Clinical trial results:
An extension to study protocol CVAL489K2302 to evaluate the long term safety, tolerability and efficacy of valsartan children 6 to 17 years of age with hypertension, versus enalapril treatment for 14 weeks, or combined with enalapril for 66 weeks in chronic kidney disease patients.

Summary

EudraCT number	2006-005408-14
Trial protocol	BE DE GB HU FR SE CZ IT
Global end of trial date	22 June 2009

Results information

Result version number	v1 (current)
This version publication date	13 July 2016
First version publication date	02 August 2015

Trial information

Trial identification

Sponsor protocol code	CVAL489K2302E1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00446511
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	22 June 2009
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 June 2009
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to assess the long-term safety and tolerability of valsartan and enalapril alone or in combination in children aged 6-17 years old with hypertension and stratified on the basis of underlying chronic kidney disease (CKD).

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:

Enalapril, an angiotensin-converting-enzyme (ACE) inhibitor, is approved in most European Union (EU) countries for the treatment of hypertension in children aged 2 months – 16 years based on its well-established pharmacokinetics, and on efficacy and safety data in 6 – 16 year old children. Enalapril was used as an active-comparator in this study as it is also dosed once daily, similar to experimental study treatment - valsartan.

Actual start date of recruitment	28 June 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: 83
Country: Number of subjects enrolled	Belgium: 25
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Hungary: 62
Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	India: 25
Country: Number of subjects enrolled	Turkey: 12
Country: Number of subjects enrolled	United States: 31
Worldwide total number of subjects	250
EEA total number of subjects	182

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)	72
Adolescents (12-17 years)	178
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 50 centres in 9 countries.

Pre-assignment

Screening details:

A total of 250 subjects were enrolled in the study, and were stratified on basis of underlying chronic kidney disease (CKD) i.e. 38 CKD and 212 non-CKD subjects.

Period 1

Period 1 title	Overall Study (overall period)
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	Valsartan+Enalapril (CKD Stratum)

Arm description:

Subjects with underlying chronic kidney disease (CKD), assigned to valsartan in the core study received combination therapy of valsartan and enalapril in the extension phase.

Arm type	Experimental
Investigational medicinal product name	Valsartan+Enalapril
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Weight stratified dose of combination therapy of valsartan + enalapril (80/10, 160/20, 320/40 mg) administered orally once daily (OD) at approximately the same time each day, with or without food. Subjects whose body weight was greater than (≥) 18 kilogram (kg) and less than (<) 35 kg received valsartan/enalapril 80/10 mg; ≥ 35 kg and < 80 kg received valsartan/enalapril 160/20 mg and ≥ 80 kg and less than or equal to (≤) 160 kg received valsartan/enalapril 320/40 mg.

Arm title	Enalapril + Placebo (CKD Stratum)

Arm description:

Subjects with CKD who were assigned to enalapril in the core study received enalapril and placebo (matching to valsartan tablet) in the extension phase.

Arm type	Active comparator
Investigational medicinal product name	Enalapril
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Weight stratified dose of enalapril (10, 20, 40 mg) was administered OD at approximately the same time each day, with or without food. Subjects whose body weight was ≥ 18 kg and < 35 kg received 10 mg; ≥ 35 kg and < 80 kg received 20 mg, and ≥ 80 kg and ≤ 160 kg received 40 mg of enalapril.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo tablets (matching to valsartan) was administered OD at approximately the same time each day, with or without food. Subjects whose body weight was ≥ 18 kg and < 35 kg received 80 mg; ≥ 35 kg and < 80 kg received 160 mg, and ≥ 80 kg and ≤ 160 kg received 320 mg of placebo (matching to valsartan tablet).

Arm title	Valsartan + Placebo (Non-CKD Stratum)

Arm description:

Subjects without CKD who were assigned to valsartan in the core study continued their valsartan monotherapy treatment along with matching placebo to enalapril tablets in the extension phase.

Arm type	Experimental
Investigational medicinal product name	Valsartan
Investigational medicinal product code	VAL489
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Weight stratified dose of valsartan (80, 160, 320 mg) administered OD at approximately the same time each day, with or without food. Subjects whose body weight was greater than (≥) 18 kilogram (kg) and less than (<) 35 kg received 80 mg; ≥ 35 kg and < 80 kg received 160 mg and ≥ 80 kg and less than or equal to (≤) 160 kg received 320 mg of valsartan.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo tablets (matching to enalapril) was administered OD at approximately the same time each day, with or without food. Subjects whose body weight was greater than (≥) 18 kilogram (kg) and less than (<) 35 kg received 10 mg; ≥ 35 kg and < 80 kg received 20 mg and ≥ 80 kg and less than or equal to (≤) 160 kg received 40 mg of matching placebo to enalapril tablet.

Arm title	Enalapril + Placebo (Non-CKD Stratum)

Arm description:

Subjects without CKD who were assigned to enalapril in the core study continued their enalapril monotherapy treatment with matching placebo to valsartan tablets in the extension phase.

Arm type	Active comparator
Investigational medicinal product name	Enalapril
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Weight stratified dose of enalapril (10, 20, 40 mg) administered OD at approximately the same time each day, with or without food. Subjects whose body weight was ≥ 18 kg and < 35 kg received 10 mg; ≥ 35 kg and < 80 kg received 20 mg, and ≥ 80 kg and ≤ 160 kg received 40 mg of enalapril.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo tablets (matching to valsartan) was administered OD at approximately the same time each day, with or without food. Subjects whose body weight was ≥ 18 kg and < 35 kg received 80 mg; ≥ 35 kg and < 80 kg received 160 mg, and ≥ 80 kg and ≤ 160 kg received 320 mg of matching placebo to valsartan.

Number of subjects in period 1	Valsartan+Enalapril (CKD Stratum)	Enalapril + Placebo (CKD Stratum)	Valsartan + Placebo (Non-CKD Stratum)
Started	21	17	103
Completed	11	15	96
Not completed	10	2	7
Consent withdrawn by subject	-	-	-
Adverse event, non-fatal	7	2	3
Administrative Problems	3	-	4
Protocol deviation	-	-	-

Number of subjects in period 1	Enalapril + Placebo (Non-CKD Stratum)
Started	109
Completed	103
Not completed	6
Consent withdrawn by subject	3
Adverse event, non-fatal	1
Administrative Problems	1
Protocol deviation	1

Baseline characteristics

Reporting groups	
Reporting group title	Valsartan+Enalapril (CKD Stratum)
Reporting group description:	
Subjects with underlying chronic kidney disease (CKD), assigned to valsartan in the core study received combination therapy of valsartan and enalapril in the extension phase.	
Reporting group title	Enalapril + Placebo (CKD Stratum)
Reporting group description:	
Subjects with CKD who were assigned to enalapril in the core study received enalapril and placebo (matching to valsartan tablet) in the extension phase.	
Reporting group title	Valsartan + Placebo (Non-CKD Stratum)
Reporting group description:	
Subjects without CKD who were assigned to valsartan in the core study continued their valsartan monotherapy treatment along with matching placebo to enalapril tablets in the extension phase.	
Reporting group title	Enalapril + Placebo (Non-CKD Stratum)
Reporting group description:	
Subjects without CKD who were assigned to enalapril in the core study continued their enalapril monotherapy treatment with matching placebo to valsartan tablets in the extension phase.	

Reporting group values	Valsartan+Enalapril (CKD Stratum)	Enalapril + Placebo (CKD Stratum)	Valsartan + Placebo (Non-CKD Stratum)
Number of subjects	21	17	103
Age categorical			
Units: Subjects			
Children (6-12 years)	12	8	42
Adolescents (13-17 years)	9	9	61
Age continuous			
Units: years			
arithmetic mean	11.4	12.1	13.1
standard deviation	± 3.4	± 3.07	± 2.75
Gender categorical			
Units: Subjects			
Female	8	5	41
Male	13	12	62

Reporting group values	Enalapril + Placebo (Non-CKD Stratum)	Total	
Number of subjects	109	250	
Age categorical			
Units: Subjects			
Children (6-12 years)	34	96	
Adolescents (13-17 years)	75	154	
Age continuous			
Units: years			
arithmetic mean	13.3		
standard deviation	± 2.81	-	
Gender categorical			
Units: Subjects			
Female	27	81	
Male	82	169	

End points

End points reporting groups

Reporting group title	Valsartan+Enalapril (CKD Stratum)
Reporting group description:	
Subjects with underlying chronic kidney disease (CKD), assigned to valsartan in the core study received combination therapy of valsartan and enalapril in the extension phase.	
Reporting group title	Enalapril + Placebo (CKD Stratum)
Reporting group description:	
Subjects with CKD who were assigned to enalapril in the core study received enalapril and placebo (matching to valsartan tablet) in the extension phase.	
Reporting group title	Valsartan + Placebo (Non-CKD Stratum)
Reporting group description:	
Subjects without CKD who were assigned to valsartan in the core study continued their valsartan monotherapy treatment along with matching placebo to enalapril tablets in the extension phase.	
Reporting group title	Enalapril + Placebo (Non-CKD Stratum)
Reporting group description:	
Subjects without CKD who were assigned to enalapril in the core study continued their enalapril monotherapy treatment with matching placebo to valsartan tablets in the extension phase.	

Primary: Number of subjects with adverse events (AEs), serious adverse events (SAEs)

End point title	Number of subjects with adverse events (AEs), serious adverse events (SAEs)[1]
End point description:	
An AE was defined as any undesirable sign, symptom or medical condition occurring after starting study drug (i.e. valsartan, enalapril or placebo) even if the event was not considered to be related to study drug. A SAE was defined as an event which was fatal or life threatening, required or prolonged hospitalisation, was significantly or permanently disabling or incapacitating, constituted a congenital anomaly or a birth defect, or encompassed any other clinically significant event that could jeopardize the subject or require medical or surgical intervention to prevent one of the aforementioned outcomes.	
End point type	Primary
End point timeframe:	
From Week 13 (start of extension phase) to end of extension phase (Week 26 in non-CKD subjects and Week 50 in CKD subjects)	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive summary statistics was planned for this outcome measure

End point values	Valsartan+Enalapril (CKD Stratum)	Enalapril + Placebo (CKD Stratum)	Valsartan + Placebo (Non-CKD Stratum)	Enalapril + Placebo (Non-CKD Stratum)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	17	103	109
Units: Number of subjects				
number (not applicable)				
AEs	16	11	51	53
SAEs	7	0	1	2

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Mean Sitting Systolic Blood Pressure (MSSBP) in non-CKD stratum at Week 26

End point title	Change from Baseline in Mean Sitting Systolic Blood Pressure (MSSBP) in non-CKD stratum at Week 26[2]

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. Analysis was performed in non-CKD stratum of extension Intent-to-Treat (ITT) population, defined as all extension subjects who had at least one post-Week 12 assessment of any efficacy variable during the extension.

End point type	Secondary

End point timeframe:

Baseline to Week 26

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint was planned to evaluate treatment arms in non-CKD subjects only.

End point values	Valsartan + Placebo (Non-CKD Stratum)	Enalapril + Placebo (Non-CKD Stratum)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103	108		
Units: mmHg				
arithmetic mean (standard deviation)	-11.6 (± 9.74)	-10.2 (± 9.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Mean Sitting Diastolic Blood Pressure (MSDBP) in non-CKD stratum at Week 26

End point title	Change from Baseline in Mean Sitting Diastolic Blood Pressure (MSDBP) in non-CKD stratum at Week 26[3]

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 diastolic blood pressure (SDBP) measurements were used as the average sitting office blood pressure for that visit. Analysis was performed in non-CKD stratum of extension ITT population.

End point type	Secondary

End point timeframe:

Baseline to Week 26

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was planned to evaluate treatment arms in non-CKD subjects only.

End point values	Valsartan + Placebo (Non-CKD Stratum)	Enalapril + Placebo (Non-CKD Stratum)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103	108		
Units: mmHg				
arithmetic mean (standard deviation)	-7.5 (± 8.47)	-7.2 (± 8.99)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects in non-CKD stratum achieving systolic and diastolic blood pressure (BP) control

End point title	Percentage of subjects in non-CKD stratum achieving systolic and diastolic blood pressure (BP) control[4]

End point description:

Treatment response or BP control (systolic and diastolic) was defined as 'Yes' for subjects whose MSSBP and MSDBP decreased to <95th percentile for gender, age, and height after 12 weeks treatment with valsartan compared to enalapril. Analysis was performed in non-CKD stratum of extension ITT population.

End point type	Secondary

End point timeframe:

Baseline to Week 26

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was planned to evaluate treatment arms in non-CKD subjects only.

End point values	Valsartan + Placebo (Non-CKD Stratum)	Enalapril + Placebo (Non-CKD Stratum)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103	108		
Units: Percentage of subjects				
number (not applicable)				
Systolic Responders	66	63		
Diastolic Responders	95.1	91.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in post-dosing 24-hour mean ambulatory systolic and diastolic blood pressure (ASBP, ADBP) at Week 20

End point title	Change from baseline in post-dosing 24-hour mean ambulatory systolic and diastolic blood pressure (ASBP, ADBP) at Week 20

End point description:

Ambulatory Blood Pressure Monitoring (ABPM) was performed over a 24-hour period using an automatic ABPM device to record the blood pressure as per study defined criteria. The subjects who were selected for this evaluation wore the ABPM device for 24 hours, returned to the clinic upon completion of the 24-hour monitoring period for removal of device and BP assessments. The subjects were then administered with the study medication while in the clinic. Analysis was performed in ABPM set defined as subset of extension ITT subjects from selected centres who consented to undergo ABPM at baseline and at Week 20. Here, 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively.

End point type	Secondary

End point timeframe:

Baseline to Week 20

End point values	Valsartan+Enalapril (CKD Stratum)	Enalapril + Placebo (CKD Stratum)	Valsartan + Placebo (Non-CKD Stratum)	Enalapril + Placebo (Non-CKD Stratum)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	2	14	23
Units: mmHg				
arithmetic mean (standard deviation)				
Change in ASBP (n=5,2,10,21)	-23.3 (± 11.6)	-0.3 (± 14.42)	-11.5 (± 7.81)	-4.1 (± 11.49)
Change in ADBP (n=5,2,10,21)	-17.8 (± 3.2)	2.9 (± 10.81)	-12.2 (± 6.6)	-4.5 (± 7.59)

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

Adverse event reporting additional description:

AE additional description

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.1

Reporting groups

Reporting group title	Valsartan + Enalapril (CKD patients)

Reporting group description:

Subjects with underlying chronic kidney disease (CKD), assigned to valsartan in the core study received combination therapy of valsartan and enalapril in the extension phase.

Reporting group title	Valsartan + Placebo (Non-CKD Stratum)

Reporting group description:

Subjects without CKD who were assigned to valsartan in the core study continued their valsartan monotherapy treatment along with matching placebo to enalapril tablets in the extension phase.

Reporting group title	Enalapril + Placebo (Non-CKD Stratum)

Reporting group description:

Subjects without CKD who were assigned to enalapril in the core study continued their enalapril monotherapy treatment with matching placebo to valsartan tablets in the extension phase.

Reporting group title	Enalapril + Placebo (CKD patients)

Reporting group description:

Subjects with CKD who were assigned to enalapril in the core study received enalapril and placebo (matching to valsartan tablet) in the extension phase.

Serious adverse events	Valsartan + Enalapril (CKD patients)	Valsartan + Placebo (Non-CKD Stratum)	Enalapril + Placebo (Non-CKD Stratum)
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 21 (33.33%)	1 / 103 (0.97%)	2 / 109 (1.83%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
White blood cell count decreased			
subjects affected / exposed	1 / 21 (4.76%)	0 / 103 (0.00%)	0 / 109 (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
Congenital, familial and genetic disorders			
Adrenogenital syndrome			

subjects affected / exposed	0 / 21 (0.00%)	1 / 103 (0.97%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 21 (4.76%)	0 / 103 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 21 (0.00%)	0 / 103 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Kidney transplant rejection			
subjects affected / exposed	1 / 21 (4.76%)	0 / 103 (0.00%)	0 / 109 (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
Musculoskeletal and connective tissue disorders			
Synostosis			
subjects affected / exposed	1 / 21 (4.76%)	0 / 103 (0.00%)	0 / 109 (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
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 103 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	1 / 21 (4.76%)	0 / 103 (0.00%)	0 / 109 (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
Metabolism and nutrition disorders			
Hyperkalaemia			

subjects affected / exposed	3 / 21 (14.29%)	0 / 103 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	5 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Enalapril + Placebo (CKD patients)		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 17 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
White blood cell count decreased			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Adrenogenital syndrome			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Kidney transplant rejection			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			

Synostosis			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Valsartan + Enalapril (CKD patients)	Valsartan + Placebo (Non-CKD Stratum)	Enalapril + Placebo (Non-CKD Stratum)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 21 (66.67%)	25 / 103 (24.27%)	42 / 109 (38.53%)
Vascular disorders			
Hypotension			
subjects affected / exposed	2 / 21 (9.52%)	0 / 103 (0.00%)	0 / 109 (0.00%)
occurrences (all)	3	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 21 (9.52%)	1 / 103 (0.97%)	1 / 109 (0.92%)
occurrences (all)	2	1	1
Epilepsy			
subjects affected / exposed	0 / 21 (0.00%)	0 / 103 (0.00%)	0 / 109 (0.00%)
occurrences (all)	0	0	0

Headache			
subjects affected / exposed	4 / 21 (19.05%)	11 / 103 (10.68%)	16 / 109 (14.68%)
occurrences (all)	4	12	22
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	3 / 21 (14.29%)	5 / 103 (4.85%)	4 / 109 (3.67%)
occurrences (all)	3	5	4
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 21 (0.00%)	2 / 103 (1.94%)	4 / 109 (3.67%)
occurrences (all)	0	2	4
Nausea			
subjects affected / exposed	0 / 21 (0.00%)	0 / 103 (0.00%)	2 / 109 (1.83%)
occurrences (all)	0	0	2
Vomiting			
subjects affected / exposed	2 / 21 (9.52%)	0 / 103 (0.00%)	3 / 109 (2.75%)
occurrences (all)	2	0	4
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 21 (4.76%)	2 / 103 (1.94%)	1 / 109 (0.92%)
occurrences (all)	1	2	1
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	1 / 21 (4.76%)	1 / 103 (0.97%)	0 / 109 (0.00%)
occurrences (all)	1	1	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 21 (0.00%)	6 / 103 (5.83%)	9 / 109 (8.26%)
occurrences (all)	0	6	9
Pharyngitis			
subjects affected / exposed	2 / 21 (9.52%)	7 / 103 (6.80%)	11 / 109 (10.09%)
occurrences (all)	3	7	14
Sinusitis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 103 (0.97%)	0 / 109 (0.00%)
occurrences (all)	0	1	0
Urinary tract infection			

subjects affected / exposed	2 / 21 (9.52%)	1 / 103 (0.97%)	2 / 109 (1.83%)
occurrences (all)	2	2	4
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	4 / 21 (19.05%)	0 / 103 (0.00%)	3 / 109 (2.75%)
occurrences (all)	4	0	3
Hypertriglyceridaemia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 103 (0.97%)	0 / 109 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Enalapril + Placebo (CKD patients)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 17 (64.71%)		
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Epilepsy			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	2		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Nausea			

subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1 0 / 17 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	 2 / 17 (11.76%) 2		
Musculoskeletal and connective tissue disorders Pain in extremity subjects affected / exposed occurrences (all)	 1 / 17 (5.88%) 2		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Pharyngitis subjects affected / exposed occurrences (all) Sinusitis subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	 1 / 17 (5.88%) 1 2 / 17 (11.76%) 2 1 / 17 (5.88%) 1 1 / 17 (5.88%) 1		
Metabolism and nutrition disorders Hyperkalaemia subjects affected / exposed occurrences (all) Hypertriglyceridaemia subjects affected / exposed occurrences (all)	 2 / 17 (11.76%) 2 1 / 17 (5.88%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 June 2007	• The timing of the 24-hour ABPM was moved from Week 26 (Visit 11) to Week 20 (Visit 10). • Matching placebo was added to the doses of non-CKD patients. • The dose form was corrected to state that study medication would be provided in blister packs instead of bottles. • The reasons for discontinuation were clarified. • A statement was added to inform investigators that unscheduled visits could be conducted at their discretion. • Instructions were added to contact the IVRS whenever patients were prematurely discontinued. • The visit schedule was revised, removing the requirement for patients to be fasting before laboratory evaluations, and adding that CKD patients had to have a specimen drawn for hematology tests at Week 16 (Visit 9). • Instructions regarding the collection and reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs) were added. • The calculation for GFR was clarified, deleting the formula for creatinine clearance, and adding the formula for calculating GFR. • A statement was added to the laboratory evaluations section to allow for additional testing in the event of clinically significant abnormalities.
30 September 2008	The 52 weeks prolongation of study was for CKD patients only and for a total of approximately 18 months, focusing on change in GFR and proteinuria. The protocol title and relevant sections were updated for CKD subjects. An independent External Safety Monitoring Committee (ESMC) was added to enhance the monitoring of liver function, renal function and serum potassium alerts in all subjects. However, after CKD patients completed the initial 14 week extension period, only 3 of these patients were eligible to continue into the 52 week "long term" CKD extension. As no meaningful conclusions could be drawn owing to small patient numbers, the study was terminated prematurely with these 3 CKD patients progressing to a maximum of Visit 13.

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 study intended to compare the valsartan+enalapril vs enalapril for 66 weeks in children with CKD. The 66 week assessment of CKD subjects was terminated earlier (Week 50) in agreement with EMEA due to small number of analysable subjects.

Notes: