Clinical trial results:
A multicenter, double-blind, randomized, 52-week, extension study to evaluate the long term safety, tolerability and efficacy of aliskiren compared to enalapril in pediatric hypertensive patients 6-17 years of age

Summary

EudraCT number	2009-017029-20
Trial protocol	SK DE HU BE FR PL Outside EU/EEA
Global end of trial date	13 August 2015

Results information

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

Trial information

Trial identification

Sponsor protocol code	CSPP100A2365E1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01151410
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)	Yes
EMA paediatric investigation plan number(s)	EMEA-000362-PIP01-08
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	13 August 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 August 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and tolerability of long term administration (52 weeks) of aliskiren compared to enalapril in hypertensive children aged 6-17 years (age at baseline in Study CSPP100A2365).

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: -

Actual start date of recruitment	20 August 2010
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	Guatemala: 17
Country: Number of subjects enrolled	Hungary: 48
Country: Number of subjects enrolled	Poland: 10
Country: Number of subjects enrolled	Slovakia: 55
Country: Number of subjects enrolled	Turkey: 3
Country: Number of subjects enrolled	United States: 75
Worldwide total number of subjects	208
EEA total number of subjects	113

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)	101

Adolescents (12-17 years)	107
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 208 patients were randomized in this study. The number of patients by treatment group included in the efficacy and safety analyses differed due to a treatment crossover in one patient (caused by kit dispensing error).

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Aliskiren

Arm description:

Patients will receive one of the following doses based on the their weight: Low weight (≥20 to <50 kg) patients: Starting dose 37.5 mg with optional titration to 75 and then 150 mg Mid weight (≥50 to <80 kg) patients: Starting dose 75 mg with optional titration to 150 and then 300 mg High weight (≥80 to ≤150 kg) patients: Starting dose 150 mg with optional titration to 300 and then 600 mg

Arm type	Experimental
Investigational medicinal product name	Aliskiren
Investigational medicinal product code	SPP100
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Aliskiren dispensing capsules containing minitablets (3.125 mg per minitablet) with a total dose of 37.5 mg/capsule, 75 mg/capsule or 150 mg/capsule. Patients used one or more capsules to reach assigned dose. Low weight patients: Starting dose 37.5 mg with optional titration to 75 and then 150 mg Mid weight patients: Starting dose 75 mg with optional titration to 150 and then 300 mg High weight patients: Starting dose 150 mg with optional titration to 300 and then 600 mg

Arm title	Enalapril

Arm description:

Patients will receive one of the following doses based on their weight: Low weight (≥20 to <50 kg) patients: Starting dose 2.5 mg with optional titration to 5 and then 10 mg Mid weight (≥50 to <80 kg) patients: Starting dose 5 mg with optional titration to 10 and then 20 mg High weight (≥80 to ≤150 kg) patients: Starting dose 10 mg with optional titration to 20 and then 40 mg

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

Dosage and administration details:

Enalapril was provided as tablets with 2.5 mg/tablet, 5 mg/tablet, 10 mg/tablet and 20 mg/tablet. Patient took one or more tablets to reach assigned dose. Low weight (≥20 to <50 kg) patients: Starting dose 2.5 mg with optional titration to 5 and then 10 mg Mid weight (≥50 to <80 kg) patients: Starting dose 5 mg with optional titration to 10 and then 20 mg High weight (≥80 to ≤150 kg) patients: Starting dose 10 mg with optional titration to 20 and then 40 mg

Number of subjects in period 1	Aliskiren	Enalapril
Started	104	104
Completed	93	89
Not completed	11	15
Abnormal laboratory value(s)	-	1
Consent withdrawn by subject	3	5
Adverse event, non-fatal	1	2
Protocol deviation	2	1
Unsatisfactory therapeutic effect	1	1
Administrative problems	1	1
Lost to follow-up	3	4

Baseline characteristics

Reporting groups	
Reporting group title	Aliskiren
Reporting group description:	
Patients will receive one of the following doses based on the their weight: Low weight (≥20 to <50 kg) patients: Starting dose 37.5 mg with optional titration to 75 and then 150 mg Mid weight (≥50 to <80 kg) patients: Starting dose 75 mg with optional titration to 150 and then 300 mg High weight (≥80 to ≤150 kg) patients: Starting dose 150 mg with optional titration to 300 and then 600 mg	
Reporting group title	Enalapril
Reporting group description:	
Patients will receive one of the following doses based on their weight: Low weight (≥20 to <50 kg) patients: Starting dose 2.5 mg with optional titration to 5 and then 10 mg Mid weight (≥50 to <80 kg) patients: Starting dose 5 mg with optional titration to 10 and then 20 mg High weight (≥80 to ≤150 kg) patients: Starting dose 10 mg with optional titration to 20 and then 40 mg	

Reporting group values	Aliskiren	Enalapril	Total
Number of subjects	104	104	208
Age, Customized Units: participants			
Children 6 – 11 years	50	51	101
Adolescents 12 – 17 years	54	53	107
Age Continuous Units: years			
arithmetic mean	11.7	11.9	
standard deviation	± 3.4	± 3.4	-
Gender, Male/Female Units: participants			
Male	64	72	136
Female	40	32	72

End points

End points reporting groups

Reporting group title	Aliskiren
Reporting group description:	
Patients will receive one of the following doses based on the their weight: Low weight (≥20 to <50 kg) patients: Starting dose 37.5 mg with optional titration to 75 and then 150 mg Mid weight (≥50 to <80 kg) patients: Starting dose 75 mg with optional titration to 150 and then 300 mg High weight (≥80 to ≤150 kg) patients: Starting dose 150 mg with optional titration to 300 and then 600 mg	
Reporting group title	Enalapril
Reporting group description:	
Patients will receive one of the following doses based on their weight: Low weight (≥20 to <50 kg) patients: Starting dose 2.5 mg with optional titration to 5 and then 10 mg Mid weight (≥50 to <80 kg) patients: Starting dose 5 mg with optional titration to 10 and then 20 mg High weight (≥80 to ≤150 kg) patients: Starting dose 10 mg with optional titration to 20 and then 40 mg	

Primary: Change from baseline in mean sitting systolic blood pressure (msSBP) at end of study

End point title	Change from baseline in mean sitting systolic blood pressure (msSBP) at end of study
End point description:	
Sitting blood pressure was measured using a calibrated standard sphygmomanometer after the participants remained in sitting position for 5 minutes at clinic during the visit. The repeat sitting measurements were made at 2 to 3 minute intervals and the mean of three sSBP measurements were used as the average sitting office blood pressure for that visit.	
End point type	Primary
End point timeframe:	
Baseline - end of study (Week 52 or Last observation carried forward (LOCF)	

End point values	Aliskiren	Enalapril		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	104	104		
Units: millimeter(s) of mercury (mmHg)				
least squares mean (standard error)	-7.63 (± 1.16)	-7.94 (± 1.14)		

Statistical analyses

Statistical analysis title	Change from baseline in msSBP
Comparison groups	Aliskiren v Enalapril
Number of subjects included in analysis	208
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.004
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.31

Confidence interval	
level	95 %
sides	1-sided
lower limit	-2.4

Secondary: Change in mean sitting diastolic blood pressure (msDBP) from Baseline to end of study

End point title	Change in mean sitting diastolic blood pressure (msDBP) from Baseline to end of study

End point description:

Sitting blood pressure was measured using a calibrated standard sphygmomanometer after the participants remained in sitting position for 5 minutes at clinic during the visit. The repeat sitting measurements were made at 2 to 3 minute intervals and the mean of three sDBP measurements were used as the average sitting office blood pressure for that visit.

End point type	Secondary

End point timeframe:

Baseline - end of study (Week 52 or Last observation carried forward (LOCF)

End point values	Aliskiren	Enalapril		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	104	104		
Units: mmHg				
least squares mean (standard error)	-3.9 (± 0.87)	-4.94 (± 0.85)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in mean arterial pressure (MAP) (mmHg) from baseline to end of study

End point title	Change in mean arterial pressure (MAP) (mmHg) from baseline to end of study

End point description:

MAP was defined as the average arterial pressure during a single cardiac cycle. The MAP was measured as sum of diastolic blood pressure (DBP) and one third of difference between systolic blood pressure (SBP) and DBP i.e. MAP = DBP+1/3*(SBP - DBP).

End point type	Secondary

End point timeframe:

Baseline to end of study (Week 52 or LOCF)

End point values	Aliskiren	Enalapril		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	104	104		
Units: mmHg				
least squares mean (standard error)	-5.15 (± 0.89)	-5.95 (± 0.87)		

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	18.0

Reporting groups

Reporting group title	Aliskiren

Reporting group description:

Patients will receive one of the following doses based on the their weight: Low weight (≥20 to <50 kg) patients: Starting dose 37.5 mg with optional titration to 75 and then 150 mg Mid weight (≥50 to <80 kg) patients: Starting dose 75 mg with optional titration to 150 and then 300 mg High weight (≥80 to ≤150 kg) patients: Starting dose 150 mg with optional titration to 300 and then 600 mg

Reporting group title	Enalapril

Reporting group description:

Patients will receive one of the following doses based on their weight: Low weight (≥20 to <50 kg) patients: Starting dose 2.5 mg with optional titration to 5 and then 10 mg Mid weight (≥50 to <80 kg) patients: Starting dose 5 mg with optional titration to 10 and then 20 mg High weight (≥80 to ≤150 kg) patients: Starting dose 10 mg with optional titration to 20 and then 40 mg

Serious adverse events	Aliskiren	Enalapril	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 105 (2.86%)	12 / 103 (11.65%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Weight decreased			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dislocation of vertebra			

subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skull fractured base			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 105 (0.95%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 105 (0.95%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			

subjects affected / exposed	1 / 105 (0.95%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device malfunction			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Paraesthesia oral			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychosomatic disease			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral stenosis			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			

subjects affected / exposed	2 / 105 (1.90%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 105 (0.95%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Tetany			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Aliskiren	Enalapril	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	52 / 105 (49.52%)	51 / 103 (49.51%)	
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 105 (6.67%)	15 / 103 (14.56%)	
occurrences (all)	12	19	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	6 / 105 (5.71%)	5 / 103 (4.85%)	
occurrences (all)	8	5	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	8 / 105 (7.62%)	5 / 103 (4.85%)	
occurrences (all)	10	6	
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	8 / 105 (7.62%)	9 / 103 (8.74%)	
occurrences (all)	10	11	
Oropharyngeal pain			
subjects affected / exposed	6 / 105 (5.71%)	7 / 103 (6.80%)	
occurrences (all)	6	7	
Infections and infestations			
Bronchitis			
subjects affected / exposed	5 / 105 (4.76%)	7 / 103 (6.80%)	
occurrences (all)	6	8	
Nasopharyngitis			
subjects affected / exposed	8 / 105 (7.62%)	6 / 103 (5.83%)	
occurrences (all)	9	9	
Pharyngitis			
subjects affected / exposed	7 / 105 (6.67%)	2 / 103 (1.94%)	
occurrences (all)	7	2	
Upper respiratory tract infection			
subjects affected / exposed	15 / 105 (14.29%)	15 / 103 (14.56%)	
occurrences (all)	21	23	
Viral infection			
subjects affected / exposed	10 / 105 (9.52%)	8 / 103 (7.77%)	
occurrences (all)	17	9	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 October 2010	Amendment issued seven weeks after study start, introduced the followingchanges.•Added itraconazole as a prohibited concomitant medication. Itraconazole is an anti-fungal agent and a P-glycoprotein inhibitor. When used concomitantly with aliskiren (a Pglycoprotein substrate), itraconazole increased the Cmax and AUC of aliskiren (150 mg) by 5.8 fold and by 6.5 fold, respectively (Tapaninen et al 2011). The clinical relevance of this interaction is such that the level of exposure to aliskiren exceeded the approved upper dose limit. In order to avoid any potential safety concerns associated with increased concentrations of aliskiren, the Rasilez Core Data Sheet was updated to add a contraindication for the concomitant use of aliskiren and itraconazole. Accordingly, the protocol was amended to reflect the change.•Added a standing BP measurement to visits 11, 12, 14 and 15. With this addition, standing BP was taken at every clinic visit, which increased the margin of safety ensuring that the patients were evaluated for orthostatic hypotension at every visit. This was important given the potential for add-on medication (HCTZ and amlodipine) as described in the protocol for the study. •Clarified exclusion of patients taking cyclosporine (already included in disallowed concomitant medication) and those with atrial fibrillation noted at visit 6 (already notedfor visit 1). •Simplified study medication packaging description and clarified the possible number of capsules/tablets per bottle/box. •Clarified discontinuation criteria regarding laboratory values •Clarified that the Week 104 long term follow up details would be provided in a separate protocol. •Required IVRS call to be made at visit 7 for all patients, regardless of whether or not their study medication was up titrated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported