0 / 704 (0.00%)	1 / 310 (0.32%)	0 / 303 (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
Pyelonephritis acute			
subjects affected / exposed	1 / 704 (0.14%)	0 / 310 (0.00%)	0 / 303 (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
Pneumonia bacterial			

subjects affected / exposed	1 / 704 (0.14%)	0 / 310 (0.00%)	0 / 303 (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
Pneumonia			
subjects affected / exposed	2 / 704 (0.28%)	2 / 310 (0.65%)	0 / 303 (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
Sepsis			
subjects affected / exposed	0 / 704 (0.00%)	0 / 310 (0.00%)	0 / 303 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 704 (0.14%)	0 / 310 (0.00%)	0 / 303 (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
Diverticulitis			
subjects affected / exposed	1 / 704 (0.14%)	0 / 310 (0.00%)	0 / 303 (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
Diabetic gangrene			
subjects affected / exposed	1 / 704 (0.14%)	0 / 310 (0.00%)	0 / 303 (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
Peritonsillar abscess			
subjects affected / exposed	0 / 704 (0.00%)	0 / 310 (0.00%)	0 / 303 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	1 / 704 (0.14%)	0 / 310 (0.00%)	0 / 303 (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
Urinary tract infection			

subjects affected / exposed	1 / 704 (0.14%)	0 / 310 (0.00%)	0 / 303 (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
Ureteritis			
subjects affected / exposed	1 / 704 (0.14%)	0 / 310 (0.00%)	0 / 303 (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
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	1 / 704 (0.14%)	0 / 310 (0.00%)	0 / 303 (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
Hyperkalaemia			
subjects affected / exposed	2 / 704 (0.28%)	0 / 310 (0.00%)	0 / 303 (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

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

Non-serious adverse events	Aprocitentan 12.5 mg in Part 1 (Double-blind)	Aprocitentan 25 mg in Part 1 (Double-blind)	Placebo in Part 1 (Double-blind)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 243 (6.58%)	34 / 245 (13.88%)	5 / 242 (2.07%)
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	16 / 243 (6.58%)	34 / 245 (13.88%)	5 / 242 (2.07%)
occurrences (all)	16	34	5

Non-serious adverse events	Aprocitentan 25 mg in Part 2 (Single-blind, single arm)	Aprocitentan 25 mg in Part 3 (Double-blind withdrawal)	Placebo in Part 3 (Double-blind withdrawal)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	95 / 704 (13.49%)	6 / 310 (1.94%)	4 / 303 (1.32%)
General disorders and administration site conditions			
Oedema peripheral			

subjects affected / exposed	95 / 704 (13.49%)	6 / 310 (1.94%)	4 / 303 (1.32%)
occurrences (all)	102	7	4

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 October 2018	<p>Global Amendment 1, resulting in Global Protocol Version 2 dated 19 September 2018.</p> <p>Components of several local amendments were merged, to address feedback from health authorities regarding Global Protocol Version 1, and to provide consistency in the performance of the study across all participating countries. Changes were made to the exclusion criteria, allowed concomitant therapy, guidance for diagnosis of fluid retention cases requiring treatment with diuretics, forbidden medication, acceptable methods of contraception and blood chemistry variables.</p> <p>Additional minor changes were made to several protocol sections, primarily to provide clarification and improve wording.</p>
26 March 2020	<p>Global Amendment 2, resulting in Global Protocol Version 3 dated 27 February 2020.</p> <p>The main changes to the protocol concerned inclusion and exclusion criteria, study-specific discontinuation criteria, and forbidden medications.</p> <p>Additional minor changes were made, e.g., to clarify and provide definitions for overdose, abuse, and misuse.</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/36356632>

<http://www.ncbi.nlm.nih.gov/pubmed/35686330>