



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
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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
Arm title	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.

Arm title	Period 1: Medium dose Valsartan
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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.

Arm title	Period 1: High dose Valsartan
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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.

Number of subjects in period 1	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
Arm title	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.

Arm title	Period 2: Placebo
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Arm description:

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

Arm type	Placebo
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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.

Number of subjects in period 2	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: 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: 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: 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 Units: Subjects			

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

Reporting group values	Total		
Number of subjects	74		
Age categorical Units: Subjects			

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

End points

End points reporting groups

Reporting group title	Period 1: Low dose Valsartan
Reporting group description: 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: 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: Valsartan 4.0 mg/kg (high dose) oral suspension was administered OD for 6 weeks.	
Reporting group title	Period 2: Valsartan
Reporting group description: Valsartan oral suspension was administered OD for 2 weeks.	
Reporting group title	Period 2: Placebo
Reporting group description: 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: 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: 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

Statistical analysis title	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
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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
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End point timeframe:

Week 6 to Week 8

End point values	Period 2: Valsartan	Period 2: 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
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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
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End point timeframe:

Week 6 to Week 8

End point values	Period 2: Valsartan	Period 2: 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

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
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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
Serious adverse events			
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

Non-serious adverse events	Low Dose Valsartan in both periods	Low Dose Valsartan, then Placebo	High Dose Valsartan, then Placebo
Total subjects affected by non-serious adverse events subjects affected / exposed	8 / 15 (53.33%)	10 / 15 (66.67%)	11 / 15 (73.33%)
Nervous system disorders Headache subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 15 (6.67%) 2	0 / 15 (0.00%) 0
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 15 (0.00%) 0	1 / 15 (6.67%) 1
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 15 (0.00%) 0	3 / 15 (20.00%) 3
Ear and labyrinth disorders Otorrhoea subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 15 (0.00%) 0	0 / 15 (0.00%) 0
Immune system disorders Allergy to arthropod bite subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 15 (0.00%) 0	0 / 15 (0.00%) 0
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Aphthous stomatitis subjects affected / exposed occurrences (all) Cheilitis subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 2 0 / 15 (0.00%) 0 0 / 15 (0.00%) 0 0 / 15 (0.00%) 0	2 / 15 (13.33%) 2 0 / 15 (0.00%) 0 0 / 15 (0.00%) 0 0 / 15 (0.00%) 0	1 / 15 (6.67%) 3 1 / 15 (6.67%) 1 1 / 15 (6.67%) 1 0 / 15 (0.00%) 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 occurrences (all)	0 / 15 (0.00%) 0	0 / 15 (0.00%) 0	1 / 15 (6.67%) 1
Rash subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 15 (6.67%) 1	1 / 15 (6.67%) 1
Pruritus generalised subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 15 (0.00%) 0	0 / 15 (0.00%) 0
Urticaria subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 15 (0.00%) 0	1 / 15 (6.67%) 1
Infections and infestations Acute tonsillitis subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 15 (0.00%) 0	1 / 15 (6.67%) 1
Bronchitis subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	1 / 15 (6.67%) 2	1 / 15 (6.67%) 1
Gastroenteritis subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 15 (6.67%) 1	0 / 15 (0.00%) 0
Gastroenteritis viral subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 15 (0.00%) 0	0 / 15 (0.00%) 0
Impetigo subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 15 (0.00%) 0	1 / 15 (6.67%) 1
Nasopharyngitis subjects affected / exposed occurrences (all)	2 / 15 (13.33%) 2	1 / 15 (6.67%) 1	0 / 15 (0.00%) 0
Pharyngitis subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 15 (6.67%) 1	0 / 15 (0.00%) 0
Pharyngotonsillitis subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 15 (0.00%) 0	1 / 15 (6.67%) 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

Non-serious adverse events	Medium Dose Valsartan, then Placebo	High Dose Valsartan in both periods	Medium Dose Valsartan in both periods
Total subjects affected by non-serious 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 occurrences (all)	0 / 8 (0.00%) 0	0 / 15 (0.00%) 0	0 / 6 (0.00%) 0
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	2 / 15 (13.33%) 2	0 / 6 (0.00%) 0
Ear and labyrinth disorders Otorrhoea subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 15 (0.00%) 0	0 / 6 (0.00%) 0
Immune system disorders Allergy to arthropod bite subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	1 / 15 (6.67%) 1	0 / 6 (0.00%) 0
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Aphthous stomatitis subjects affected / exposed occurrences (all) Cheilitis subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0 0 / 8 (0.00%) 0 0 / 8 (0.00%) 0 0 / 8 (0.00%) 0 0 / 8 (0.00%) 0 0 / 8 (0.00%) 0 0 / 8 (0.00%) 0	2 / 15 (13.33%) 4 0 / 15 (0.00%) 0 0 / 15 (0.00%) 0 0 / 15 (0.00%) 0 2 / 15 (13.33%) 2 0 / 15 (0.00%) 0 0 / 15 (0.00%) 0	0 / 6 (0.00%) 0 0 / 6 (0.00%) 0 0 / 6 (0.00%) 0 1 / 6 (16.67%) 1 0 / 6 (0.00%) 0 0 / 6 (0.00%) 0 1 / 6 (16.67%) 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 occurrences (all)	0 / 8 (0.00%) 0	0 / 15 (0.00%) 0	0 / 6 (0.00%) 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 subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 15 (0.00%) 0	0 / 6 (0.00%) 0
Urinary tract infection subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 15 (0.00%) 0	0 / 6 (0.00%) 0
Varicella subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 15 (6.67%) 1	0 / 6 (0.00%) 0
Metabolism and nutrition disorders			
Hyperkalaemia subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	2 / 15 (13.33%) 2	0 / 6 (0.00%) 0
Hypertriglyceridaemia subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 15 (6.67%) 1	0 / 6 (0.00%) 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 < 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 < 1 year prior to Visit 1.</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported