# 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 |

**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 |

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<br>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<br>Units: years | | | |
| arithmetic mean | 11.5 | 11.0 | |
| standard deviation | ± 6.5 | ± 6.2 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 123 | 119 | 242 |
| Male | 180 | 186 | 366 |
| Race/ethnicity<br>Units: Subjects | | | |
| white | 266 | 260 | 526 |
| black | 21 | 25 | 46 |
| asian | 6 | 10 | 16 |
| other | 10 | 10 | 20 |
| Presence of causal FBN1 mutation<br>Units: Subjects | | | |
| yes | 93 | 88 | 181 |
| no | 9 | 15 | 24 |
| unknown | 201 | 202 | 403 |
| Family history of Marfan<br>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<br>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<br>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 | - |

## 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 (± 0.013) | -0.107 (± 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 |
|---|---|

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: cm/year | | | | |
| least squares mean (standard error) | 0.069 (± 0.004) | 0.075 (± 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. |
|---|---|

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 | 296 | 303 | | |
| Units: z-score/year | | | | |
| least squares mean (standard error) | -0.140 (± 0.013) | -0.114 (± 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 |
|---|---|

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 | 296 | 303 | | |
| Units: cm/year | | | | |
| least squares mean (standard error) | 0.039 (± 0.004) | 0.044 (± 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 |
|---|---|

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 | 302 | 304 | | |
| Units: z-score/year | | | | |
| least squares mean (standard error) | -0.279 (± 0.018) | -0.175 (± 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 |
|---|---|

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 | 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 |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

up to 3 years following ramdomization

| 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 |
|---|---|

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: kg/year | | | | |
| least squares mean (standard error) | 0.239 (± 0.153) | 0.229 (± 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 |
|---|---|

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 | 270 | 278 | | |
| Units: z-score/year | | | | |
| least squares mean (standard error) | 0.011 (± 0.013) | 0.019 (± 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 |
|---|---|

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 | 58 | 61 | | |
| Units: z-score/year | | | | |
| least squares mean (standard error) | -0.001 (± 0.072) | -0.157 (± 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 |
|---|---|

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: cm/year | | | | |
| least squares mean (standard error) | 0.822 (± 0.204) | 0.935 (± 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 |
|---|---|

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 | 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 |
|---|---|

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 | 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 |
|---|---|

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 | 250 | 263 | | |
| Units: z-score/year | | | | |
| least squares mean (standard error) | 0.007 (± 0.022) | 0.021 (± 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 |
|---|---|

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 | 301 | 303 | | |
| Units: 1/year | | | | |
| least squares mean (standard error) | 0.001 (± 0.001) | 0.001 (± 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 |
|---|---|

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 | 301 | 301 | | |
| Units: 1/year | | | | |
| least squares mean (standard error) | -0.014 (± 0.002) | -0.015 (± 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 |
|---|---|

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 | 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 |
|---|---|

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) | 6.4 (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 |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

at baseline

| End point values | atenolol | Losartan | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 303 | 305 | | |
| Units: partipants | | | | |
| headache, any severity | 112 | 114 | | |
| headache, bothersom | 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 seveity | 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 consiousness any severity | 5 | 9 | | |
| fainting with loss of consiousness, 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 |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

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 |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 6.0 |

### 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).

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

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 303 (0.33%) | 0 / 305 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Fatigue | | | |
| subjects affected / exposed | 18 / 303 (5.94%) | 11 / 305 (3.61%) | |
| occurrences (all) | 19 | 12 | |
| Hypothermia | | | |
| subjects affected / exposed | 0 / 303 (0.00%) | 1 / 305 (0.33%) | |
| occurrences (all) | 0 | 1 | |
| influenza-like illness | | | |
| subjects affected / exposed | 1 / 303 (0.33%) | 0 / 305 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Nightmare | | | |
| subjects affected / exposed | 7 / 303 (2.31%) | 13 / 305 (4.26%) | |
| occurrences (all) | 8 | 13 | |
| pain-other (right hip pain) | | | |
| subjects affected / exposed | 1 / 303 (0.33%) | 0 / 305 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Pain-other:chest pain/costochondritis (diagnosed in ER as costochondritis) | | | |
| subjects affected / exposed | 1 / 303 (0.33%) | 0 / 305 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Immune system disorders | | | |
| Allergy/Immunology - Other (rash) | | | |
| subjects affected / exposed | 0 / 303 (0.00%) | 1 / 305 (0.33%) | |
| occurrences (all) | 0 | 1 | |
| Hypersensitivity NOS | | | |
| subjects affected / exposed | 0 / 303 (0.00%) | 1 / 305 (0.33%) | |
| occurrences (all) | 0 | 1 | |
| Reproductive system and breast disorders | | | |
| gyneacomastia | | | |
| subjects affected / exposed | 1 / 303 (0.33%) | 0 / 305 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Vaginal haemorrhage | | | |
| subjects affected / exposed | 0 / 303 (0.00%) | 1 / 305 (0.33%) | |
| occurrences (all) | 0 | 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 | 0 / 303 (0.00%) | 1 / 305 (0.33%) | |
| occurrences (all) | 0 | 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 | 1 / 303 (0.33%) | 0 / 305 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Injury, poisoning and procedural complications | | | |
| Haematoma | | | |
| subjects affected / exposed | 1 / 303 (0.33%) | 0 / 305 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Cardiac disorders | | | |
| cardiac general, other, murmur | | | |
| subjects affected / exposed | 0 / 303 (0.00%) | 1 / 305 (0.33%) | |
| occurrences (all) | 0 | 1 | |
| cardiac general- other - nonresponsive and pale | | | |
| subjects affected / exposed | 1 / 303 (0.33%) | 0 / 305 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Palpitations | | | |
| subjects affected / exposed | 9 / 303 (2.97%) | 10 / 305 (3.28%) | |
| occurrences (all) | 9 | 10 | |
| Sinus tachycardia | | | |
| subjects affected / exposed | 1 / 303 (0.33%) | 0 / 305 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 0 / 303 (0.00%) | 1 / 305 (0.33%) | |
| occurrences (all) | 0 | 1 | |
| Nervous system disorders | | | |
| Cognitive disorder | | | |
| subjects affected / exposed | 2 / 303 (0.66%) | 2 / 305 (0.66%) | |
| occurrences (all) | 2 | 2 | |
| Convulsions NOS | | | |
| subjects affected / exposed | 3 / 303 (0.99%) | 0 / 305 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Dizziness | | | |
| subjects affected / exposed | 29 / 303 (9.57%) | 17 / 305 (5.57%) | |
| occurrences (all) | 29 | 18 | |
| dizziness upon standing | | | |
| subjects affected / exposed | 1 / 303 (0.33%) | 1 / 305 (0.33%) | |
| occurrences (all) | 1 | 1 | |
| Extrapyramidal disorder | | | |

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|---|---|---|---|
| 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) | | | |

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

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|---|---|---|---|
| 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 | | | |

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|---|---|---|---|
| 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 | | | |

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| 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 | | | |

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|---|---|---|---|
| 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 ariway 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 | | | |

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|---|---|---|---|
| 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<br>a. subject availability and aditional PHN Trial Ceners<br>b. subject re-consent<br>c. protocol windows<br>d. interim monitoring<br>e. drug preperations<br><br>Brief description of the changes<br>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.<br>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.<br>c. protocol Windows: timeframes for completing each drug Uptitration Cycle and for obtaining the end of uptitration safety labs are clarified.<br>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.<br>e. Drug Preparations: requires that both suspensions will now require refrigeration. |
| 19 September 2009 | Reasons for substantial amendment: Addition of site<br>Brief description of the changes: Addition of site: Cliniques Universitaires Saint-Luc - UCL |
| 05 March 2010 | Reasons for substantial amendment: change in drug preparations<br>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

http://www.ncbi.nlm.nih.gov/pubmed/30270167

http://www.ncbi.nlm.nih.gov/pubmed/32586526

http://www.ncbi.nlm.nih.gov/pubmed/25405392