



## Clinical trial results:

A randomized, multicenter, double-blind, 6 week study to evaluate the dose response of valsartan on blood pressure reduction in children 6 months-5 years old with hypertension, followed by a 2 week placebo withdrawal period.

## Summary

|                          |                         |
|--------------------------|-------------------------|
| EudraCT number           | 2006-005261-19          |
| Trial protocol           | BE DE HU FR SE PL IT GB |
| Global end of trial date | 21 January 2009         |

## Results information

|                                |                |
|--------------------------------|----------------|
| Result version number          | v1 (current)   |
| This version publication date  | 13 July 2016   |
| First version publication date | 01 August 2015 |

## Trial information

### Trial identification

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | CVAL489K2303 |
|-----------------------|--------------|

### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT00435162 |
| WHO universal trial number (UTN)   | -           |

Notes:

## Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Novartis Pharma AG   |
| Sponsor organisation address | CH-4002, Basel, Switzerland,                                   |
| Public contact               | Clinical Disclosure Office, Novartis Pharma AG, +41 613241111, |
| Scientific contact           | Clinical Disclosure Office, Novartis Pharma AG, +41 613241111, |

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                       | 21 January 2009 |
| Is this the analysis of the primary completion data? | No              |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 21 January 2009 |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

The main objective of the trial was to evaluate a dose dependent reduction in Mean Sitting Systolic Blood Pressure (MSSBP) when comparing three doses of valsartan (0.25 milligram/kilogram [mg/kg], 1 mg/kg and 4 mg/kg ) over a 6 week period in hypertensive children aged 6 months to 5 years.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

|   |               |
|---|---------------|
| Actual start date of recruitment                          | 21 March 2007 |
| Long term follow-up planned                               | No            |
| Independent data monitoring committee (IDMC) involvement? | Yes           |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                  |
|--------------------------------------|------------------|
| Country: Number of subjects enrolled | Poland: 10       |
| Country: Number of subjects enrolled | Belgium: 11      |
| Country: Number of subjects enrolled | France: 5        |
| Country: Number of subjects enrolled | Hungary: 3       |
| Country: Number of subjects enrolled | Italy: 2         |
| Country: Number of subjects enrolled | India: 20        |
| Country: Number of subjects enrolled | Brazil: 10       |
| Country: Number of subjects enrolled | Turkey: 2        |
| Country: Number of subjects enrolled | South Africa: 5  |
| Country: Number of subjects enrolled | United States: 6 |
| Worldwide total number of subjects   | 74               |
| EEA total number of subjects         | 31               |

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) | 12 |
| Children (2-11 years)                    | 62 |
| Adolescents (12-17 years)                | 0  |
| Adults (18-64 years)                     | 0  |
| From 65 to 84 years                      | 0  |
| 85 years and over                        | 0  |

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted at 39 centers in 10 countries.

### Pre-assignment

Screening details:

81 subjects were enrolled into single-blind period with placebo medication (min. 4 day, max. 28 days). 75 subjects were randomized after screening period. One subject who was enrolled and included in randomized population was excluded from all analyses due to good clinical practice issues and is not counted in any table reported in this result record

### Period 1

|                              |   |
|------------------------------|---|
| Period 1 title               | Period 1: Dose ranging                        |
| Is this the baseline period? | Yes   |
| Allocation method            | Randomised - controlled                       |
| Blinding used                | Double blind                                  |
| Roles blinded                | Subject, Investigator, Data analyst, Assessor |

Blinding implementation details:

The identity of the treatments was concealed by the use of study drugs that were all identical in packaging, labeling and schedule. Unblinding was allowed only in case of subjects emergencies and at the conclusion of the study.

### Arms

|                              |                              |
|------------------------------|------------------------------|
| Are arms mutually exclusive? | Yes                          |
| <b>Arm title</b>             | Period 1: Low dose Valsartan |

Arm description:

Valsartan 0.25 milligram/kilogram (mg/kg) (low dose) oral suspension was administered once daily (OD) for 6 weeks.

|  |  |
|--|--|
| Arm type                               | Experimental   |
| Investigational medicinal product name | Valsartan Low dose                                       |
| Investigational medicinal product code | VAL489   |
| Other name                             |  |
| Pharmaceutical forms                   | Suspension and effervescent granules for oral suspension |
| Routes of administration               | Oral use   |

Dosage and administration details:

Extemporaneous Valsartan 0.25 mg/kg (low dose) oral suspension administered OD for 6 weeks in period 1.

|                  |                                 |
|------------------|---------------------------------|
| <b>Arm title</b> | Period 1: Medium dose Valsartan |
|------------------|---------------------------------|

Arm description:

Valsartan 1.0 mg/kg (medium dose) oral suspension was administered OD for 6 weeks.

|  |  |
|--|--|
| Arm type                               | Experimental   |
| Investigational medicinal product name | Valsartan Medium dose                                    |
| Investigational medicinal product code | VAL489   |
| Other name                             |  |
| Pharmaceutical forms                   | Suspension and effervescent granules for oral suspension |
| Routes of administration               | Oral use   |

Dosage and administration details:

Extemporaneous Valsartan 1.0 mg/kg (medium dose) oral suspension was administered OD for 6 weeks in period 1.

|                  |                               |
|------------------|-------------------------------|
| <b>Arm title</b> | Period 1: High dose Valsartan |
|------------------|-------------------------------|

Arm description:

Valsartan 4.0 mg/kg (high dose) oral suspension was administered OD for 6 weeks.

|  |  |
|--|--|
| Arm type                               | Experimental   |
| Investigational medicinal product name | Valsartan High dose                                      |
| Investigational medicinal product code | VAL489   |
| Other name                             |  |
| Pharmaceutical forms                   | Suspension and effervescent granules for oral suspension |
| Routes of administration               | Oral use   |

Dosage and administration details:

Extemporaneous Valsartan 4.0 mg/kg(high dose) oral suspension was administered OD for 6 weeks in period 1.

| <b>Number of subjects in period 1</b> | Period 1: Low dose Valsartan | Period 1: Medium dose Valsartan | Period 1: High dose Valsartan |
|---------------------------------------|------------------------------|---------------------------------|-------------------------------|
| Started                               | 30                           | 14                              | 30                            |
| Completed                             | 30                           | 14                              | 30                            |

## Period 2

|                              |   |
|------------------------------|---|
| Period 2 title               | Period 2: Placebo withdrawal                  |
| Is this the baseline period? | No  |
| Allocation method            | Randomised - controlled                       |
| Blinding used                | Double blind                                  |
| Roles blinded                | Subject, Investigator, Data analyst, Assessor |

Blinding implementation details:

The identity of the treatments was concealed by the use of study drugs that were all identical in packaging, labeling and schedule. Unblinding was allowed only in case of subjects emergencies and at the conclusion of the study.

## Arms

|                              |                     |
|------------------------------|---------------------|
| Are arms mutually exclusive? | Yes                 |
| <b>Arm title</b>             | Period 2: Valsartan |

Arm description:

Valsartan oral suspension was administered OD for 2 weeks.

|  |  |
|--|--|
| Arm type                               | Experimental   |
| Investigational medicinal product name | Valsartan  |
| Investigational medicinal product code | VAL489   |
| Other name                             |  |
| Pharmaceutical forms                   | Suspension and effervescent granules for oral suspension |
| Routes of administration               | Oral use   |

Dosage and administration details:

Extemporaneous Valsartan oral suspension was administered OD for 2 weeks in period 2.

|                  |                   |
|------------------|-------------------|
| <b>Arm title</b> | Period 2: Placebo |
|------------------|-------------------|

Arm description:

Placebo matched to Valsartan oral suspension was administered OD for 2 weeks.

|          |         |
|----------|---------|
| Arm type | Placebo |
|----------|---------|

|  |  |
|--|--|
| Investigational medicinal product name | Placebo  |
| Investigational medicinal product code |  |
| Other name                             |  |
| Pharmaceutical forms                   | Suspension and effervescent granules for oral suspension |
| Routes of administration               | Oral use   |

Dosage and administration details:

Placebo matched to Valsartan oral suspension was administered OD for 2 weeks in period 2.

| <b>Number of subjects in period 2</b> | Period 2: Valsartan | Period 2: Placebo |
|---------------------------------------|---------------------|-------------------|
| Started                               | 36                  | 38                |
| Completed                             | 35                  | 38                |
| Not completed                         | 1                   | 0                 |
| Adverse event, non-fatal              | 1                   | -                 |

## Baseline characteristics

### Reporting groups

|  |                                 |
|--|---------------------------------|
| Reporting group title  | Period 1: Low dose Valsartan    |
| Reporting group description:<br>Valsartan 0.25 milligram/kilogram (mg/kg) (low dose) oral suspension was administered once daily (OD) for 6 weeks. |                                 |
| Reporting group title  | Period 1: Medium dose Valsartan |
| Reporting group description:<br>Valsartan 1.0 mg/kg(medium dose) oral suspension was administered OD for 6 weeks.                                  |                                 |
| Reporting group title  | Period 1: High dose Valsartan   |
| Reporting group description:<br>Valsartan 4.0 mg/kg(high dose) oral suspension was administered OD for 6 weeks.                                    |                                 |

| Reporting group values             | Period 1: Low dose Valsartan | Period 1: Medium dose Valsartan | Period 1: High dose Valsartan |
|------------------------------------|------------------------------|---------------------------------|-------------------------------|
| Number of subjects                 | 30                           | 14                              | 30                            |
| Age categorical<br>Units: Subjects |                              |                                 |                               |

|   |               |               |               |
|---|---------------|---------------|---------------|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 3.4<br>± 1.28 | 3.2<br>± 1.48 | 3.3<br>± 1.53 |
| Gender categorical<br>Units: Subjects                                   |               |               |               |
| Female  | 13            | 4             | 9             |
| Male  | 17            | 10            | 21            |

| Reporting group values             | Total |  |  |
|------------------------------------|-------|--|--|
| Number of subjects                 | 74    |  |  |
| Age categorical<br>Units: Subjects |       |  |  |

|   |    |  |  |
|---|----|--|--|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | -  |  |  |
| Gender categorical<br>Units: Subjects                                   |    |  |  |
| Female  | 26 |  |  |
| Male  | 48 |  |  |

## End points

### End points reporting groups

|  |                                 |
|--|---------------------------------|
| Reporting group title  | Period 1: Low dose Valsartan    |
| Reporting group description:<br>Valsartan 0.25 milligram/kilogram (mg/kg) (low dose) oral suspension was administered once daily (OD) for 6 weeks. |                                 |
| Reporting group title  | Period 1: Medium dose Valsartan |
| Reporting group description:<br>Valsartan 1.0 mg/kg (medium dose) oral suspension was administered OD for 6 weeks.                                 |                                 |
| Reporting group title  | Period 1: High dose Valsartan   |
| Reporting group description:<br>Valsartan 4.0 mg/kg (high dose) oral suspension was administered OD for 6 weeks.                                   |                                 |
| Reporting group title  | Period 2: Valsartan             |
| Reporting group description:<br>Valsartan oral suspension was administered OD for 2 weeks.   |                                 |
| Reporting group title  | Period 2: Placebo               |
| Reporting group description:<br>Placebo matched to Valsartan oral suspension was administered OD for 2 weeks.                                      |                                 |

### Primary: Change From Baseline in Mean Sitting Systolic Blood Pressure (MSSBP) at Week 6

|   |  |
|---|--|
| End point title   | Change From Baseline in Mean Sitting Systolic Blood Pressure (MSSBP) at Week 6 |
| End point description:<br>Sitting blood pressure was measured using a calibrated standard sphygmomanometer after the subject remained in sitting position for 5 minutes at clinic during the visit. The repeat sitting measurements were made at 1-2 minute intervals and the mean of three sitting systolic blood pressure (SSBP) measurements were used as the average sitting office blood pressure for that visit. Change from baseline in MSSBP was evaluated. Analysis was performed in Intent-to-Treat (ITT) population defined as all randomized subjects who had both baseline and at least one post-baseline assessment of any efficacy variable. |  |
| End point type  | Primary  |
| End point timeframe:<br>Baseline to Week 6  |  |

| End point values                     | Period 1: Low dose Valsartan | Period 1: Medium dose Valsartan | Period 1: High dose Valsartan |  |
|--------------------------------------|------------------------------|---------------------------------|-------------------------------|--|
| Subject group type                   | Reporting group              | Reporting group                 | Reporting group               |  |
| Number of subjects analysed          | 30                           | 14                              | 30                            |  |
| Units: millimeters of mercury (mmHg) |                              |                                 |                               |  |
| arithmetic mean (standard deviation) | -8.3 (± 10.44)               | -10.3 (± 9.83)                  | -14.4 (± 10.93)               |  |

### Statistical analyses



|   |  |
|---|--|
| <b>Statistical analysis title</b>   | Change From Baseline in MSSBP at Week 6  |
| Statistical analysis description:   |  |
| Slope was based on an ANCOVA model with terms including continuing prior antihypertensive therapy strata and race strata as factors, and centered baseline MSSBP and dose per body weight as continuous covariates. |  |
| Comparison groups   | Period 1: High dose Valsartan v Period 1: Low dose Valsartan v Period 1: Medium dose Valsartan |
| Number of subjects included in analysis   | 74   |
| Analysis specification  | Pre-specified  |
| Analysis type   | other  |
| P-value   | = 0.099  |
| Method  | ANCOVA   |
| Parameter estimate  | Slope estimate   |
| Point estimate  | -1.05  |
| Confidence interval   |  |
| level   | 95 %   |
| sides   | 2-sided  |
| lower limit   | -2.31  |
| upper limit   | 0.2  |
| Variability estimate  | Standard error of the mean   |
| Dispersion value  | 0.63   |

### Secondary: Change From Baseline in Mean Sitting Diastolic Blood Pressure (MSDBP) at Week 6

|  |   |
|--|---|
| End point title  | Change From Baseline in Mean Sitting Diastolic Blood Pressure (MSDBP) at Week 6 |
| End point description:   |   |
| Sitting blood pressure was measured using a calibrated standard sphygmomanometer after the subject remained in sitting position for 5 minutes at clinic during the visit. The repeat sitting measurements were made at 1-2 minute intervals and the mean of three SDBP measurements were used as the average sitting office blood pressure for that visit. Analysis was performed in ITT population. |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| Baseline to Week 6   |   |

| End point values                     | Period 1: Low dose Valsartan | Period 1: Medium dose Valsartan | Period 1: High dose Valsartan |  |
|--------------------------------------|------------------------------|---------------------------------|-------------------------------|--|
| Subject group type                   | Reporting group              | Reporting group                 | Reporting group               |  |
| Number of subjects analysed          | 30                           | 14                              | 30                            |  |
| Units: mmHg                          |                              |                                 |                               |  |
| arithmetic mean (standard deviation) | -4.7 (± 9.53)                | -8.6 (± 12.43)                  | -6.7 (± 10.61)                |  |

### Statistical analyses

No statistical analyses for this end point

**Secondary: Change From Week 6 in Mean Sitting Systolic Blood Pressure (MSSBP) at Week 8**

|                 |  |
|-----------------|--|
| End point title | Change From Week 6 in Mean Sitting Systolic Blood Pressure (MSSBP) at Week 8 |
|-----------------|--|

End point description:

Sitting blood pressure was measured using a calibrated standard sphygmomanometer after the subject remained in sitting position for 5 minutes at clinic during the visit. The repeat sitting measurements were made at 1-2 minute intervals and the mean of three SSBP measurements were used as the average sitting office blood pressure for that visit. Analysis was performed in ITT population.

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

End point timeframe:

Week 6 to Week 8

| End point values                     | Period 2:<br>Valsartan | Period 2:<br>Placebo |  |  |
|--------------------------------------|------------------------|----------------------|--|--|
| Subject group type                   | Reporting group        | Reporting group      |  |  |
| Number of subjects analysed          | 35                     | 38                   |  |  |
| Units: mmHg                          |                        |                      |  |  |
| arithmetic mean (standard deviation) | 2.6 (± 8.38)           | 4.1 (± 9.66)         |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Change From Week 6 in Mean Sitting Diastolic Blood Pressure (MSDBP) at Week 8**

|                 |   |
|-----------------|---|
| End point title | Change From Week 6 in Mean Sitting Diastolic Blood Pressure (MSDBP) at Week 8 |
|-----------------|---|

End point description:

Sitting blood pressure was measured using a calibrated standard sphygmomanometer after the subject remained in sitting position for 5 minutes at clinic during the visit. The repeat sitting measurements were made at 1-2 minute intervals and the mean of three SDBP measurements were used as the average sitting office blood pressure for that visit. Analysis was performed in ITT population.

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

End point timeframe:

Week 6 to Week 8

| End point values                     | Period 2:<br>Valsartan | Period 2:<br>Placebo |  |  |
|--------------------------------------|------------------------|----------------------|--|--|
| Subject group type                   | Reporting group        | Reporting group      |  |  |
| Number of subjects analysed          | 35                     | 38                   |  |  |
| Units: mmHg                          |                        |                      |  |  |
| arithmetic mean (standard deviation) | 1.8 (± 8.99)           | 3.4 (± 8.74)         |  |  |

## **Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 11.1   |

### Reporting groups

|  |                                       |
|--|---------------------------------------|
| Reporting group title                                      | Low Dose Valsartan in both periods    |
| Reporting group description:                               |                                       |
| Valsartan 0.25 mg/kg in both periods                       |                                       |
| Reporting group title                                      | Low Dose Valsartan, then Placebo      |
| Reporting group description:                               |                                       |
| Valsartan 0.25 mg/kg in period 1, then placebo in period 2 |                                       |
| Reporting group title                                      | High Dose Valsartan, then Placebo     |
| Reporting group description:                               |                                       |
| Valsartan 4.0 mg/kg in period 1, then placebo in period 2  |                                       |
| Reporting group title                                      | Medium Dose Valsartan, then Placebo   |
| Reporting group description:                               |                                       |
| Valsartan 1.0 mg/kg in period 1, then placebo in period 2  |                                       |
| Reporting group title                                      | High Dose Valsartan in both periods   |
| Reporting group description:                               |                                       |
| Valsartan 4.0 mg/kg in both periods                        |                                       |
| Reporting group title                                      | Medium Dose Valsartan in both periods |
| Reporting group description:                               |                                       |
| Valsartan 1.0 mg/kg in both periods                        |                                       |

| Serious adverse events                            | Low Dose Valsartan in both periods | Low Dose Valsartan, then Placebo | High Dose Valsartan, then Placebo |
|---|------------------------------------|----------------------------------|-----------------------------------|
| Total subjects affected by serious adverse events |                                    |                                  |                                   |
| subjects affected / exposed                       | 1 / 15 (6.67%)                     | 0 / 15 (0.00%)                   | 2 / 15 (13.33%)                   |
| number of deaths (all causes)                     | 0                                  | 0                                | 0                                 |
| number of deaths resulting from adverse events    | 0                                  | 0                                | 0                                 |
| Gastrointestinal disorders                        |                                    |                                  |                                   |
| Enteritis   |                                    |                                  |                                   |
| subjects affected / exposed                       | 0 / 15 (0.00%)                     | 0 / 15 (0.00%)                   | 1 / 15 (6.67%)                    |
| occurrences causally related to treatment / all   | 0 / 0                              | 0 / 0                            | 0 / 1                             |
| deaths causally related to treatment / all        | 0 / 0                              | 0 / 0                            | 0 / 0                             |
| Gastritis   |                                    |                                  |                                   |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                       | 1 / 15 (6.67%) | 0 / 15 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all   | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all        | 0 / 0          | 0 / 0          | 0 / 0          |
| Respiratory, thoracic and mediastinal disorders   |                |                |                |
| Bronchospasm                                      |                |                |                |
| subjects affected / exposed                       | 0 / 15 (0.00%) | 0 / 15 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all   | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all        | 0 / 0          | 0 / 0          | 0 / 0          |
| Renal and urinary disorders                       |                |                |                |
| Nephrotic syndrome                                |                |                |                |
| subjects affected / exposed                       | 1 / 15 (6.67%) | 0 / 15 (0.00%) | 1 / 15 (6.67%) |
| occurrences causally related to treatment / all   | 0 / 2          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all        | 0 / 0          | 0 / 0          | 0 / 0          |
| Infections and infestations                       |                |                |                |
| Respiratory tract infection                       |                |                |                |
| subjects affected / exposed                       | 1 / 15 (6.67%) | 0 / 15 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all   | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all        | 0 / 0          | 0 / 0          | 0 / 0          |
| Upper respiratory tract infection                 |                |                |                |
| subjects affected / exposed                       | 1 / 15 (6.67%) | 0 / 15 (0.00%) | 1 / 15 (6.67%) |
| occurrences causally related to treatment / all   | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all        | 0 / 0          | 0 / 0          | 0 / 0          |
| Metabolism and nutrition disorders                |                |                |                |
| Dehydration                                       |                |                |                |
| subjects affected / exposed                       | 0 / 15 (0.00%) | 0 / 15 (0.00%) | 1 / 15 (6.67%) |
| occurrences causally related to treatment / all   | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all        | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>Serious adverse events</b>                     |                |                |                |
| Total subjects affected by serious adverse events |                |                |                |
| subjects affected / exposed                       | 1 / 8 (12.50%) | 0 / 15 (0.00%) | 0 / 6 (0.00%)  |
| number of deaths (all causes)                     | 0              | 0              | 0              |
| number of deaths resulting from adverse events    | 0              | 0              | 0              |
| Gastrointestinal disorders                        |                |                |                |

|   |                |                |               |
|---|----------------|----------------|---------------|
| Enteritis                                       |                |                |               |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 15 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Gastritis                                       |                |                |               |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 15 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Respiratory, thoracic and mediastinal disorders |                |                |               |
| Bronchospasm                                    |                |                |               |
| subjects affected / exposed                     | 1 / 8 (12.50%) | 0 / 15 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Renal and urinary disorders                     |                |                |               |
| Nephrotic syndrome                              |                |                |               |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 15 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Infections and infestations                     |                |                |               |
| Respiratory tract infection                     |                |                |               |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 15 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Upper respiratory tract infection               |                |                |               |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 15 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Metabolism and nutrition disorders              |                |                |               |
| Dehydration                                     |                |                |               |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 15 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |

| <b>Non-serious adverse events</b>  | Low Dose Valsartan<br>in both periods  | Low Dose Valsartan,<br>then Placebo   | High Dose<br>Valsartan, then<br>Placebo  |
|--|--|---|--|
| Total subjects affected by non-serious<br>adverse events<br>subjects affected / exposed  | 8 / 15 (53.33%)  | 10 / 15 (66.67%)  | 11 / 15 (73.33%)   |
| Nervous system disorders<br>Headache<br>subjects affected / exposed<br>occurrences (all)   | 0 / 15 (0.00%)<br>0  | 1 / 15 (6.67%)<br>2   | 0 / 15 (0.00%)<br>0  |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all)  | 0 / 15 (0.00%)<br>0  | 0 / 15 (0.00%)<br>0   | 1 / 15 (6.67%)<br>1  |
| General disorders and administration<br>site conditions<br>Pyrexia<br>subjects affected / exposed<br>occurrences (all)   | 0 / 15 (0.00%)<br>0  | 0 / 15 (0.00%)<br>0   | 3 / 15 (20.00%)<br>3   |
| Ear and labyrinth disorders<br>Otorrhoea<br>subjects affected / exposed<br>occurrences (all)   | 0 / 15 (0.00%)<br>0  | 0 / 15 (0.00%)<br>0   | 0 / 15 (0.00%)<br>0  |
| Immune system disorders<br>Allergy to arthropod bite<br>subjects affected / exposed<br>occurrences (all)   | 0 / 15 (0.00%)<br>0  | 0 / 15 (0.00%)<br>0   | 0 / 15 (0.00%)<br>0  |
| Gastrointestinal disorders<br>Abdominal pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Aphthous stomatitis<br>subjects affected / exposed<br>occurrences (all)<br><br>Cheilitis<br>subjects affected / exposed<br>occurrences (all)<br><br>Constipation<br>subjects affected / exposed<br>occurrences (all) | 1 / 15 (6.67%)<br>2<br><br>0 / 15 (0.00%)<br>0<br><br>0 / 15 (0.00%)<br>0<br><br>0 / 15 (0.00%)<br>0 | 2 / 15 (13.33%)<br>2<br><br>0 / 15 (0.00%)<br>0<br><br>0 / 15 (0.00%)<br>0<br><br>0 / 15 (0.00%)<br>0 | 1 / 15 (6.67%)<br>3<br><br>1 / 15 (6.67%)<br>1<br><br>1 / 15 (6.67%)<br>1<br><br>0 / 15 (0.00%)<br>0 |

|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| Diarrhoea                                       |                 |                |                 |
| subjects affected / exposed                     | 0 / 15 (0.00%)  | 1 / 15 (6.67%) | 2 / 15 (13.33%) |
| occurrences (all)                               | 0               | 1              | 3               |
| Nausea  |                 |                |                 |
| subjects affected / exposed                     | 0 / 15 (0.00%)  | 0 / 15 (0.00%) | 1 / 15 (6.67%)  |
| occurrences (all)                               | 0               | 0              | 1               |
| Vomiting  |                 |                |                 |
| subjects affected / exposed                     | 3 / 15 (20.00%) | 0 / 15 (0.00%) | 1 / 15 (6.67%)  |
| occurrences (all)                               | 3               | 0              | 1               |
| Respiratory, thoracic and mediastinal disorders |                 |                |                 |
| Asthmatic crisis                                |                 |                |                 |
| subjects affected / exposed                     | 0 / 15 (0.00%)  | 0 / 15 (0.00%) | 0 / 15 (0.00%)  |
| occurrences (all)                               | 0               | 0              | 0               |
| Cough   |                 |                |                 |
| subjects affected / exposed                     | 1 / 15 (6.67%)  | 0 / 15 (0.00%) | 0 / 15 (0.00%)  |
| occurrences (all)                               | 1               | 0              | 0               |
| Increased upper airway secretion                |                 |                |                 |
| subjects affected / exposed                     | 0 / 15 (0.00%)  | 0 / 15 (0.00%) | 0 / 15 (0.00%)  |
| occurrences (all)                               | 0               | 0              | 0               |
| Rhinorrhoea                                     |                 |                |                 |
| subjects affected / exposed                     | 1 / 15 (6.67%)  | 0 / 15 (0.00%) | 1 / 15 (6.67%)  |
| occurrences (all)                               | 1               | 0              | 2               |
| Skin and subcutaneous tissue disorders          |                 |                |                 |
| Dermatitis                                      |                 |                |                 |
| subjects affected / exposed                     | 0 / 15 (0.00%)  | 0 / 15 (0.00%) | 1 / 15 (6.67%)  |
| occurrences (all)                               | 0               | 0              | 1               |
| Dermatitis bullous                              |                 |                |                 |
| subjects affected / exposed                     | 0 / 15 (0.00%)  | 0 / 15 (0.00%) | 1 / 15 (6.67%)  |
| occurrences (all)                               | 0               | 0              | 1               |
| Dermatitis diaper                               |                 |                |                 |
| subjects affected / exposed                     | 1 / 15 (6.67%)  | 0 / 15 (0.00%) | 0 / 15 (0.00%)  |
| occurrences (all)                               | 1               | 0              | 0               |
| Dry skin  |                 |                |                 |
| subjects affected / exposed                     | 0 / 15 (0.00%)  | 0 / 15 (0.00%) | 1 / 15 (6.67%)  |
| occurrences (all)                               | 0               | 0              | 1               |
| Pruritus  |                 |                |                 |



|  |                      |                     |                     |
|--|----------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all)   | 0 / 15 (0.00%)<br>0  | 0 / 15 (0.00%)<br>0 | 1 / 15 (6.67%)<br>1 |
| Rash<br>subjects affected / exposed<br>occurrences (all)   | 0 / 15 (0.00%)<br>0  | 1 / 15 (6.67%)<br>1 | 1 / 15 (6.67%)<br>1 |
| Pruritus generalised<br>subjects affected / exposed<br>occurrences (all)                             | 1 / 15 (6.67%)<br>1  | 0 / 15 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0 |
| Urticaria<br>subjects affected / exposed<br>occurrences (all)  | 1 / 15 (6.67%)<br>1  | 0 / 15 (0.00%)<br>0 | 1 / 15 (6.67%)<br>1 |
| Infections and infestations<br>Acute tonsillitis<br>subjects affected / exposed<br>occurrences (all) | 0 / 15 (0.00%)<br>0  | 0 / 15 (0.00%)<br>0 | 1 / 15 (6.67%)<br>1 |
| Bronchitis<br>subjects affected / exposed<br>occurrences (all)                                       | 1 / 15 (6.67%)<br>1  | 1 / 15 (6.67%)<br>2 | 1 / 15 (6.67%)<br>1 |
| Gastroenteritis<br>subjects affected / exposed<br>occurrences (all)                                  | 0 / 15 (0.00%)<br>0  | 1 / 15 (6.67%)<br>1 | 0 / 15 (0.00%)<br>0 |
| Gastroenteritis viral<br>subjects affected / exposed<br>occurrences (all)                            | 0 / 15 (0.00%)<br>0  | 0 / 15 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0 |
| Impetigo<br>subjects affected / exposed<br>occurrences (all)   | 0 / 15 (0.00%)<br>0  | 0 / 15 (0.00%)<br>0 | 1 / 15 (6.67%)<br>1 |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                                  | 2 / 15 (13.33%)<br>2 | 1 / 15 (6.67%)<br>1 | 0 / 15 (0.00%)<br>0 |
| Pharyngitis<br>subjects affected / exposed<br>occurrences (all)                                      | 0 / 15 (0.00%)<br>0  | 1 / 15 (6.67%)<br>1 | 0 / 15 (0.00%)<br>0 |
| Pharyngotonsillitis<br>subjects affected / exposed<br>occurrences (all)                              | 0 / 15 (0.00%)<br>0  | 0 / 15 (0.00%)<br>0 | 1 / 15 (6.67%)<br>1 |

|                                    |                |                 |                 |
|------------------------------------|----------------|-----------------|-----------------|
| Rhinitis                           |                |                 |                 |
| subjects affected / exposed        | 0 / 15 (0.00%) | 1 / 15 (6.67%)  | 0 / 15 (0.00%)  |
| occurrences (all)                  | 0              | 2               | 0               |
| Scarlet fever                      |                |                 |                 |
| subjects affected / exposed        | 0 / 15 (0.00%) | 0 / 15 (0.00%)  | 1 / 15 (6.67%)  |
| occurrences (all)                  | 0              | 0               | 1               |
| Tonsillitis                        |                |                 |                 |
| subjects affected / exposed        | 1 / 15 (6.67%) | 0 / 15 (0.00%)  | 0 / 15 (0.00%)  |
| occurrences (all)                  | 1              | 0               | 0               |
| Upper respiratory tract infection  |                |                 |                 |
| subjects affected / exposed        | 1 / 15 (6.67%) | 3 / 15 (20.00%) | 2 / 15 (13.33%) |
| occurrences (all)                  | 1              | 3               | 2               |
| Urinary tract infection            |                |                 |                 |
| subjects affected / exposed        | 1 / 15 (6.67%) | 0 / 15 (0.00%)  | 1 / 15 (6.67%)  |
| occurrences (all)                  | 1              | 0               | 1               |
| Varicella                          |                |                 |                 |
| subjects affected / exposed        | 0 / 15 (0.00%) | 1 / 15 (6.67%)  | 0 / 15 (0.00%)  |
| occurrences (all)                  | 0              | 1               | 0               |
| Metabolism and nutrition disorders |                |                 |                 |
| Hyperkalaemia                      |                |                 |                 |
| subjects affected / exposed        | 0 / 15 (0.00%) | 0 / 15 (0.00%)  | 1 / 15 (6.67%)  |
| occurrences (all)                  | 0              | 0               | 1               |
| Hypertriglyceridaemia              |                |                 |                 |
| subjects affected / exposed        | 0 / 15 (0.00%) | 0 / 15 (0.00%)  | 0 / 15 (0.00%)  |
| occurrences (all)                  | 0              | 0               | 0               |

| <b>Non-serious adverse events</b>                        | Medium Dose<br>Valsartan, then<br>Placebo | High Dose Valsartan<br>in both periods | Medium Dose<br>Valsartan in both<br>periods |
|--|---|--|---|
| Total subjects affected by non-serious<br>adverse events |   |  |   |
| subjects affected / exposed                              | 4 / 8 (50.00%)                            | 9 / 15 (60.00%)                        | 3 / 6 (50.00%)                              |
| Nervous system disorders                                 |   |  |   |
| Headache   |   |  |   |
| subjects affected / exposed                              | 0 / 8 (0.00%)                             | 1 / 15 (6.67%)                         | 0 / 6 (0.00%)                               |
| occurrences (all)  | 0   | 1                                      | 0   |
| Blood and lymphatic system disorders                     |   |  |   |
| Anaemia  |   |  |   |

|   |  |  |  |
|---|--|--|--|
| subjects affected / exposed<br>occurrences (all)  | 0 / 8 (0.00%)<br>0   | 0 / 15 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0   |
| General disorders and administration<br>site conditions<br>Pyrexia<br>subjects affected / exposed<br>occurrences (all)  | 0 / 8 (0.00%)<br>0   | 2 / 15 (13.33%)<br>2   | 0 / 6 (0.00%)<br>0   |
| Ear and labyrinth disorders<br>Otorrhoea<br>subjects affected / exposed<br>occurrences (all)  | 1 / 8 (12.50%)<br>1  | 0 / 15 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0   |
| Immune system disorders<br>Allergy to arthropod bite<br>subjects affected / exposed<br>occurrences (all)  | 1 / 8 (12.50%)<br>1  | 1 / 15 (6.67%)<br>1  | 0 / 6 (0.00%)<br>0   |
| Gastrointestinal disorders<br>Abdominal pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Aphthous stomatitis<br>subjects affected / exposed<br>occurrences (all)<br><br>Cheilitis<br>subjects affected / exposed<br>occurrences (all)<br><br>Constipation<br>subjects affected / exposed<br>occurrences (all)<br><br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all)<br><br>Nausea<br>subjects affected / exposed<br>occurrences (all)<br><br>Vomiting<br>subjects affected / exposed<br>occurrences (all) | 0 / 8 (0.00%)<br>0<br><br>0 / 8 (0.00%)<br>0<br><br>0 / 8 (0.00%)<br>0<br><br>0 / 8 (0.00%)<br>0<br><br>0 / 8 (0.00%)<br>0<br><br>0 / 8 (0.00%)<br>0<br><br>0 / 8 (0.00%)<br>0 | 2 / 15 (13.33%)<br>4<br><br>0 / 15 (0.00%)<br>0<br><br>0 / 15 (0.00%)<br>0<br><br>0 / 15 (0.00%)<br>0<br><br>2 / 15 (13.33%)<br>2<br><br>0 / 15 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0<br><br>0 / 6 (0.00%)<br>0<br><br>0 / 6 (0.00%)<br>0<br><br>1 / 6 (16.67%)<br>1<br><br>0 / 6 (0.00%)<br>0<br><br>0 / 6 (0.00%)<br>0<br><br>1 / 6 (16.67%)<br>1 |

|   |                |                 |               |
|---|----------------|-----------------|---------------|
| Respiratory, thoracic and mediastinal disorders |                |                 |               |
| Asthmatic crisis                                |                |                 |               |
| subjects affected / exposed                     | 1 / 8 (12.50%) | 0 / 15 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                               | 1              | 0               | 0             |
| Cough   |                |                 |               |
| subjects affected / exposed                     | 1 / 8 (12.50%) | 2 / 15 (13.33%) | 0 / 6 (0.00%) |
| occurrences (all)                               | 1              | 2               | 0             |
| Increased upper airway secretion                |                |                 |               |
| subjects affected / exposed                     | 1 / 8 (12.50%) | 0 / 15 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                               | 1              | 0               | 0             |
| Rhinorrhoea                                     |                |                 |               |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 15 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                               | 0              | 0               | 0             |
| Skin and subcutaneous tissue disorders          |                |                 |               |
| Dermatitis                                      |                |                 |               |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 15 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                               | 0              | 0               | 0             |
| Dermatitis bullous                              |                |                 |               |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 15 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                               | 0              | 0               | 0             |
| Dermatitis diaper                               |                |                 |               |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 15 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                               | 0              | 0               | 0             |
| Dry skin  |                |                 |               |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 15 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                               | 0              | 0               | 0             |
| Pruritus  |                |                 |               |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 15 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                               | 0              | 0               | 0             |
| Rash  |                |                 |               |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 15 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                               | 0              | 0               | 0             |
| Pruritus generalised                            |                |                 |               |
| subjects affected / exposed                     | 0 / 8 (0.00%)  | 0 / 15 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                               | 0              | 0               | 0             |
| Urticaria                                       |                |                 |               |

|  |                    |                     |                    |
|--|--------------------|---------------------|--------------------|
| subjects affected / exposed<br>occurrences (all) | 0 / 8 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |
| Infections and infestations                      |                    |                     |                    |
| Acute tonsillitis                                |                    |                     |                    |
| subjects affected / exposed                      | 0 / 8 (0.00%)      | 0 / 15 (0.00%)      | 0 / 6 (0.00%)      |
| occurrences (all)                                | 0                  | 0                   | 0                  |
| Bronchitis                                       |                    |                     |                    |
| subjects affected / exposed                      | 0 / 8 (0.00%)      | 1 / 15 (6.67%)      | 0 / 6 (0.00%)      |
| occurrences (all)                                | 0                  | 2                   | 0                  |
| Gastroenteritis                                  |                    |                     |                    |
| subjects affected / exposed                      | 0 / 8 (0.00%)      | 0 / 15 (0.00%)      | 0 / 6 (0.00%)      |
| occurrences (all)                                | 0                  | 0                   | 0                  |
| Gastroenteritis viral                            |                    |                     |                    |
| subjects affected / exposed                      | 1 / 8 (12.50%)     | 0 / 15 (0.00%)      | 0 / 6 (0.00%)      |
| occurrences (all)                                | 1                  | 0                   | 0                  |
| Impetigo   |                    |                     |                    |
| subjects affected / exposed                      | 0 / 8 (0.00%)      | 0 / 15 (0.00%)      | 0 / 6 (0.00%)      |
| occurrences (all)                                | 0                  | 0                   | 0                  |
| Nasopharyngitis                                  |                    |                     |                    |
| subjects affected / exposed                      | 0 / 8 (0.00%)      | 0 / 15 (0.00%)      | 1 / 6 (16.67%)     |
| occurrences (all)                                | 0                  | 0                   | 1                  |
| Pharyngitis                                      |                    |                     |                    |
| subjects affected / exposed                      | 1 / 8 (12.50%)     | 0 / 15 (0.00%)      | 0 / 6 (0.00%)      |
| occurrences (all)                                | 1                  | 0                   | 0                  |
| Pharyngotonsillitis                              |                    |                     |                    |
| subjects affected / exposed                      | 0 / 8 (0.00%)      | 0 / 15 (0.00%)      | 0 / 6 (0.00%)      |
| occurrences (all)                                | 0                  | 0                   | 0                  |
| Rhinitis   |                    |                     |                    |
| subjects affected / exposed                      | 0 / 8 (0.00%)      | 0 / 15 (0.00%)      | 0 / 6 (0.00%)      |
| occurrences (all)                                | 0                  | 0                   | 0                  |
| Scarlet fever                                    |                    |                     |                    |
| subjects affected / exposed                      | 0 / 8 (0.00%)      | 0 / 15 (0.00%)      | 0 / 6 (0.00%)      |
| occurrences (all)                                | 0                  | 0                   | 0                  |
| Tonsillitis                                      |                    |                     |                    |
| subjects affected / exposed                      | 0 / 8 (0.00%)      | 0 / 15 (0.00%)      | 0 / 6 (0.00%)      |
| occurrences (all)                                | 0                  | 0                   | 0                  |

|   |                    |                      |                    |
|---|--------------------|----------------------|--------------------|
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 0 / 8 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0 |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)           | 0 / 8 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0 |
| Varicella<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 8 (0.00%)<br>0 | 1 / 15 (6.67%)<br>1  | 0 / 6 (0.00%)<br>0 |
| Metabolism and nutrition disorders  |                    |                      |                    |
| Hyperkalaemia<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 8 (0.00%)<br>0 | 2 / 15 (13.33%)<br>2 | 0 / 6 (0.00%)<br>0 |
| Hypertriglyceridaemia<br>subjects affected / exposed<br>occurrences (all)             | 0 / 8 (0.00%)<br>0 | 1 / 15 (6.67%)<br>1  | 0 / 6 (0.00%)<br>0 |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment  |
|-------------------|--|
| 26 July 2007      | <p>Deleted inclusion criterion allowing subjects with previous solid organ transplantation more than 1 year ago and rephrased to exclude solid organ transplantation &lt; 1 year ago.</p> <p>Exclusion criterion was changed to allow enrolment of subjects with electrocardiogram (ECG) abnormalities associated with left ventricular hypertrophy. Further, cardiac insufficiency was added to the list of examples of clinically significant ECG abnormalities considered exclusionary.</p> <p>Exclusion criterion was revised and deleted the renal artery stenosis. Unilateral, bilateral and graft renal artery stenosis was added to the exclusion criterion.</p> <p>Specified that a decrease in estimated glomerular filtration rate (GFR) from baseline by more than 50% required discontinuation from the study.</p> <p>Specified that an Ora-plus and Ora-sweet preparation (not Ora-Blend) was used to prepare the extemporaneous suspension of valsartan.</p> <p>Acute dehydration and hyperkalemia were added to the requirements for discontinuation of study drug.</p> <p>The section describing the process for collecting information on screening failures was simplified.</p> <p>A description of the collection and reporting of suspected, unexpected serious adverse event (SUSARs) was added to the section on serious adverse event reporting.</p> |
| 30 September 2008 | <p>Lowered the age limit from 1 year to 6 months old for entry criteria into the study ( EMA request)</p> <p>Included recommendation of External Safety Monitoring Committee ( ESMC) to enhance monitoring of liver function, renal function and serum potassium alert in all patients</p> <p>The screening period was started with Day -28.</p> <p>Inclusion criterion was elaborated in order to state that for all subjects, mean seated systolic blood pressure had to be equal to or greater than 95th percentile at randomization.</p> <p>Exclusion criterion was further revised to exclude subjects with previous solid organ transplantation less &lt; 1 year prior to Visit 1.</p>   |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported