



Clinical trial results:

Trial of beta blocker therapy (atenolol) vs. angiotensin II receptor blocker therapy (losartan) in individuals with Marfan syndrome

Summary

EudraCT number	2006-003991-37
Trial protocol	BE
Global end of trial date	13 February 2013

Results information

Result version number	v1 (current)
This version publication date	15 August 2021
First version publication date	15 August 2021
Summary attachment (see zip file)	Statement (2006-003991-37 (2).docx)

Trial information

Trial identification

Sponsor protocol code	AGO/2006/009
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00429364
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	New England Research Institutes
Sponsor organisation address	480 Pleasant, St, Watertown, MA 02472, United States,
Public contact	HIRUZ CTU, Ghent University Hospital, HIRUZ CTU, Ghent University Hospital, +32 93320500, hiruz.ctu@uzgent.be
Scientific contact	HIRUZ CTU, Ghent University Hospital, HIRUZ CTU, Ghent University Hospital, +32 93320500, hiruz.ctu@uzgent.be

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 February 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 February 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the effect of beta blockers therapy to that of angiotension II receptor blocker therapy on the rates of aortic growth and progression of aortic regurgitation.

Protection of trial subjects:

ethics review and approval, informed consent, supportive care and routine monitoring

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 January 2007
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	Belgium: 37
Country: Number of subjects enrolled	United States: 571
Worldwide total number of subjects	608
EEA total number of subjects	37

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)	608
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

All children and young adults (6 months to 25 years old) diagnosed with Marfan Syndrome, according to Ghent criteria and aortic root Z-score greater than 3.0

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Assessor ^[1]

Arms

Are arms mutually exclusive?	Yes
Arm title	atenolol

Arm description:

Participants with Marfan's syndrome and ≥ 3 maximum aortic root z-score received 0.5 - 4.0 mg/kg/day Atenolol (not to exceed a total dose of 250 mg), with a goal of a 20% or greater decrease in the mean heart rate.

Arm type	Experimental
Investigational medicinal product name	atenolol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for oral suspension, Tablet
Routes of administration	Oral use

Dosage and administration details:

commercially available atenolol tablets, 25mg, 50mg and 100mg will be used in this trial. The 25mg tablet will be cut in half to provide 12.5mg doses. For young children and older patients who cannot or prefer not to take tablets, a 2mg/mL suspension will be used.

Arm title	Losartan
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Arm description:

Participants with Marfan's syndrome and ≥ 3 maximum aortic root z-score received 0.4 - 1.4 mg/kg/day Losartan (not to exceed a total dose of 100 mg).

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

Dosage and administration details:

Clinical images (unmarked, plain white versions) of COZAAR (losartan Potassium Tablets), 12.5 mg, 25 mg and 50mg will be used in this trial. For young children and older patients who cannot or prefer not to take tablets, a 2.5 mg /mL suspension will be used.

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: It will not be possible to mask all of the subjects or their care providers to the study drug assignment. Valid treatment comparisons can be made without masking, as long as care is taken to avoid treatment-related biases in outcome assessment. This will be achieved because the physicians at the echocardiography core laboratory evaluating the primary end point and many secondary end points will be masked to treatment assignment. In addition, every effort will be made to prevent the study

subject

Number of subjects in period 1	atenolol	Losartan
Started	303	305
Completed	303	305

Baseline characteristics

Reporting groups

Reporting group title	atenolol
Reporting group description:	
Participants with Marfan's syndrome and ≥ 3 maximum aortic root z-score received 0.5 - 4.0 mg/kg/day Atenolol (not to exceed a total dose of 250 mg), with a goal of a 20% or greater decrease in the mean heart rate.	
Reporting group title	Losartan
Reporting group description:	
Participants with Marfan's syndrome and ≥ 3 maximum aortic root z-score received 0.4 - 1.4 mg/kg/day Losartan (not to exceed a total dose of 100 mg).	

Reporting group values	atenolol	Losartan	Total
Number of subjects	303	305	608
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
arithmetic mean	11.5	11.0	
standard deviation	± 6.5	± 6.2	-
Gender categorical			
Units: Subjects			
Female	123	119	242
Male	180	186	366
Race/ethnicity			
Units: Subjects			
white	266	260	526
black	21	25	46
asian	6	10	16
other	10	10	20
Presence of causal FBN1 mutation			
Units: Subjects			
yes	93	88	181
no	9	15	24
unknown	201	202	403
Family history of Marfan			
Units: Subjects			
yes	180	181	361

no	115	109	224
unknown	8	15	23
Maximum aortic-root diameter z-score			
Data are based on readings at a central echocardiographic laboratory. Echocardiographic data were missing for one participant in the losartan group because of an unreadable echocardiogram			
Units: Subjects			
≥z-score of 4.5	106	114	220
<z-score of 4.5	197	191	388
Had medical history of cardiac surgery			
Units: Subjects			
yes	6	6	12
no	297	299	596
Had medical history of cardiovascular disorder			
Cardiovascular disorder was defined by exercise intolerance, syncope; arrhythmia, hypertension, or hypotension requiring therapy; chest pain, shortness of breath; or other cardiovascular conditions.			
Units: Subjects			
yes	39	36	75
no	264	269	533
Prior use of beta-blocker			
Units: Subjects			
yes	173	171	344
no	130	134	264
Had medical history of endocrine disorder			
Endocrine disorder was defined by either the use of hormone therapy to limit growth, delayed puberty.			
Units: Subjects			
yes	7	0	7
no	296	305	601
Had medical history of neurodevelopmental disorder			
Neurodevelopmental disorder was defined as attention deficit-hyperactivity disorder requiring therapy, developmental delay requiring therapy, learning disability requiring services, or other neurodevelopmental conditions.			
Units: Subjects			
yes	56	61	117
no	247	244	491
Had medical history of psychiatric disorder			
Psychiatric disorder was defined as depression requiring therapy, anxiety, or other psychiatric conditions.			
Units: Subjects			
yes	23	16	39
no	280	289	569
Maximum aortic-root diameter			
Data are based on readings at a central echocardiographic laboratory. Echocardiographic data were missing for one participant in the losartan group because of an unreadable echocardiogram.			
Units: cm			
arithmetic mean	3.4	3.4	
standard deviation	± 0.7	± 0.7	-
Maximum aortic-root diameter z-score			
Data are based on readings at a central echocardiographic laboratory. Echocardiographic data were missing for one participant in the losartan group because of an unreadable echocardiogram.			
Units: Z-score			
median	4.0	4.0	

inter-quartile range (Q1-Q3)	3.5 to 4.8	3.3 to 5.0	-
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End points

End points reporting groups

Reporting group title	atenolol
Reporting group description: Participants with Marfan's syndrome and ≥ 3 maximum aortic root z-score received 0.5 - 4.0 mg/kg/day Atenolol (not to exceed a total dose of 250 mg), with a goal of a 20% or greater decrease in the mean heart rate.	
Reporting group title	Losartan
Reporting group description: Participants with Marfan's syndrome and ≥ 3 maximum aortic root z-score received 0.4 - 1.4 mg/kg/day Losartan (not to exceed a total dose of 100 mg).	

Primary: Annual Rate of Change in Aortic Root (Sinuses of Valsalva) Body-surface-area-adjusted Z-score

End point title	Annual Rate of Change in Aortic Root (Sinuses of Valsalva) Body-surface-area-adjusted Z-score
End point description: The rate of aortic root enlargement, expressed as the annual change in the maximum aortic-root-diameter z score indexed to body-surface area over a 3-year period following randomization	
End point type	Primary
End point timeframe: Up to 3 years following randomization.	

End point values	atenolol	Losartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	303	305		
Units: z-score/year				
least squares mean (standard error)	-0.139 ($\pm$ 0.013)	-0.107 ($\pm$ 0.013)		

Statistical analyses

Statistical analysis title	linear regression mixed-effect model
Statistical analysis description: P values are based on a linear regression mixed-effect model comparing slopes under compound symmetry, with adjustment for baseline.	
Comparison groups	atenolol v Losartan
Number of subjects included in analysis	608
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.08
Method	Mixed models analysis

Secondary: Annual Rate of Change in Aortic Root (Sinuses of Valsalva) Absolute Dimension

End point title	Annual Rate of Change in Aortic Root (Sinuses of Valsalva) Absolute Dimension
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End point description:

End point type	Secondary
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End point timeframe:

Up to 3 years following randomization.

End point values	atenolol	Losartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	303	305		
Units: cm/year				
least squares mean (standard error)	0.069 ($\pm$ 0.004)	0.075 ($\pm$ 0.004)		

Statistical analyses

No statistical analyses for this end point

Secondary: Annual Rate of Change in Ascending-aorta-diameter Z Score, Adjusted by Body-surface-area.

End point title	Annual Rate of Change in Ascending-aorta-diameter Z Score, Adjusted by Body-surface-area.
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End point description:

End point type	Secondary
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End point timeframe:

Up to 3 years following randomization.

End point values	atenolol	Losartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	296	303		
Units: z-score/year				
least squares mean (standard error)	-0.140 ($\pm$ 0.013)	-0.114 ($\pm$ 0.013)		

Statistical analyses

No statistical analyses for this end point

Secondary: Annual Rate of Change in the Absolute Diameter of the Ascending Aorta

End point title	Annual Rate of Change in the Absolute Diameter of the Ascending Aorta
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End point description:

End point type	Secondary
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End point timeframe:

Up to 3 years following randomization.

End point values	atenolol	Losartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	296	303		
Units: cm/year				
least squares mean (standard error)	0.039 ($\pm$ 0.004)	0.044 ($\pm$ 0.004)		

Statistical analyses

No statistical analyses for this end point

Secondary: Annual Rate of Change in Aortic-annulus-diameter Z Score, Adjusted by Body-surface Area

End point title	Annual Rate of Change in Aortic-annulus-diameter Z Score, Adjusted by Body-surface Area
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End point description:

End point type	Secondary
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End point timeframe:

Up to 3 years following randomization

End point values	atenolol	Losartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	302	304		
Units: z-score/year				
least squares mean (standard error)	-0.279 ($\pm$ 0.018)	-0.175 ($\pm$ 0.018)		

Statistical analyses

No statistical analyses for this end point

Secondary: Annual Rate of Change in the Absolute Diameter of the Aortic Annulus

End point title	Annual Rate of Change in the Absolute Diameter of the Aortic Annulus
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End point description:

End point type	Secondary
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End point timeframe:

Up to 3 years following randomization

End point values	atenolol	Losartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	302	304		
Units: cm/year				
least squares mean (standard error)	0.015 (± 0.003)	0.030 (± 0.003)		

Statistical analyses

No statistical analyses for this end point

Secondary: Annual Rate of Change in Total Aortic Proximal Regurgitant Jet Area Indexed to Body-surface-area

End point title	Annual Rate of Change in Total Aortic Proximal Regurgitant Jet Area Indexed to Body-surface-area
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End point description:

End point type	Secondary
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End point timeframe:

up to 3 years following randomization

End point values	atenolol	Losartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	301	303		
Units: (mm ² /m ²)/year				
least squares mean (standard error)	0.005 (± 0.003)	0.001 (± 0.003)		

Statistical analyses

No statistical analyses for this end point

Secondary: Annual Rate of Change in Weight

End point title	Annual Rate of Change in Weight
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End point description:

End point type	Secondary
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End point timeframe:

up to 3 years following randomization

End point values	atenolol	Losartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	303	305		
Units: kg/year				
least squares mean (standard error)	0.239 ($\pm$ 0.153)	0.229 ($\pm$ 0.154)		

Statistical analyses

No statistical analyses for this end point

Secondary: Annual Rate of Change in Weight-for-age Z-score

End point title	Annual Rate of Change in Weight-for-age Z-score
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End point description:

End point type	Secondary
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End point timeframe:

up to 3 years following randomization

End point values	atenolol	Losartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	270	278		
Units: z-score/year				
least squares mean (standard error)	0.011 ($\pm$ 0.013)	0.019 ($\pm$ 0.013)		

Statistical analyses

No statistical analyses for this end point

Secondary: Annual Rate of Change in Weight-for-height Z-score

End point title	Annual Rate of Change in Weight-for-height Z-score
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End point description:

End point type	Secondary
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End point timeframe:

Up to 3 years following randomization.

End point values	atenolol	Losartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	61		
Units: z-score/year				
least squares mean (standard error)	-0.001 ($\pm$ 0.072)	-0.157 ($\pm$ 0.076)		

Statistical analyses

No statistical analyses for this end point

Secondary: Annual Rate of Change in Height

End point title	Annual Rate of Change in Height
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End point description:

End point type	Secondary
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End point timeframe:

up to 3 years following randomization

End point values	atenolol	Losartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	303	305		
Units: cm/year				
least squares mean (standard error)	0.822 ($\pm$ 0.204)	0.935 ($\pm$ 0.202)		

Statistical analyses

No statistical analyses for this end point

Secondary: Annual Rate of Change in Height-for-age Z-score

End point title	Annual Rate of Change in Height-for-age Z-score
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End point description:

End point type	Secondary
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End point timeframe:

up to 3 years following randomization

End point values	atenolol	Losartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	269	272		
Units: z-score/year				
least squares mean (standard error)	0.046 (± 0.013)	0.019 (± 0.013)		

Statistical analyses

No statistical analyses for this end point

Secondary: Annual Rate of Change in Body Mass Index

End point title	Annual Rate of Change in Body Mass Index
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End point description:

End point type	Secondary
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End point timeframe:

up to 3 years following randomization

End point values	atenolol	Losartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	283	295		
Units: kg/m ² per year				
least squares mean (standard error)	0.063 (± 0.044)	0.076 (± 0.044)		

Statistical analyses

No statistical analyses for this end point

Secondary: Annual Rate of Change in Body Mass Index for Age Z-score

End point title	Annual Rate of Change in Body Mass Index for Age Z-score
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End point description:

End point type	Secondary
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End point timeframe:

up to 3 years following randomization

End point values	atenolol	Losartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	250	263		
Units: z-score/year				
least squares mean (standard error)	0.007 ($\pm$ 0.022)	0.021 ($\pm$ 0.022)		

Statistical analyses

No statistical analyses for this end point

Secondary: Annual Rate of Change in Arm Span to Height Ratio

End point title	Annual Rate of Change in Arm Span to Height Ratio
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End point description:

End point type	Secondary
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End point timeframe:

up to 3 years following randomization

End point values	atenolol	Losartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	301	303		
Units: 1/year				
least squares mean (standard error)	0.001 ($\pm$ 0.001)	0.001 ($\pm$ 0.001)		

Statistical analyses

No statistical analyses for this end point

Secondary: Annual Rate of Change in Upper to Lower Segment Ratio

End point title	Annual Rate of Change in Upper to Lower Segment Ratio
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End point description:

End point type	Secondary
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End point timeframe:
up to 3 years following randomization

End point values	atenolol	Losartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	301	301		
Units: 1/year				
least squares mean (standard error)	-0.014 ($\pm$ 0.002)	-0.015 ($\pm$ 0.002)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Aortic Dissection.

End point title	Number of Participants With Aortic Dissection.
End point description:	
End point type	Secondary
End point timeframe:	
up to 3 years following randomization	

End point values	atenolol	Losartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	303	305		
Units: participants	0	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Event Rate of Aortic Dissection

End point title	Event Rate of Aortic Dissection
End point description:	
End point type	Secondary
End point timeframe:	
up to 3 years following randomization	

End point values	atenolol	Losartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	303	305		
Units: percentage of participants				
number (confidence interval 95%)	0 (0 to 0)	0.7 (0.2 to 2.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Aortic-root Surgery

End point title	Number of Participants With Aortic-root Surgery
End point description:	
End point type	Secondary
End point timeframe:	
up to 3 years following randomization	

End point values	atenolol	Losartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	303	305		
Units: participants	10	18		

Statistical analyses

No statistical analyses for this end point

Secondary: Event Rate of Aortic-Root Surgery

End point title	Event Rate of Aortic-Root Surgery
End point description:	
End point type	Secondary
End point timeframe:	
up to 3 years following randomization	

End point values	atenolol	Losartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	303	305		
Units: percentage of participants				
number (confidence interval 95%)	3.4 (1.9 to 6.3)	6.0 (3.8 to 9.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Death

End point title	Number of Death
End point description:	
End point type	Secondary
End point timeframe:	
up to 3 years following randomization	

End point values	atenolol	Losartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	303	305		
Units: participants	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Event Rate of Death

End point title	Event Rate of Death
End point description:	
End point type	Secondary
End point timeframe:	
up to 3 years following randomization	

End point values	atenolol	Losartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	303	305		
Units: percentage of participants				
number (confidence interval 95%)	0 (0 to 0)	0.3 (0 to 2.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With the Composite Adverse Clinical Outcomes, Including Aortic Dissection, Aortic-root Surgery and Death

End point title	Number of Participants With the Composite Adverse Clinical Outcomes, Including Aortic Dissection, Aortic-root Surgery and Death
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End point description:

End point type	Secondary
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End point timeframe:

up to 3 years following randomization

End point values	atenolol	Losartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	303	305		
Units: participants	10	19		

Statistical analyses

No statistical analyses for this end point

Secondary: Event Rate of the Composite Adverse Clinical Outcomes, Including Aortic Dissection, Aortic-root Surgery and Death

End point title	Event Rate of the Composite Adverse Clinical Outcomes, Including Aortic Dissection, Aortic-root Surgery and Death
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End point description:

End point type	Secondary
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End point timeframe:

up to 3 years following randomization

End point values	atenolol	Losartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	303	305		
Units: percentage of participants				
number (confidence interval 95%)	3.4 (1.9 to 6.3)	6.4 (4.1 to 9.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: adverse drug reactions reported at the baseline visit

End point title	adverse drug reactions reported at the baseline visit
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End point description:

End point type	Secondary
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End point timeframe:

at baseline

End point values	atenolol	Losartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	303	305		
Units: participants				
headache, any severity	112	114		
headache, bothersome	10	10		
fatigue, any severity	84	105		
fatigue, bothersome	0	0		
mood alterations, any severity	54	49		
mood alterations, bothersome	7	3		
behavior changes, any severity	21	23		
behavior changes, bothersome	2	1		
insomnia, any severity	60	61		
insomnia, bothersome	2	2		
nightmares, any severity	52	53		
nightmares, bothersome	2	3		
dizziness with standing, any severity	60	58		
dizziness with standing, bothersome	0	2		
dizziness - other, any severity	25	27		
dizziness - other, bothersome	0	1		
fainting with loss of consciousness any severity	5	9		
fainting with loss of consciousness, bothersome	5	9		
palpitations, any severity	60	53		
palpitations, bothersome	0	0		
chest pain, any severity	54	58		
chest pain, bothersome	1	5		

dyspnea, any severity	43	38		
dyspnea, bothersome	3	0		
wheezing, any severity	15	14		
wheezing, bothersome	2	1		
upper respiratory/nasal congestion, any severity	106	117		
upper respiratory/nasal congestion, bothersome	0	2		
cough, any severity	47	59		
cough, bothersome	1	0		
dysgeusia, any severity	10	3		
dysgeusia, bothersome	0	0		
stomach pain/indigestion, any severity	47	61		
stomach pain/indigestion, bothersome	0	1		
nausea, any severity	30	35		
nausea, bothersome	1	0		
vomiting, any severity	23	23		
vomiting, bothersome	0	0		
diarrhea, any severity	35	43		
diarrhea, bothersome	1	1		
constipation, any severity	44	35		
constipation, bothersome	0	0		
vascular (hands, feet), any severity	35	34		
vascular (hands, feet) bothersome	0	1		
muscle pain or cramps, any severity	59	58		
muscle pain or cramps, bothersome	2	4		
back pain, any severity	60	67		
back pain, bothersome	3	2		
periorbital edema, any severity	13	15		
periorbital edema, bothersome	0	0		
pedal edema, any severity	2	3		
pedal edema, bothersome	0	0		
other, any severity	21	16		
other, bothersome	3	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Adverse Drug Reactions Reported During Routine Follow-up Surveillance

End point title	Adverse Drug Reactions Reported During Routine Follow-up Surveillance
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End point description:

End point type	Secondary
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End point timeframe:

From 6 months to 3 years following randomization

End point values	atenolol	Losartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	291	297		
Units: participants				
headache, any severity	202	208		
headache, bothersome	27	20		
fatigue, any severity	152	153		
fatigue, bothersome	7	5		
mood alterations, any severity	89	86		
mood alterations, bothersome	13	13		
behavior changes, any severity	51	46		
behaviour changes, bothersome	5	8		
insomnia, any severity	108	107		
insomnia, bothersome	6	4		
nightmares, any severity	100	94		
nightmares, bothersome	7	4		
dizziness with standing, any severity	119	105		
dizziness with standing, bothersome	6	0		
dizziness - other, any severity	60	61		
dizziness - other, bothersome	2	0		
fainting with loss of consciousness, any severity	21	16		
fainting with loss of consciousness, bothersome	21	16		
palpitations, any severity	86	101		
palpitations, bothersome	0	0		
chest pain, any severity	114	106		
chest pain, bothersome	14	1		
dyspnea, any severity	75	72		
dyspnea, bothersome	1	3		
wheezing, any severity	36	32		
wheezing, bothersome	2	5		
upper respiratory/nasal congestion, any severity	188	186		
upper respiratory/nasal cangestion, bothersome	3	3		
cough, any severity	117	113		
cough, bothersome	1	1		
dysgeusia, any severity	29	16		
dysgeusia, bothersome	0	0		
stomach pain/indigestion, any severity	119	121		
stomach pain/indigestion, bothersome	2	8		
nausea, any severity	99	78		
nausea, bothersome	0	0		
vomiting, any severity	81	75		
vomiting, bothersome	1	2		
diarrhea, any severity	94	90		
diarrhea, bothersome	1	3		
constipation, any severity	77	66		

constipation, bothersome	1	0		
vascular (hands, feet) any severity	73	66		
vascular (hands, feet), bothersome	0	0		
muscle pain or cramps, any severity	148	124		
muscle pain or cramps, bothersome	6	7		
back pain, any severity	137	134		
back pain, bothersome	5	8		
periorbital edema, any severity	22	27		
periorbital edema, bothersome	0	1		
pedal edema, any severity	6	5		
pedal edema, bothersome	0	0		
other, any severity	105	108		
other, bothersome	10	12		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The adverse event (AE) data were collected since randomization till the end of the study, for up to 3 years.

Adverse event reporting additional description:

Serious AEs and important medical events (including pregnancy) were reported within 24 hours of first knowledge of event; Non-Serious AEs were reported within 7 calendar days of first knowledge of event.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	6.0
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Reporting groups

Reporting group title	atenolol
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Reporting group description:

Participants with Marfan's syndrome and ≥ 3 maximum aortic root z-score received 0.5 - 4.0 mg/kg/day Atenolol (not to exceed a total dose of 250 mg), with a goal of a 20% or greater decrease in the mean heart rate.

Reporting group title	Losartan
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Reporting group description:

Participants with Marfan's syndrome and ≥ 3 maximum aortic root z-score received 0.4 - 1.4 mg/kg/day Losartan (not to exceed a total dose of 100 mg).

Serious adverse events	atenolol	Losartan	
Total subjects affected by serious adverse events			
subjects affected / exposed	27 / 303 (8.91%)	33 / 305 (10.82%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Thrombosis			
subjects affected / exposed	1 / 303 (0.33%)	1 / 305 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
aortic root enlargement			
subjects affected / exposed	1 / 303 (0.33%)	0 / 305 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
cardiac general-other: mitral valve replacement			

subjects affected / exposed	1 / 303 (0.33%)	0 / 305 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Pregnancy			
subjects affected / exposed	1 / 303 (0.33%)	2 / 305 (0.66%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 303 (0.33%)	2 / 305 (0.66%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Autoimmune disorder NOS			
subjects affected / exposed	1 / 303 (0.33%)	1 / 305 (0.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity NOS			
subjects affected / exposed	0 / 303 (0.00%)	1 / 305 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Serum sickness			
subjects affected / exposed	0 / 303 (0.00%)	1 / 305 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Uterine haemorrhage			
subjects affected / exposed	0 / 303 (0.00%)	1 / 305 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumonia			

subjects affected / exposed	4 / 303 (1.32%)	1 / 305 (0.33%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchospasm			
subjects affected / exposed	1 / 303 (0.33%)	0 / 305 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 303 (0.33%)	0 / 305 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 303 (0.00%)	1 / 305 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pneumonitis NOS			
subjects affected / exposed	0 / 303 (0.00%)	1 / 305 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pneumothorax NOS			
subjects affected / exposed	3 / 303 (0.99%)	5 / 305 (1.64%)	
occurrences causally related to treatment / all	0 / 3	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
pulmonary/upper respiratory - other			
subjects affected / exposed	0 / 303 (0.00%)	1 / 305 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 303 (0.33%)	2 / 305 (0.66%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			

subjects affected / exposed	2 / 303 (0.66%)	0 / 305 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	3 / 303 (0.99%)	1 / 305 (0.33%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
psychosis aggravated			
subjects affected / exposed	1 / 303 (0.33%)	1 / 305 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Weight decreased			
subjects affected / exposed	1 / 303 (0.33%)	0 / 305 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Haematoma			
subjects affected / exposed	1 / 303 (0.33%)	0 / 305 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
vascular: vessel injury-artery, other NOS			
subjects affected / exposed	0 / 303 (0.00%)	1 / 305 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 303 (0.00%)	2 / 305 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			

subjects affected / exposed	0 / 303 (0.00%)	1 / 305 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pericarditis NOS			
subjects affected / exposed	1 / 303 (0.33%)	0 / 305 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 303 (0.33%)	1 / 305 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
valvular heart disease NOS			
subjects affected / exposed	0 / 303 (0.00%)	3 / 305 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	0 / 303 (0.00%)	1 / 305 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
cerebral abscess			
subjects affected / exposed	1 / 303 (0.33%)	0 / 305 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
convulsions NOS			
subjects affected / exposed	0 / 303 (0.00%)	1 / 305 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 303 (0.33%)	0 / 305 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			

subjects affected / exposed	1 / 303 (0.33%)	0 / 305 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Blood/bone marrow(sickle cell crisis)			
subjects affected / exposed	0 / 303 (0.00%)	1 / 305 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal detachment			
subjects affected / exposed	0 / 303 (0.00%)	1 / 305 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
abdominal pain NOS			
subjects affected / exposed	0 / 303 (0.00%)	1 / 305 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
diarrhoea NOS			
subjects affected / exposed	0 / 303 (0.00%)	1 / 305 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pancreatitis NOS			
subjects affected / exposed	1 / 303 (0.33%)	1 / 305 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
culture wound negative			
subjects affected / exposed	0 / 303 (0.00%)	1 / 305 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urethral obstruction			

subjects affected / exposed	0 / 303 (0.00%)	1 / 305 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Scoliosis			
subjects affected / exposed	0 / 303 (0.00%)	1 / 305 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pyrexia			
subjects affected / exposed	1 / 303 (0.33%)	1 / 305 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 303 (0.33%)	0 / 305 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection NOS			
subjects affected / exposed	1 / 303 (0.33%)	0 / 305 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection NOS			
subjects affected / exposed	0 / 303 (0.00%)	1 / 305 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
urinary tract infection NOS			
subjects affected / exposed	1 / 303 (0.33%)	0 / 305 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	0 / 303 (0.00%)	1 / 305 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

wound - snake bite			
subjects affected / exposed	0 / 303 (0.00%)	1 / 305 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 303 (0.00%)	1 / 305 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	3 / 303 (0.99%)	0 / 305 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	atenolol	Losartan	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	135 / 303 (44.55%)	121 / 305 (39.67%)	
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 303 (0.33%)	0 / 305 (0.00%)	
occurrences (all)	1	0	
Hypertension			
subjects affected / exposed	1 / 303 (0.33%)	0 / 305 (0.00%)	
occurrences (all)	1	0	
Hypotension			
subjects affected / exposed	0 / 303 (0.00%)	3 / 305 (0.98%)	
occurrences (all)	0	3	
Raynaud's phenomenon			
subjects affected / exposed	2 / 303 (0.66%)	1 / 305 (0.33%)	
occurrences (all)	2	1	
Thrombosis			
subjects affected / exposed	0 / 303 (0.00%)	1 / 305 (0.33%)	
occurrences (all)	0	1	
Surgical and medical procedures			

cardiac general-chest tightness subjects affected / exposed occurrences (all)	0 / 303 (0.00%) 0	1 / 305 (0.33%) 1	
Pregnancy, puerperium and perinatal conditions			
Sexual/reproductive function-other (4.5 cm cyst on right ovary) subjects affected / exposed occurrences (all)	0 / 303 (0.00%) 0	1 / 305 (0.33%) 1	
Sexual/reproductive function-other (abnormal pap smear) subjects affected / exposed occurrences (all)	0 / 303 (0.00%) 0	1 / 305 (0.33%) 1	
General disorders and administration site conditions			
bilateral pedal edema subjects affected / exposed occurrences (all)	0 / 303 (0.00%) 0	1 / 305 (0.33%) 1	
Chest pain subjects affected / exposed occurrences (all)	16 / 303 (5.28%) 18	17 / 305 (5.57%) 18	
Constitutional symptoms -other(flu) subjects affected / exposed occurrences (all)	1 / 303 (0.33%) 1	0 / 305 (0.00%) 0	
Constitutional symptoms-other (unusual dreams) subjects affected / exposed occurrences (all)	1 / 303 (0.33%) 1	0 / 305 (0.00%) 0	
Constitutional-other (general body cold sensation) subjects affected / exposed occurrences (all)	0 / 303 (0.00%) 0	1 / 305 (0.33%) 1	
Edema:head and neck subjects affected / exposed occurrences (all)	2 / 303 (0.66%) 2	2 / 305 (0.66%) 2	
Edema: limb subjects affected / exposed occurrences (all)	1 / 303 (0.33%) 1	1 / 305 (0.33%) 2	
falling asleep			

subjects affected / exposed occurrences (all)	1 / 303 (0.33%) 1	0 / 305 (0.00%) 0	
Fatigue subjects affected / exposed occurrences (all)	18 / 303 (5.94%) 19	11 / 305 (3.61%) 12	
Hypothermia subjects affected / exposed occurrences (all)	0 / 303 (0.00%) 0	1 / 305 (0.33%) 1	
influenza-like illness subjects affected / exposed occurrences (all)	1 / 303 (0.33%) 1	0 / 305 (0.00%) 0	
Nightmare subjects affected / exposed occurrences (all)	7 / 303 (2.31%) 8	13 / 305 (4.26%) 13	
pain-other (right hip pain) subjects affected / exposed occurrences (all)	1 / 303 (0.33%) 1	0 / 305 (0.00%) 0	
Pain-other:chest pain/costochondritis (diagnosed in ER as costochondritis) subjects affected / exposed occurrences (all)	1 / 303 (0.33%) 1	0 / 305 (0.00%) 0	
Immune system disorders Allergy/Immunology - Other (rash) subjects affected / exposed occurrences (all)	0 / 303 (0.00%) 0	1 / 305 (0.33%) 1	
Hypersensitivity NOS subjects affected / exposed occurrences (all)	0 / 303 (0.00%) 0	1 / 305 (0.33%) 1	
Reproductive system and breast disorders gyneacomastia subjects affected / exposed occurrences (all)	1 / 303 (0.33%) 1	0 / 305 (0.00%) 0	
Vaginal haemorrhage subjects affected / exposed occurrences (all)	0 / 303 (0.00%) 0	1 / 305 (0.33%) 1	
Respiratory, thoracic and mediastinal disorders			

Pneumonia		
subjects affected / exposed	1 / 303 (0.33%)	4 / 305 (1.31%)
occurrences (all)	1	4
Bronchospasm		
subjects affected / exposed	3 / 303 (0.99%)	4 / 305 (1.31%)
occurrences (all)	3	4
Cough		
subjects affected / exposed	3 / 303 (0.99%)	4 / 305 (1.31%)
occurrences (all)	3	4
Dyspnoea		
subjects affected / exposed	6 / 303 (1.98%)	5 / 305 (1.64%)
occurrences (all)	6	5
Epistaxis		
subjects affected / exposed	9 / 303 (2.97%)	7 / 305 (2.30%)
occurrences (all)	9	7
Hemorrhage/Bleeding - other		
subjects affected / exposed	1 / 303 (0.33%)	0 / 305 (0.00%)
occurrences (all)	1	0
Hypoxia		
subjects affected / exposed	1 / 303 (0.33%)	0 / 305 (0.00%)
occurrences (all)	1	0
Nasal congestion		
subjects affected / exposed	2 / 303 (0.66%)	3 / 305 (0.98%)
occurrences (all)	2	3
Nasal congestion/inf with unk ANC upper airway NOS		
subjects affected / exposed	1 / 303 (0.33%)	0 / 305 (0.00%)
occurrences (all)	1	0
Obstructive sleep apnea		
subjects affected / exposed	0 / 303 (0.00%)	1 / 305 (0.33%)
occurrences (all)	0	1
Pulmonary/upper respiratory-other		
subjects affected / exposed	1 / 303 (0.33%)	0 / 305 (0.00%)
occurrences (all)	1	0
Upper Respiratory - Other		

subjects affected / exposed occurrences (all)	0 / 303 (0.00%) 0	1 / 305 (0.33%) 1	
Psychiatric disorders			
Agitation			
subjects affected / exposed	11 / 303 (3.63%)	3 / 305 (0.98%)	
occurrences (all)	12	3	
Anxiety			
subjects affected / exposed	5 / 303 (1.65%)	2 / 305 (0.66%)	
occurrences (all)	5	2	
Confusional state			
subjects affected / exposed	1 / 303 (0.33%)	0 / 305 (0.00%)	
occurrences (all)	1	0	
Depression			
subjects affected / exposed	9 / 303 (2.97%)	2 / 305 (0.66%)	
occurrences (all)	11	3	
Insomnia			
subjects affected / exposed	10 / 303 (3.30%)	12 / 305 (3.93%)	
occurrences (all)	10	12	
mood alteration			
subjects affected / exposed	1 / 303 (0.33%)	0 / 305 (0.00%)	
occurrences (all)	1	0	
Neurology-other (expression of anger and sadness)			
subjects affected / exposed	1 / 303 (0.33%)	0 / 305 (0.00%)	
occurrences (all)	1	0	
Neurology-other (irritability)			
subjects affected / exposed	0 / 303 (0.00%)	1 / 305 (0.33%)	
occurrences (all)	0	1	
Personality change			
subjects affected / exposed	6 / 303 (1.98%)	3 / 305 (0.98%)	
occurrences (all)	6	3	
Investigations			
neutrphil count			
subjects affected / exposed	0 / 303 (0.00%)	1 / 305 (0.33%)	
occurrences (all)	0	1	
Weight decreased			

subjects affected / exposed occurrences (all)	1 / 303 (0.33%) 1	0 / 305 (0.00%) 0	
Injury, poisoning and procedural complications Haematoma subjects affected / exposed occurrences (all)	1 / 303 (0.33%) 1	0 / 305 (0.00%) 0	
Cardiac disorders cardiac general, other, murmur subjects affected / exposed occurrences (all)	0 / 303 (0.00%) 0	1 / 305 (0.33%) 1	
cardiac general- other - nonresponsive and pale subjects affected / exposed occurrences (all)	1 / 303 (0.33%) 1	0 / 305 (0.00%) 0	
Palpitations subjects affected / exposed occurrences (all)	9 / 303 (2.97%) 9	10 / 305 (3.28%) 10	
Sinus tachycardia subjects affected / exposed occurrences (all)	1 / 303 (0.33%) 1	0 / 305 (0.00%) 0	
Supraventricular tachycardia subjects affected / exposed occurrences (all)	0 / 303 (0.00%) 0	1 / 305 (0.33%) 1	
Nervous system disorders Cognitive disorder subjects affected / exposed occurrences (all)	2 / 303 (0.66%) 2	2 / 305 (0.66%) 2	
Convulsions NOS subjects affected / exposed occurrences (all)	3 / 303 (0.99%) 3	0 / 305 (0.00%) 0	
Dizziness subjects affected / exposed occurrences (all)	29 / 303 (9.57%) 29	17 / 305 (5.57%) 18	
dizziness upon standing subjects affected / exposed occurrences (all)	1 / 303 (0.33%) 1	1 / 305 (0.33%) 1	
Extrapyramidal disorder			

subjects affected / exposed	2 / 303 (0.66%)	0 / 305 (0.00%)	
occurrences (all)	2	0	
Headache			
subjects affected / exposed	31 / 303 (10.23%)	18 / 305 (5.90%)	
occurrences (all)	36	19	
Memory impairment			
subjects affected / exposed	0 / 303 (0.00%)	1 / 305 (0.33%)	
occurrences (all)	0	1	
Mental status changes			
subjects affected / exposed	1 / 303 (0.33%)	1 / 305 (0.33%)	
occurrences (all)	1	1	
neuralgia NOS			
subjects affected / exposed	0 / 303 (0.00%)	1 / 305 (0.33%)	
occurrences (all)	0	1	
neurology - other			
subjects affected / exposed	0 / 303 (0.00%)	2 / 305 (0.66%)	
occurrences (all)	0	2	
Neurology-other (panic attacks)			
subjects affected / exposed	0 / 303 (0.00%)	1 / 305 (0.33%)	
occurrences (all)	0	2	
panick attacks			
subjects affected / exposed	1 / 303 (0.33%)	0 / 305 (0.00%)	
occurrences (all)	1	0	
Syncope			
subjects affected / exposed	13 / 303 (4.29%)	9 / 305 (2.95%)	
occurrences (all)	14	9	
syncope vasovagal			
subjects affected / exposed	2 / 303 (0.66%)	2 / 305 (0.66%)	
occurrences (all)	2	3	
Tremor			
subjects affected / exposed	0 / 303 (0.00%)	1 / 305 (0.33%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	0 / 303 (0.00%)	1 / 305 (0.33%)	
occurrences (all)	0	1	

Haemoglobin			
subjects affected / exposed	0 / 303 (0.00%)	2 / 305 (0.66%)	
occurrences (all)	0	2	
Lymph node pain			
subjects affected / exposed	1 / 303 (0.33%)	0 / 305 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
auditory/ear-other			
subjects affected / exposed	0 / 303 (0.00%)	1 / 305 (0.33%)	
occurrences (all)	0	1	
Hypersensitivity to sound			
subjects affected / exposed	0 / 303 (0.00%)	1 / 305 (0.33%)	
occurrences (all)	0	1	
Eye disorders			
Conjunctivitis			
subjects affected / exposed	3 / 303 (0.99%)	1 / 305 (0.33%)	
occurrences (all)	3	1	
eyelid function disorder NOS			
subjects affected / exposed	1 / 303 (0.33%)	0 / 305 (0.00%)	
occurrences (all)	1	0	
Lacrimation increased			
subjects affected / exposed	0 / 303 (0.00%)	1 / 305 (0.33%)	
occurrences (all)	0	1	
Ocular-other (L eye burning/redness 4 mos. s/p lensectomy with lens insertion)			
subjects affected / exposed	1 / 303 (0.33%)	0 / 305 (0.00%)	
occurrences (all)	1	0	
Ocular - other (right eye hemorrhage)			
subjects affected / exposed	1 / 303 (0.33%)	0 / 305 (0.00%)	
occurrences (all)	1	0	
Ocular/Visual - Squinting of OS to see things more clearly			
subjects affected / exposed	1 / 303 (0.33%)	0 / 305 (0.00%)	
occurrences (all)	1	0	
Ocular/visual-other (redness and itching of eyes)			

subjects affected / exposed occurrences (all)	0 / 303 (0.00%) 0	1 / 305 (0.33%) 1	
Photopsia subjects affected / exposed occurrences (all)	0 / 303 (0.00%) 0	1 / 305 (0.33%) 1	
Vision blurred subjects affected / exposed occurrences (all)	1 / 303 (0.33%) 1	0 / 305 (0.00%) 0	
Gastrointestinal disorders			
abdominal pain NOS subjects affected / exposed occurrences (all)	7 / 303 (2.31%) 7	7 / 305 (2.30%) 7	
Constipation subjects affected / exposed occurrences (all)	4 / 303 (1.32%) 4	2 / 305 (0.66%) 2	
diarrhoea NOS subjects affected / exposed occurrences (all)	4 / 303 (1.32%) 6	2 / 305 (0.66%) 2	
Dysgeusia subjects affected / exposed occurrences (all)	3 / 303 (0.99%) 3	2 / 305 (0.66%) 2	
Dyspepsia subjects affected / exposed occurrences (all)	1 / 303 (0.33%) 1	0 / 305 (0.00%) 0	
Dysphagia subjects affected / exposed occurrences (all)	0 / 303 (0.00%) 0	1 / 305 (0.33%) 1	
Gastrointestinal - HERNIA subjects affected / exposed occurrences (all)	0 / 303 (0.00%) 0	1 / 305 (0.33%) 1	
Haemorrhoids subjects affected / exposed occurrences (all)	1 / 303 (0.33%) 1	0 / 305 (0.00%) 0	
intestinal hernia subjects affected / exposed occurrences (all)	1 / 303 (0.33%) 1	0 / 305 (0.00%) 0	

Nausea			
subjects affected / exposed	2 / 303 (0.66%)	2 / 305 (0.66%)	
occurrences (all)	2	3	
Oesophageal pain			
subjects affected / exposed	0 / 303 (0.00%)	1 / 305 (0.33%)	
occurrences (all)	0	1	
Oral pain			
subjects affected / exposed	1 / 303 (0.33%)	0 / 305 (0.00%)	
occurrences (all)	1	0	
oesophagitis NOS			
subjects affected / exposed	1 / 303 (0.33%)	0 / 305 (0.00%)	
occurrences (all)	1	0	
peridontal disorder NOS			
subjects affected / exposed	1 / 303 (0.33%)	0 / 305 (0.00%)	
occurrences (all)	1	0	
stomach discomfort			
subjects affected / exposed	5 / 303 (1.65%)	3 / 305 (0.98%)	
occurrences (all)	5	3	
tooth disorder NOS			
subjects affected / exposed	1 / 303 (0.33%)	0 / 305 (0.00%)	
occurrences (all)	1	0	
vomiting NOS			
subjects affected / exposed	2 / 303 (0.66%)	5 / 305 (1.64%)	
occurrences (all)	3	7	
Skin and subcutaneous tissue disorders			
acne NOS			
subjects affected / exposed	2 / 303 (0.66%)	2 / 305 (0.66%)	
occurrences (all)	2	2	
Alopecia			
subjects affected / exposed	1 / 303 (0.33%)	4 / 305 (1.31%)	
occurrences (all)	1	4	
burn on skin			
subjects affected / exposed	1 / 303 (0.33%)	0 / 305 (0.00%)	
occurrences (all)	1	0	
decubitis ulcer			

subjects affected / exposed	1 / 303 (0.33%)	0 / 305 (0.00%)
occurrences (all)	1	0
Derm/skin-other (Poison Ivy)		
subjects affected / exposed	1 / 303 (0.33%)	0 / 305 (0.00%)
occurrences (all)	1	0
Derm/skin-other (mild chin rash)		
subjects affected / exposed	1 / 303 (0.33%)	0 / 305 (0.00%)
occurrences (all)	1	0
Derm/skin-other (possible eczema)		
subjects affected / exposed	1 / 303 (0.33%)	0 / 305 (0.00%)
occurrences (all)	1	0
Derm/skin-other (worsening of underlying hand skin disorder)		
subjects affected / exposed	0 / 303 (0.00%)	1 / 305 (0.33%)
occurrences (all)	0	1
Dermatitis exfoliative NOS		
subjects affected / exposed	1 / 303 (0.33%)	0 / 305 (0.00%)
occurrences (all)	1	0
Dermatology - other - Erythema Nodosum		
subjects affected / exposed	1 / 303 (0.33%)	0 / 305 (0.00%)
occurrences (all)	1	0
Dermatology/skin-other (cervical dysplasia)		
subjects affected / exposed	1 / 303 (0.33%)	0 / 305 (0.00%)
occurrences (all)	1	0
Dermatology/skin-other (papules on legs)		
subjects affected / exposed	0 / 303 (0.00%)	1 / 305 (0.33%)
occurrences (all)	0	1
Dermatology/skin-other (rash: nonspecific maculopapular rash)		
subjects affected / exposed	0 / 303 (0.00%)	1 / 305 (0.33%)
occurrences (all)	0	1
Ecchymosis		
subjects affected / exposed	1 / 303 (0.33%)	2 / 305 (0.66%)
occurrences (all)	1	2
Eczema		

subjects affected / exposed	1 / 303 (0.33%)	1 / 305 (0.33%)	
occurrences (all)	1	1	
Erythema multiforme			
subjects affected / exposed	0 / 303 (0.00%)	1 / 305 (0.33%)	
occurrences (all)	0	1	
Pruritus			
subjects affected / exposed	3 / 303 (0.99%)	0 / 305 (0.00%)	
occurrences (all)	4	0	
Rash			
subjects affected / exposed	1 / 303 (0.33%)	0 / 305 (0.00%)	
occurrences (all)	1	0	
rash on torso and neck			
subjects affected / exposed	0 / 303 (0.00%)	1 / 305 (0.33%)	
occurrences (all)	0	1	
Skin irritation			
subjects affected / exposed	1 / 303 (0.33%)	2 / 305 (0.66%)	
occurrences (all)	1	3	
sweating increased			
subjects affected / exposed	1 / 303 (0.33%)	0 / 305 (0.00%)	
occurrences (all)	1	0	
Urticaria			
subjects affected / exposed	3 / 303 (0.99%)	4 / 305 (1.31%)	
occurrences (all)	3	4	
Renal and urinary disorders			
Chromaturia			
subjects affected / exposed	0 / 303 (0.00%)	1 / 305 (0.33%)	
occurrences (all)	0	1	
Pollakiuria			
subjects affected / exposed	1 / 303 (0.33%)	0 / 305 (0.00%)	
occurrences (all)	1	0	
Renal/genitourinary-increased urinary frequency, daytime only, associated w/ po water intake			
subjects affected / exposed	0 / 303 (0.00%)	1 / 305 (0.33%)	
occurrences (all)	0	1	
Urinary incontinence			

subjects affected / exposed	1 / 303 (0.33%)	0 / 305 (0.00%)	
occurrences (all)	2	0	
Urogenital haemorrhage			
subjects affected / exposed	1 / 303 (0.33%)	0 / 305 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			
hot flushes NOS			
subjects affected / exposed	1 / 303 (0.33%)	1 / 305 (0.33%)	
occurrences (all)	1	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 303 (0.99%)	3 / 305 (0.98%)	
occurrences (all)	3	3	
Back pain			
subjects affected / exposed	8 / 303 (2.64%)	8 / 305 (2.62%)	
occurrences (all)	8	8	
chest wall pain			
subjects affected / exposed	6 / 303 (1.98%)	5 / 305 (1.64%)	
occurrences (all)	6	5	
joint disorder NOS			
subjects affected / exposed	0 / 303 (0.00%)	1 / 305 (0.33%)	
occurrences (all)	0	1	
Joint effusion			
subjects affected / exposed	0 / 303 (0.00%)	1 / 305 (0.33%)	
occurrences (all)	0	1	
Msk/soft tissue, other (Nodule on back)			
subjects affected / exposed	0 / 303 (0.00%)	1 / 305 (0.33%)	
occurrences (all)	0	1	
Muscle weakness, generalized or specific area			
subjects affected / exposed	1 / 303 (0.33%)	0 / 305 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal (other) (loose joints-causing pain)			
subjects affected / exposed	1 / 303 (0.33%)	0 / 305 (0.00%)	
occurrences (all)	1	0	

Musculoskeletal/soft tissue - other (patellar dislocation)			
subjects affected / exposed	1 / 303 (0.33%)	0 / 305 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal/soft tissue-other (Bursa on left shoulder blade due to back brace)			
subjects affected / exposed	0 / 303 (0.00%)	1 / 305 (0.33%)	
occurrences (all)	0	1	
Musculoskeletal/soft tissue-other (nodule on back)			
subjects affected / exposed	0 / 303 (0.00%)	1 / 305 (0.33%)	
occurrences (all)	0	1	
Musculoskeletal/soft tissue-other(left arm pain)			
subjects affected / exposed	0 / 303 (0.00%)	1 / 305 (0.33%)	
occurrences (all)	0	1	
Myalgia			
subjects affected / exposed	3 / 303 (0.99%)	12 / 305 (3.93%)	
occurrences (all)	3	12	
Neck pain			
subjects affected / exposed	1 / 303 (0.33%)	2 / 305 (0.66%)	
occurrences (all)	1	2	
Pain in extremity			
subjects affected / exposed	5 / 303 (1.65%)	4 / 305 (1.31%)	
occurrences (all)	5	4	
Infections and infestations			
Pyrexia			
subjects affected / exposed	4 / 303 (1.32%)	2 / 305 (0.66%)	
occurrences (all)	6	2	
abcessed tooth			
subjects affected / exposed	1 / 303 (0.33%)	0 / 305 (0.00%)	
occurrences (all)	1	0	
bronchitis NOS			
subjects affected / exposed	0 / 303 (0.00%)	1 / 305 (0.33%)	
occurrences (all)	0	1	
Gum infection			
subjects affected / exposed	0 / 303 (0.00%)	1 / 305 (0.33%)	
occurrences (all)	0	1	

infection - Eye NOS		
subjects affected / exposed	1 / 303 (0.33%)	0 / 305 (0.00%)
occurrences (all)	1	0
infection - other - parvovirus		
subjects affected / exposed	0 / 303 (0.00%)	1 / 305 (0.33%)
occurrences (all)	0	1
infection Pharynx		
subjects affected / exposed	1 / 303 (0.33%)	1 / 305 (0.33%)
occurrences (all)	1	1
Infection with unknown ANC-eye, NOS		
subjects affected / exposed	0 / 303 (0.00%)	1 / 305 (0.33%)
occurrences (all)	0	1
Infection with unknown ANC-middle ear		
subjects affected / exposed	0 / 303 (0.00%)	1 / 305 (0.33%)
occurrences (all)	0	1
Infection with unknown ANC-pharynx		
subjects affected / exposed	0 / 303 (0.00%)	2 / 305 (0.66%)
occurrences (all)	0	2
Infection with unknown ANC-sinus		
subjects affected / exposed	0 / 303 (0.00%)	1 / 305 (0.33%)
occurrences (all)	0	1
Infection with unknown ANC-upper airway NOS		
subjects affected / exposed	2 / 303 (0.66%)	0 / 305 (0.00%)
occurrences (all)	2	0
Infection-bladder(urinary)		
subjects affected / exposed	0 / 303 (0.00%)	1 / 305 (0.33%)
occurrences (all)	0	1
Infection-other (sinus, bronchitis, pharyngeal)		
subjects affected / exposed	1 / 303 (0.33%)	0 / 305 (0.00%)
occurrences (all)	1	0
Infection-other (skin on foot)		
subjects affected / exposed	0 / 303 (0.00%)	1 / 305 (0.33%)
occurrences (all)	0	1
Infection-other-Lyme disease		

subjects affected / exposed	0 / 303 (0.00%)	1 / 305 (0.33%)	
occurrences (all)	0	1	
Infection: Dental - Tooth			
subjects affected / exposed	1 / 303 (0.33%)	0 / 305 (0.00%)	
occurrences (all)	1	0	
middle ear infection			
subjects affected / exposed	1 / 303 (0.33%)	2 / 305 (0.66%)	
occurrences (all)	1	2	
mononucleosis			
subjects affected / exposed	3 / 303 (0.99%)	1 / 305 (0.33%)	
occurrences (all)	3	1	
shingles			
subjects affected / exposed	0 / 303 (0.00%)	1 / 305 (0.33%)	
occurrences (all)	0	1	
sinus infection			
subjects affected / exposed	2 / 303 (0.66%)	0 / 305 (0.00%)	
occurrences (all)	2	0	
sinusitis NOS			
subjects affected / exposed	2 / 303 (0.66%)	1 / 305 (0.33%)	
occurrences (all)	2	1	
Urinary tract infection NOS			
subjects affected / exposed	0 / 303 (0.00%)	1 / 305 (0.33%)	
occurrences (all)	0	1	
vaginitis			
subjects affected / exposed	1 / 303 (0.33%)	0 / 305 (0.00%)	
occurrences (all)	1	0	
Viral infection coxsackievirus			
subjects affected / exposed	1 / 303 (0.33%)	0 / 305 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
anorexia			
subjects affected / exposed	1 / 303 (0.33%)	3 / 305 (0.98%)	
occurrences (all)	1	3	
Dehydration			
subjects affected / exposed	1 / 303 (0.33%)	1 / 305 (0.33%)	
occurrences (all)	1	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 February 2008	Reasons for substantial amendment a. subject availability and additional PHN Trial Centers b. subject re-consent c. protocol windows d. interim monitoring e. drug preparations Brief description of the changes a. Subject Availability and Additional PHN Trial Centers: minor protocol modifications were made to highlight the addition of new auxiliary centers and to characterize the development of referral centers as ways to fulfill trial recruitment goals. b. Subject Re-consent: U.S. and Canadian trial subjects who reach the age of consent, as determined by the local Regulatory agency, during their trial participation will undergo the informed consent process as an adult and will be required to sign the subject (adult) Informed Consent Form. c. protocol Windows: timeframes for completing each drug Uptitration Cycle and for obtaining the end of uptitration safety labs are clarified. d. Interim Monitoring: clarifies how variation in within- and between-subject measurements may influence statistical power and to define methods that would be employed if an increase in sample size is required. e. Drug Preparations: requires that both suspensions will now require refrigeration.
19 September 2009	Reasons for substantial amendment: Addition of site Brief description of the changes: Addition of site: Cliniques Universitaires Saint-Luc - UCL
05 March 2010	Reasons for substantial amendment: change in drug preparations Brief description of the changes: Change in drug preparations - the atenolol suspension preparation recipe has been amended based on results of the atenolol suspension stability study required by the FDA
18 November 2010	Reasons for substantial amendment: Addition of ancillary study: "Musculoskeletal Phenotype of Marfan Patients"
02 February 2012	Reasons for substantial amendment: The protocol is amended to conform to the new FDA Final Rule for Safety Reporting in IND Trials.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The effect of losartan on TGF- β was not assessed. The study results do not apply to Marfan subjects whose BSA-adj. aortic-root z score is ≤ 3 .

Subjects may find their treatment based on the appearance of the drug.

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/17892982>

<http://www.ncbi.nlm.nih.gov/pubmed/30115424>

<http://www.ncbi.nlm.nih.gov/pubmed/29631804>

<http://www.ncbi.nlm.nih.gov/pubmed/29948025>

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