



Clinical trial results:

A Multicenter, Single-Arm Study of the Effects of Atrasentan on Spermatogenesis and Testicular Function

Summary

EudraCT number	2016-000722-19
Trial protocol	DE ES
Global end of trial date	12 July 2018

Results information

Result version number	v1 (current)
This version publication date	22 June 2019
First version publication date	22 June 2019

Trial information

Trial identification

Sponsor protocol code	M12-919
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02118714
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AbbVie Deutschland GmbH & Co. KG
Sponsor organisation address	AbbVie House, Vanwall Business Park, Vanwall Road, Maidenhead, Berkshire, United Kingdom, SL6-4UB
Public contact	Global Medical Services, AbbVie, 001 800-633-9110,
Scientific contact	Melissa Wigderson, AbbVie, melissa.wigderson@abbvie.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 July 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 July 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study was conducted to evaluate the effects of Atrasentan on sperm production and testicular function in male subjects with Type 1 or 2 Diabetes and Nephropathy.

This study included 2 periods: a Treatment Period (up to 26 weeks) followed by an Observational Period (up to an additional 52 weeks).

Protection of trial subjects:

Subject read and understood the information provided about the study and gave written permission.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 April 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 11
Country: Number of subjects enrolled	United States: 9
Worldwide total number of subjects	20
EEA total number of subjects	11

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)	14
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The Safety Analysis Set included all enrolled participants who received ≥ 1 dose of Atrasentan (N = 20); of these 20, 6 participants entered an Observational Period of up to an additional 52 weeks.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Atrasentan
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Arm description:

Atrasentan 0.75 mg administered orally once daily (QD).

Arm type	Experimental
Investigational medicinal product name	Atrasentan
Investigational medicinal product code	
Other name	Atrasentan
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Atrasentan 0.75 mg administered orally once daily (QD) for 26 weeks

Number of subjects in period 1	Atrasentan
Started	20
Completed	17
Not completed	3
Lost to follow-up	2
Protocol deviation	1

Baseline characteristics

Reporting groups

Reporting group title	Atrasentan
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Reporting group description:

Atrasentan 0.75 mg administered orally once daily (QD).

Reporting group values	Atrasentan	Total	
Number of subjects	20	20	
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	55.1		
standard deviation	± 12.94	-	
Gender categorical			
Units: Subjects			
Female	0	0	
Male	20	20	

End points

End points reporting groups

Reporting group title	Atrasentan
Reporting group description: Atrasentan 0.75 mg administered orally once daily (QD).	
Subject analysis set title	Evaluable Set
Subject analysis set type	Per protocol
Subject analysis set description: Subjects who met 1 of the following: Study drug compliance $\geq 70\%$, completed Treatment Period, all planned sperm samples collected; or 2) at least 1 dose study drug, a sperm concentration value that was <15 million/mL observed by the end of the Treatment Period or had a $\geq 50\%$ reduction from Baseline at the end of the Treatment Period.	

Primary: Percentage of Subjects With a Sperm Concentration < 15 Million Per mL by Treatment Week 26

End point title	Percentage of Subjects With a Sperm Concentration < 15 Million Per mL by Treatment Week 26 ^[1]
End point description: Percentage of Subjects with a Sperm Concentration < 15 million per mL by Treatment Week 26. Sperm concentration was calculated as measure of the number sperm per milliliter of semen. Duplicate semen samples were collected. The average of the 2 samples were used as the value for that scheduled collection period.	
End point type	Primary
End point timeframe: Up to 26 weeks	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Descriptive statistical analyses were provided based on the point estimate and its 80% and 95% confidence intervals (CI).

The percentage of subjects and a 2-sided exact 80% CI was calculated as: 23.5% (10.7 – 41.6 CI).

The percentage of subjects and a 2-sided exact 95% CI was calculated as: 23.5% (6.8 – 49.9 CI).

End point values	Evaluable Set			
Subject group type	Subject analysis set			
Number of subjects analysed	17			
Units: Percentage of subjects				
number (not applicable)	23.5			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Entered the Observation Period and Did Not Return to Within 15% of Baseline Sperm Concentration or Above During the 52-Week Observational Period

End point title	Percentage of Participants Who Entered the Observation Period and Did Not Return to Within 15% of Baseline Sperm Concentration or Above During the 52-Week Observational Period
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End point description:

The percentage of participants who entered the Observational Period and did not return to within 15% of Baseline sperm concentration or above during the 52-week Observational Period. Duplicate semen samples were to be collected during the Observational Period. Sperm concentration was calculated as measure of the number sperm per milliliter of semen. Duplicate semen samples were collected. The average of the 2 samples were used as the value for that scheduled collection period.

End point type	Secondary
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End point timeframe:

Up to 52 weeks after the Treatment Period

End point values	Evaluable Set			
Subject group type	Subject analysis set			
Number of subjects analysed	17			
Units: Percentage of participants				
number (confidence interval 80%)	11.8 (3.2 to 28.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Entered the Observation Period and Did Not Return to within 15% of Baseline Sperm Concentration or Above during the 52-Week Observational Period

End point title	Percentage of Participants Who Entered the Observation Period and Did Not Return to within 15% of Baseline Sperm Concentration or Above during the 52-Week Observational Period
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End point description:

The percentage of participants who entered the Observational Period and did not return to within 15% of Baseline sperm concentration or above during the 52-week Observational Period. Duplicate semen samples were to be collected during the Observational Period. Sperm concentration was calculated as measure of the number sperm per milliliter of semen. Duplicate semen samples were collected. The average of the 2 samples were used as the value for that scheduled collection period.

End point type	Secondary
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End point timeframe:

Up to 52 weeks after the Treatment Period

End point values	Evaluable Set			
Subject group type	Subject analysis set			
Number of subjects analysed	17			
Units: Percentage of Subjects				
number (confidence interval 95%)	11.8 (1.5 to 36.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline up to Treatment Period Week 26 and Observation Period Week 52 in Sperm Concentration

End point title	Change From Baseline up to Treatment Period Week 26 and Observation Period Week 52 in Sperm Concentration
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End point description:

Duplicate semen samples will be collected during the Treatment and Observational Periods. The average of the 2 samples were used as the value for that scheduled collection period. A negative change from baseline indicated a decrease in sperm concentration.

End point type	Secondary
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End point timeframe:

Change from Week 0 up to Treatment Period Week 26 and Observation Period Week 52 in Sperm Concentration

End point values	Atrasentan			
Subject group type	Reporting group			
Number of subjects analysed	18 ^[2]			
Units: sperm * million per milliliter($\times 10^6$ /mL)				
arithmetic mean (standard deviation)				
Treatment Period Week 13 (n = 18)	2.2 (\pm 42.21)			
Treatment Period Week 26 (n = 17)	-10.6 (\pm 53.44)			
Observation Period Week 13 (n = 6)	35.8 (\pm 113.60)			
Observation Period Week 26 (n = 2)	-16.5 (\pm 0.00)			
Observation Period Week 39 (n = 2)	-27.5 (\pm 19.09)			
Observation Period Week 52 (n = 2)	-25.8 (\pm 1.06)			

Notes:

[2] - Subjects in the Safety Analysis Set with evaluable data at both baseline and the given time point.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline up to Treatment Period Week 26 and Observation Period Week 52 in Sperm Motility

End point title	Change From Baseline up to Treatment Period Week 26 and Observation Period Week 52 in Sperm Motility
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End point description:

Duplicate semen samples will be collected during the Treatment and Observation Periods. The average

of the 2 samples were used as the value for that scheduled collection period. A negative change from baseline indicated a lower sperm motility (worsening).

End point type	Secondary
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End point timeframe:

From Week 0 up to Treatment Period Week 26 and Observation Observation Week 52

End point values	Atrasentan			
Subject group type	Reporting group			
Number of subjects analysed	18 ^[3]			
Units: Percent motility				
arithmetic mean (standard deviation)				
Treatment Period Week 13 (n = 18)	-5.8 (± 13.65)			
Treatment Period Week 26 (n = 17)	-7.4 (± 15.77)			
Observation Period Week 13 (n = 6)	-0.3 (± 19.20)			
Observation Period Week 26 (n = 2)	-6.3 (± 5.30)			
Observation Period Week 39 (n = 2)	10.8 (± 15.20)			
Observation Period Week 52 (n = 2)	1.8 (± 16.62)			

Notes:

[3] - Subjects in the Safety Analysis Set with evaluable data at both baseline and the given time point.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline up to Treatment Period Week 26 and Observation Period Week 52 in Sperm Morphology

End point title	Change From Baseline up to Treatment Period Week 26 and Observation Period Week 52 in Sperm Morphology
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End point description:

Duplicate semen samples will be collected during the Treatment and Observational Periods. The percentage of sperm with normal versus abnormal morphology will be determined via microscopic analysis. A positive change from baseline indicates an improved sperm morphology.

End point type	Secondary
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End point timeframe:

From Week 0 up to Treatment Period Week 26 and Observation Period Week 52

End point values	Atrasentan			
Subject group type	Reporting group			
Number of subjects analysed	18 ^[4]			
Units: percentage of normal				
arithmetic mean (standard deviation)				
Treatment Period Week 13 (n = 18)	-1.1 (± 4.78)			
Treatment Period Week 26 (n = 17)	-2.2 (± 7.54)			
Observation Period Week 13 (n = 6)	-0.8 (± 7.53)			
Observation Period Week 26 (n = 2)	-6.8 (± 0.35)			
Observation Period Week 39 (n = 2)	-2.3 (± 1.77)			

Observation Period Week 52 (n = 2)	1.8 (\pm 0.35)			
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Notes:

[4] - Subjects in the Safety Analysis Set with evaluable data at both baseline and the given time point.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline up to Treatment Period Week 26 and Observation Period Week 52 in Semen Volume

End point title	Change From Baseline up to Treatment Period Week 26 and Observation Period Week 52 in Semen Volume
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End point description:

Duplicate semen samples will be collected during the Treatment and Observation Periods. The average of the 2 samples were used as the value for that scheduled collection period. A negative change from baseline indicated a decrease in semen volume.

End point type	Secondary
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End point timeframe:

From Week 0 to up to Treatment Period Week 26 and Observation Period Week 52

End point values	Atrasentan			
Subject group type	Reporting group			
Number of subjects analysed	18 ^[5]			
Units: milliliter (mL)				
arithmetic mean (standard deviation)				
Treatment Period Week 13 (n = 18)	0.0 (\pm 0.65)			
Treatment Period Week 26 (n = 17)	-0.3 (\pm 0.75)			
Observation Period Week 13 (n = 6)	0.0 (\pm 1.39)			
Observation Period Week 26 (n = 2)	0.0 (\pm 0.35)			
Observation Period Week 39 (n = 2)	0.1 (\pm 0.42)			
Observation Period Week 52 (n = 2)	-0.4 (\pm 0.14)			

Notes:

[5] - Subjects in the Safety Analysis Set with evaluable data at both baseline and the given time point.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline up to Treatment Period Week 26 and Observation Period Week 52 in Serum Testosterone

End point title	Change From Baseline up to Treatment Period Week 26 and Observation Period Week 52 in Serum Testosterone
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End point description:

Serum hormones levels will be tested during the Treatment and Observational Periods. A negative change from baseline indicated a decrease in serum testosterone.

End point type	Secondary
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End point timeframe:

From Week 0 up to Treatment Period Week 26 and Observation Period Week 52

End point values	Atrasentan			
Subject group type	Reporting group			
Number of subjects analysed	18 ^[6]			
Units: nanomole/liter (nmol/L)				
arithmetic mean (standard deviation)				
Treatment Period Week 13 (n = 18)	0.2 (± 2.18)			
Treatment Period Week 26 (n = 18)	0.8 (± 2.33)			
Observation Period Week 13 (n = 5)	0.6 (± 2.08)			
Observation Period Week 26 (n = 3)	-0.3 (± 0.85)			
Observation Period Week 39 (n = 2)	-1.6 (± 1.37)			
Observation Period Week 52 (n = 2)	-1.1 (± 1.68)			

Notes:

[6] - Subjects in the Safety Analysis Set with evaluable data at both baseline and the given time point.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline up to Treatment Period Week 26 and Observation Period Week 52 in Estradiol

End point title	Change From Baseline up to Treatment Period Week 26 and Observation Period Week 52 in Estradiol
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End point description:

Serum hormones levels were tested during the Treatment and Observational Periods. A negative change from baseline indicated a decrease in serum estradiol.

End point type	Secondary
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End point timeframe:

From Week 0 up to Treatment Period Week 26 and Observation Period Week 52

End point values	Atrasentan			
Subject group type	Reporting group			
Number of subjects analysed	18 ^[7]			
Units: Picmoles per litre (pmol/L)				
arithmetic mean (standard deviation)				
Treatment Period Week 13 (n = 18)	-11.7 (± 44.57)			
Treatment Period Week 26 (n = 18)	-18.6 (± 42.04)			
Observation Period Week 13 (n = 6)	-17.8 (± 62.78)			
Observation Period Week 26 (n = 3)	-47.3 (± 39.97)			
Observation Period Week 39 (n = 2)	20.3 (± 4.78)			
Observation Period Week 52 (n = 2)	10.5 (± 45.54)			

Notes:

[7] - Subjects in the Safety Analysis Set with evaluable data at both baseline and the given time point.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline up to Treatment Period Week 26 and Observation Period Week 52 in Lutenizing Hormone (LH)

End point title	Change From Baseline up to Treatment Period Week 26 and Observation Period Week 52 in Lutenizing Hormone (LH)
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End point description:

Serum hormones levels will be tested during the Treatment and Observational Periods. A positive change from baseline indicated an increase in serum lutenizing hormone.

End point type	Secondary
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End point timeframe:

From Week 0 to up to Treatment Period Week 26 and Observation Period Week 52

End point values	Atrasentan			
Subject group type	Reporting group			
Number of subjects analysed	18 ^[8]			
Units: International Units/Liter (IU/L)				
arithmetic mean (standard deviation)				
Treatment Period Week 13 (n = 18)	1.0 (± 2.60)			
Treatment Period Week 26 (n = 18)	0.7 (± 2.44)			
Observation Period Week 13 (n = 6)	1.3 (± 1.33)			
Observation Period Week 26 (n = 3)	1.9 (± 2.35)			
Observation Period Week 39 (n = 2)	0.5 (± 0.07)			
Observation Period Week 52 (n = 2)	1.8 (± 3.46)			

Notes:

[8] - Subjects in the Safety Analysis Set with evaluable data at both baseline and the given time point.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline up to Treatment Period Week 26 and Observation Period Week 52 in in Follicle Stimulating Hormone (FSH)

End point title	Change From Baseline up to Treatment Period Week 26 and Observation Period Week 52 in in Follicle Stimulating Hormone (FSH)
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End point description:

Serum hormones levels will be tested during the Treatment and Observational Periods. A positive change from baseline indicated an increase in serum follicle stimulating hormone.

End point type	Secondary
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End point timeframe:

From Week 0 to Treatment Week 26 and Observation Week 52

End point values	Atrasentan			
Subject group type	Reporting group			
Number of subjects analysed	18 ^[9]			
Units: International Units/Liter (IU/L)				
arithmetic mean (standard deviation)				
Treatment Period Week 13 (n = 18)	1.1 (± 2.43)			
Treatment Period Week 26 (n = 18)	0.8 (± 1.91)			
Observation Period Week 13 (n = 6)	0.4 (± 1.60)			
Observation Period Week 26 (n = 3)	0.7 (± 1.49)			
Observation Period Week 39 (n = 2)	0.4 (± 1.57)			
Observation Period Week 52 (n = 2)	0.8 (± 0.59)			

Notes:

[9] - Subjects in the Safety Analysis Set with evaluable data at both baseline and the given time point.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline up to Treatment Period Week 26 and Observation Period Week 52 in Inhibin B

End point title	Change From Baseline up to Treatment Period Week 26 and Observation Period Week 52 in Inhibin B
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End point description:

Serum hormones levels will be tested during the Treatment and Observational Periods. A negative change from baseline indicated a decrease in serum Inhibin B.

End point type	Secondary
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End point timeframe:

From Week 0 up to Treatment Period Week 26 and Observation Period Week 52

End point values	Atrasentan			
Subject group type	Reporting group			
Number of subjects analysed	18 ^[10]			
Units: Picogram per milliliter (pg/mL)				
arithmetic mean (standard deviation)				
Treatment Period Week 13 (n = 18)	-2.7 (± 24.19)			
Treatment Period Week 26 (n = 18)	-8.8 (± 34.73)			
Observation Period Week 13 (n = 6)	-7.2 (± 20.77)			
Observation Period Week 26 (n = 3)	-22.7 (± 27.10)			
Observation Period Week 39 (n = 2)	-21.0 (± 16.97)			
Observation Period Week 52 (n = 2)	-5.5 (± 2.12)			

Notes:

[10] - Subjects in the Safety Analysis Set with evaluable data at both baseline and the given time point.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events (TEAEs) and serious adverse events (TESAEs) were collected from first dose of study drug until 30 days after the last dose of study drug (up to approximately 30 weeks).

Adverse event reporting additional description:

TEAEs and SAEs are defined as any AE or SAE with onset or worsening reported by a participant from the time that the first dose of atrasentan is administered until 30 days have elapsed following discontinuation of atrasentan administration. TEAEs were collected whether elicited or spontaneously reported by the participant.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Atrasentan
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Reporting group description: -

Serious adverse events	Atrasentan		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 20 (15.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
POSTOPERATIVE RESPIRATORY FAILURE			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
AORTIC DISSECTION			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
CARDIOGENIC SHOCK			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Respiratory, thoracic and mediastinal disorders			
RESPIRATORY DISTRESS			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
RESPIRATORY FAILURE			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
OSTEOMYELITIS			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
DIABETIC KETOACIDOSIS			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Atrasentan		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 20 (60.00%)		
Vascular disorders			
AORTIC ANEURYSM			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
HAEMATOMA			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
HYPERTENSION			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
HYPERTENSIVE CRISIS			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>ORTHOSTATIC HYPERTENSION</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>PERIPHERAL ARTERIAL OCCLUSIVE DISEASE</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 20 (5.00%)</p> <p>1</p> <p>1 / 20 (5.00%)</p> <p>1</p> <p>1 / 20 (5.00%)</p> <p>1</p>		
<p>General disorders and administration site conditions</p> <p>NON-CARDIAC CHEST PAIN</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>OEDEMA PERIPHERAL</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>2 / 20 (10.00%)</p> <p>2</p> <p>4 / 20 (20.00%)</p> <p>4</p>		
<p>Social circumstances</p> <p>DENTAL PROSTHESIS USER</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 20 (5.00%)</p> <p>1</p>		
<p>Respiratory, thoracic and mediastinal disorders</p> <p>DYSPNOEA</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>PULMONARY OEDEMA</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>2 / 20 (10.00%)</p> <p>2</p> <p>1 / 20 (5.00%)</p> <p>1</p>		
<p>Psychiatric disorders</p> <p>DELIRIUM TREMENS</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>DEPRESSION</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>PANIC ATTACK</p>	<p>1 / 20 (5.00%)</p> <p>1</p> <p>1 / 20 (5.00%)</p> <p>1</p>		

subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Investigations BLOOD CREATININE INCREASED subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
BLOOD PRESSURE INCREASED subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
WEIGHT INCREASED subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
WHITE BLOOD CELL COUNT INCREASED subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Injury, poisoning and procedural complications CHEST INJURY subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
POST PROCEDURAL INFLAMMATION subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
TOOTH FRACTURE subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Cardiac disorders ANGINA PECTORIS subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
LEFT VENTRICULAR HYPERTROPHY subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Nervous system disorders HEADACHE subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2		

Blood and lymphatic system disorders ANAEMIA subjects affected / exposed occurrences (all) HAEMORRHAGIC ANAEMIA subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1 1 / 20 (5.00%) 1		
Ear and labyrinth disorders EUSTACHIAN TUBE DYSFUNCTION subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Gastrointestinal disorders DIARRHOEA subjects affected / exposed occurrences (all) GASTRITIS subjects affected / exposed occurrences (all) NAUSEA subjects affected / exposed occurrences (all) TOOTH DISORDER subjects affected / exposed occurrences (all) UPPER GASTROINTESTINAL HAEMORRHAGE subjects affected / exposed occurrences (all) VOMITING subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 3 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1		
Renal and urinary disorders ACUTE KIDNEY INJURY subjects affected / exposed occurrences (all) HAEMATURIA	1 / 20 (5.00%) 1 1		

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>POLAKIURIA</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 20 (5.00%)</p> <p>1</p> <p>1 / 20 (5.00%)</p> <p>1</p>		
<p>Musculoskeletal and connective tissue disorders</p> <p>BACK PAIN</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>FLANK PAIN</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>PAIN IN EXTREMITY</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 20 (5.00%)</p> <p>1</p> <p>1 / 20 (5.00%)</p> <p>1</p> <p>1 / 20 (5.00%)</p> <p>1</p>		
<p>Infections and infestations</p> <p>BRONCHITIS</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>LOCALISED INFECTION</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>NASOPHARYNGITIS</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>PNEUMONIA</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>TINEA CRURIS</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>TOOTH INFECTION</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 20 (5.00%)</p> <p>1</p> <p>1 / 20 (5.00%)</p> <p>1</p> <p>4 / 20 (20.00%)</p> <p>5</p> <p>1 / 20 (5.00%)</p> <p>2</p> <p>1 / 20 (5.00%)</p> <p>1</p> <p>1 / 20 (5.00%)</p> <p>1</p>		
<p>Metabolism and nutrition disorders</p>			

DIABETES MELLITUS			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
FLUID OVERLOAD			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
HYPERTRIGLYCERIDAEMIA			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
HYPOGLYCAEMIA			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
HYPOKALAEMIA			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
HYPOMAGNESAEMIA			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 April 2014	The protocol was amended to remove an exclusion criterion for hypogonadism to exclude subjects with evidence or history of hypogonadism. Also included in this amendment was guidance for managing weight gain and edema during the study.
15 October 2014	The protocol was amended to revise an exclusion criterion to allow subjects with treated retrograde ejaculation to be enrolled on the study with the approval of the Study Designated Physician. Also included in this amendment was the addition of a study requirement to address retrograde ejaculation during the course of the study and allowed the investigator discretion in obtaining replacement semen samples for potentially confounding conditions.
06 May 2015	The protocol was amended to revise inclusion criteria and exclusion criteria that included the following: to clarify that subjects must be on an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB) (renin angiotensin system [RAS] inhibitor); to allow up to a serum brain natriuretic peptide (BNP) level of 200 ng/L at Screening; to clarify to include total abstinence as an allowed birth control method; and to remove an exclusion that excluded subjects with a history of occupational exposure to environmental toxins within the past 6 months.
08 April 2016	The protocol was amended to remove collection of duplicate semen samples at Treatment Week 4 (T4)/Week 6 visit and to remove collection of duplicate semen samples at T6/EOT visit if subject prematurely discontinued study drug as a result of entering the Observational Period. In addition, the inclusion criteria were amended and changes included the following: removed the requirement for being on a stable dose of ACEi or angiotensin II receptor blocker prior to the Screening Period, lowered the estimated glomerular filtration rate criterion to ≥ 35 mL/min/1.73 m ² , and increased the upper limit of systolic blood pressure to 180 mmHg and increased the serum potassium upper limit to 6.0 mEq/L. Exclusion criteria changes included removing the exclusion of subjects with moderate edema and pulmonary edema.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported