Clinical trial results:
A multicenter, randomized, double-blind, parallel-group, evaluation of 12 weeks of valsartan compared to enalapril on sitting systolic blood pressure in children 6 to 17 years of age with hypertension

Summary

EudraCT number	2006-005260-88
Trial protocol	BE FR DE HU SE CZ PL IT SK GB
Global end of trial date	17 February 2009

Results information

Result version number	v1 (current)
This version publication date	13 July 2016
First version publication date	27 July 2015

Trial information

Trial identification

Sponsor protocol code	CVAL489K2302

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00433836
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	17 February 2009
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 February 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this 12-week study was to evaluate the safety and efficacy of three different dose strengths of valsartan (80/160/320 milligrams [mg]) compared with enalapril (10/20/40 mg) on mean sitting systolic blood pressure (MSSBP) in hypertensive children aged 6 to 17 years, with or without chronic kidney disease.

Protection of trial subjects:

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

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	31 January 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	Slovakia: 2
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	Belgium: 29
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Hungary: 72
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Poland: 90
Country: Number of subjects enrolled	United States: 45
Country: Number of subjects enrolled	Turkey: 14
Country: Number of subjects enrolled	India: 29
Worldwide total number of subjects	300
EEA total number of subjects	212

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)	93
Adolescents (12-17 years)	207
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 60 centres in 11 countries.

Pre-assignment

Screening details:

A total of 348 subjects were enrolled into a single-blind placebo-run in period of the study, out of which 300 subjects completed the single-blind period and were randomized.

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

Arm description:

Subjects received body-weight stratified dose of valsartan tablets (80/160/ 320 mg) once daily through oral route (PO). 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.

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 dosages of valsartan 80/160/320 mg once daily PO

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 dosages of valsartan 80/160/320 mg once daily PO

Arm title	Enalapril

Arm description:

Subjects received body-weight stratified dose of enalapril tablets (10/20/ 40 mg) once daily PO. 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.

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 dosages of enalapril 10/20/40 mg once daily PO

Number of subjects in period 1	Valsartan	Enalapril
Started	151	149
Completed	138	143
Not completed	13	6
Consent withdrawn by subject	2	1
Physician decision	-	1
Adverse event, non-fatal	7	-
Abnormal Laboratory Values	-	1
Lost to follow-up	3	-
Lack of efficacy	1	1
Protocol deviation	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Valsartan
Reporting group description:	
Subjects received body-weight stratified dose of valsartan tablets (80/160/ 320 mg) once daily through oral route (PO). 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.	
Reporting group title	Enalapril
Reporting group description:	
Subjects received body-weight stratified dose of enalapril tablets (10/20/ 40 mg) once daily PO. 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.	

Reporting group values	Valsartan	Enalapril	Total
Number of subjects	151	149	300
Age categorical Units: Subjects			
Children (2-11 years)	52	41	93
Adolescents (12-17 years)	99	108	207
Age continuous Units: years			
arithmetic mean	12.7	13	
standard deviation	± 2.93	± 2.94	-
Gender categorical Units: Subjects			
Female	65	44	109
Male	86	105	191

End points

End points reporting groups

Reporting group title	Valsartan
Reporting group description:	
Subjects received body-weight stratified dose of valsartan tablets (80/160/ 320 mg) once daily through oral route (PO). 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.	
Reporting group title	Enalapril
Reporting group description:	
Subjects received body-weight stratified dose of enalapril tablets (10/20/ 40 mg) once daily PO. 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.	

Primary: Change From Baseline in Mean Sitting Systolic Blood Pressure (MSSBP) at Week 12

End point title	Change From Baseline in Mean Sitting Systolic Blood Pressure (MSSBP) at Week 12
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 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, Week 12	

End point values	Valsartan	Enalapril		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	148		
Units: millimeters of mercury (mmHg)				
least squares mean (standard error)	-15.4 (± 1.29)	-14.1 (± 1.28)		

Statistical analyses

Statistical analysis title	Change from baseline in MSSBP at Week 12
Statistical analysis description:	
LS mean, 95% CI and p-value for the difference between valsartan and enalapril were based on the ANCOVA model with region, weight, CKD and treatment as factors, and baseline mean sitting SBP as a covariate.	
Comparison groups	Valsartan v Enalapril

Number of subjects included in analysis	296
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	-1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.8
upper limit	1.17
Variability estimate	Standard error of the mean
Dispersion value	1.26

Notes:

[1] - Non-inferiority margin used in the non-inferiority test was 3.5 mmHg.

Secondary: Change From Baseline in Mean Sitting Diastolic Blood Pressure (MSDBP) at Week 12

End point title	Change From Baseline in Mean Sitting Diastolic Blood Pressure (MSDBP) at Week 12

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 ITT population.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Valsartan	Enalapril		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	148		
Units: mmHg				
least squares mean (standard error)	-9.4 (± 0.94)	-8.5 (± 0.95)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects achieving a treatment response at Week 12

End point title	Percentage of subjects achieving a treatment response at Week 12

End point description:

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

End point type	Secondary

End point timeframe:

Week 12

End point values	Valsartan	Enalapril		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	148		
Units: Percentage of subjects				
number (not applicable)	66.9	70.3		

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 8

End point title	Change from baseline in post-dosing 24-hour mean ambulatory systolic and diastolic blood pressure (ASBP, ADBP) at Week 8

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 patient were then administered with the study medication while in the clinic. Analysis was performed in ABPM set defined as subset of ITT subjects from selected centers who consented to undergo ABPM at baseline and at Week 8.

End point type	Secondary

End point timeframe:

Baseline, Week 8

End point values	Valsartan	Enalapril		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	30		
Units: mm Hg				
arithmetic mean (standard deviation)				
ASBP	-9.8 (± 6.75)	-6.8 (± 7.41)		
ADBP	-9.3 (± 6.27)	-5.5 (± 5.73)		

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:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.0

Reporting groups

Reporting group title	Valsartan

Reporting group description:

Subjects received body-weight stratified dose of valsartan tablets (80/160/ 320 mg) once daily PO.

Reporting group title	Enalapril

Reporting group description:

Subjects received body-weight stratified dose of enalapril tablets (10/20/ 40 mg) once daily PO.

Serious adverse events	Valsartan	Enalapril	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 151 (1.99%)	2 / 148 (1.35%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Avulsion fracture			
subjects affected / exposed	0 / 151 (0.00%)	1 / 148 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal injury			
subjects affected / exposed	0 / 151 (0.00%)	1 / 148 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Brain injury			

subjects affected / exposed	1 / 151 (0.66%)	0 / 148 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 151 (0.66%)	0 / 148 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 151 (0.66%)	0 / 148 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Valsartan	Enalapril	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	42 / 151 (27.81%)	52 / 148 (35.14%)	
Nervous system disorders			
Headache			
subjects affected / exposed	18 / 151 (11.92%)	28 / 148 (18.92%)	
occurrences (all)	26	36	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	9 / 151 (5.96%)	10 / 148 (6.76%)	
occurrences (all)	9	11	
Infections and infestations			
Pharyngitis			
subjects affected / exposed	6 / 151 (3.97%)	11 / 148 (7.43%)	
occurrences (all)	8	16	
Nasopharyngitis			
subjects affected / exposed	10 / 151 (6.62%)	8 / 148 (5.41%)	
occurrences (all)	11	10	
Upper respiratory tract infection			

subjects affected / exposed occurrences (all)	10 / 151 (6.62%) 11	7 / 148 (4.73%) 7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 June 2007	1. The definition of chronic kidney disease was corrected from glomerular filtration rate (GFR) <60 mL/min/1.73m^2 for ≥ 3 months, to GFR <90 mL/min/1.73m^2 for ≥ 3 months 2. The second ABPM was done at Week 8 instead of at end of study 3. The eligibility criterion that excluded subjects with creatinine clearance <30 mL/min/1.73m^2 was corrected to GFR <30 mL/min/1.73m^2 4. Added graft renal artery stenosis to the exclusion criteria 5. Allowed enrollment of subjects with electrocardiogram abnormalities associated with left ventricular hypertrophy 6. Added coarctation of the aorta with a gradient of ≥ 30 mmHg to the exclusion criteria 7. Specifically excluded subjects known to have tested seropositive for the human immunodeficiency virus (HIV) and concomitantly receiving anti-retroviral therapy 8. Stated that the study medication would be packaged in blister packs, not bottles. 9. Changed the dosing from q.d. to o.d. 10. Added potassium sparing diuretics, potassium supplements, potassium containing salt substitutes and/or other medications which raise the serum potassium to the list of prohibited concomitant medications. 11. Stipulated that patients with a decrease from baseline in estimated GFR >50% or serum potassium level >5.5 mmol/L had to be discontinued. 12. Added that patients with acute dehydration were to have their study medication temporarily interrupted until they had been fully hydrated for at least 3 days. 13. The section describing SAE reporting was updated to state that suspected, unexpected serious adverse reactions (SUSARs) were to be collected and reported to the competent authorities and relevant ethics committees in accordance with directive 2001/20/EC as per National regulatory requirements in participating countries. 14. Added a second ECG to the end of study evaluations. 15. Added hemoglobin, hematocrit and WBC count to Visit 5 evaluations for CKD patients
30 September 2008	1. Additional steps for monitoring of serum potassium, renal function and liver function were included. 2. The responsibilities of the External Safety Monitoring Committee (ESMC), a committee independent of Novartis, were added to the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported