Clinical trial results:
An open label extentsion study to evaluate safety, tolerability, and efficacy of 18 weeks of valsartan treatment in children 6 months -5 years old with hypertension

Summary

EudraCT number	2006-005473-21
Trial protocol	BE FR GB HU SE IT DE
Global end of trial date	25 May 2009
Results information	
Result version number	v1
This version publication date	13 July 2016
First version publication date	30 July 2015

Trial information

Trial identification	
Sponsor protocol code	CVAL489K2303E1
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00457626
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	25 May 2009
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 May 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study was to evaluate the efficacy, safety and tolerability of long-term use of valsartan (1milligram/kilogram [mg/kg] or 2 mg/kg or 4 mg/kg) 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	09 April 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	Netherlands: 10
Country: Number of subjects enrolled	United States: 4
Country: Number of subjects enrolled	South Africa: 5
Country: Number of subjects enrolled	Turkey: 2
Country: Number of subjects enrolled	Brazil: 8
Country: Number of subjects enrolled	India: 19
Country: Number of subjects enrolled	Poland: 10
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Hungary: 3
Country: Number of subjects enrolled	Italy: 2
Worldwide total number of subjects	66
EEA total number of subjects	28

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)	10
Children (2-11 years)	56
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 35 centres in 10 countries.

Pre-assignment

Screening details:

This study enrolled a total of 66 subjects who completed the core study (CVAL489K2303).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Valsartan

Arm description:

Extemporaneous oral suspension prepared from valsartan tablets was administered to subjects once daily. The starting dose of valsartan was 1mg/kg which was escalated to 2 mg/kg or 4 mg/kg based on systolic blood pressure control after 2 weeks.

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

Dosage and administration details:

Extemporaneous oral suspension prepared from valsartan tablets was administered to subjects once daily. The starting dose of valsartan was 1mg/kg which was escalated to 2 mg/kg or 4 mg/kg based on systolic blood pressure control after 2 weeks.

Number of subjects in period 1	Valsartan
Started	66
Completed	60
Not completed	6
Adverse event, non-fatal	3
Administrative problems	2
Subject's condition no longer requires study drug	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	66	66	
Age categorical Units: Subjects			
1-5 years	66	66	
Age continuous Units: years			
arithmetic mean	3.4		
standard deviation	± 14.1	-	
Gender categorical Units: Subjects			
Female	23	23	
Male	43	43	

End points

End points reporting groups

Reporting group title	Valsartan

Reporting group description:

Extemporaneous oral suspension prepared from valsartan tablets was administered to subjects once daily. The starting dose of valsartan was 1mg/kg which was escalated to 2 mg/kg or 4 mg/kg based on systolic blood pressure control after 2 weeks.

Primary: Change From Baseline in Mean Sitting Systolic Blood Pressure (MSSBP) at Week 26

End point title	Change From Baseline in Mean Sitting Systolic Blood Pressure (MSSBP) at Week 26[1]

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. The analysis was performed on Extension set, which included all subjects who entered open-label extension period with administration of at least one dose of open-label study drug. Missing data was imputed using last observation carry forward (LOCF) technique.

End point type	Primary

End point timeframe:

Baseline to Week 26

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			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: millimeters of mercury (mmHg)				
arithmetic mean (standard deviation)	-11.2 (± 12.56)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Mean Sitting Diastolic Blood Pressure (MSDBP) at Week 26

End point title	Change From Baseline in Mean Sitting Diastolic Blood Pressure (MSDBP) 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 SDBP measurements were used as the average sitting office blood pressure for that visit. The analysis was performed on Extension set. Missing data was imputed using LOCF technique.

End point type	Primary

End point timeframe:

Baseline to Week 26

Notes:

[2] - 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			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: mmHg				
arithmetic mean (standard deviation)	-6.6 (± 11.84)			

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Number of subjects with Adverse Events (AEs) and Serious Adverse Events (SAEs)[3]

End point description:

An AE was defined as any unfavourable and unintended sign, symptom, or disease temporally associated with the use of study drug, whether or not related to study drug. A SAE was defined as an event which was fatal or life threatening, required or prolonged hospitalization, 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. The analysis was performed on Extension set.

End point type	Primary

End point timeframe:

From Week 8 to Week 26 of extension phase

Notes:

[3] - 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			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: Number				
AEs	38			
SAEs	4			

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

Dictionary used

Dictionary name	MedDRA
Dictionary version	12

Reporting groups

Reporting group title	Valsartan

Reporting group description:

Extemporaneous oral suspension prepared from valsartan tablets was administered to subjects once daily. The starting dose of valsartan was 1mg/kg which was escalated to 2 mg/kg or 4 mg/kg based on systolic blood pressure control after 2 weeks.

Serious adverse events	Valsartan		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 66 (6.06%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Head injury			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Wound			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Nephrotic syndrome			

subjects affected / exposed	1 / 66 (1.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Viral infection			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Valsartan		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 66 (36.36%)		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	11 / 66 (16.67%)		
occurrences (all)	18		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 66 (6.06%)		
occurrences (all)	5		
Infections and infestations			
Bronchitis			
subjects affected / exposed	5 / 66 (7.58%)		
occurrences (all)	5		
Nasopharyngitis			
subjects affected / exposed	7 / 66 (10.61%)		
occurrences (all)	9		
Upper respiratory tract infection			
subjects affected / exposed	5 / 66 (7.58%)		
occurrences (all)	6		
Viral infection			
subjects affected / exposed	4 / 66 (6.06%)		
occurrences (all)	4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 June 2007	• A statement was added that unscheduled visits could be performed as needed at the discretion of the investigator to monitor patient safety. • Two exclusion criteria were added: Patients who experienced any AEs considered serious or drug related in the core study and patients excluded from the core study. • Details regarding study medication (including the supply, administration and preparation of the suspension) were added. • Specifics regarding the use of concomitant medication were added. • Instructions regarding study drug discontinuation, formerly missing from the protocol, were added. • Urine dipstick testing was added. • The requirement for patients to be fasting prior to laboratory evaluations was removed. • Details on the collection and reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs) were added, in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries. • GFR testing (Glomerular Filtration Rate) was added. • Several values in the tables of BP levels by age and height percentile were inaccurate. The tables (located in Appendix 3 of the protocol) were replaced to reflect correct values.
30 September 2008	• The age range of the study subjects was changed from 1 to 5 years old to 6 months to 5 years old as per recommendations from European Medicines Agency Pediatric Committee • Several changes were made to the section on discontinuation of study drug. These enhanced the monitoring of liver function, renal function and serum potassium alerts in all patients. • Instructions were also added regarding decreases in body weight. • The timing of visits was revised: all extension visits were conducted in relation to the number of days from Day 0, instead of the previous extension visit. • The section on GFR estimates was revised to include infants <1 year old. The 2 to 12 year age group was changed to 1 to 12 years. • Revisions were made to include the recommendations of an independent External Safety Monitoring Committee (ESMC). • Blood-pressure charts for children 6 months to <1 year old were added to Appendix 3 of the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported