



Clinical trial results:

An 8 day open-label, multiple-dose, multi-center study to evaluate the safety/tolerability and pharmacokinetics of aliskiren in hypertensive pediatric and adolescent patients 6 – 17 years of age.

Summary

EudraCT number	2008-005802-37
Trial protocol	HU BE Outside EU/EEA
Global end of trial date	08 January 2010

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	CSPP100A2256
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Novartis Pharma AG, Clinical Disclosure Office, +41 613241111,
Scientific contact	Novartis Pharma AG, Clinical Disclosure Office, +41 613241111,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-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	08 January 2010
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 January 2010
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 safety, tolerability, dose proportionality and age effect on pharmacokinetics of aliskiren minitables administered in children (aged 6-17 years) suffering with hypertension after single and multiple doses.

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 also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 April 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 9
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	Hungary: 14
Country: Number of subjects enrolled	Brazil: 4
Country: Number of subjects enrolled	United States: 8
Worldwide total number of subjects	39
EEA total number of subjects	27

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)	20

Adolescents (12-17 years)	19
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 14 centres in 5 countries.

Pre-assignment

Screening details:

A total of 49 subjects were enrolled into the study of which, 39 subjects were randomized.

Period 1

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

Blinding implementation details:

As the study was an open label study, this section was not applicable.

Arms

Are arms mutually exclusive?	Yes
Arm title	Aliskiren 2 mg/kg

Arm description:

Subjects received single dose of oral mini-tablets (3.125 milligram [mg]) of aliskiren at 2 milligram/kilogram (mg/kg) body weight daily for a total of 8 days.

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

Dosage and administration details:

Single dose of oral mini-tablets (3.125 mg) of aliskiren at 2 mg/kg body weight daily for a total of 8 days.

Arm title	Aliskiren 6 mg/kg
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Arm description:

Subjects received single dose of oral mini-tablets (3.125 mg) of aliskiren at 6 mg/kg body weight daily for a total of 8 days.

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

Dosage and administration details:

Single dose of oral mini-tablets (3.125 mg) of aliskiren at 6 mg/kg body weight daily for a total of 8 days.

Number of subjects in period 1	Aliskiren 2 mg/kg	Aliskiren 6 mg/kg
Started	19	20
Completed	18	19
Not completed	1	1
Consent withdrawn by subject	1	-
Lost to follow-up	-	1

Baseline characteristics

Reporting groups

Reporting group title	Aliskiren 2 mg/kg
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Reporting group description:

Subjects received single dose of oral mini-tablets (3.125 milligram [mg]) of aliskiren at 2 milligram/kilogram (mg/kg) body weight daily for a total of 8 days.

Reporting group title	Aliskiren 6 mg/kg
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Reporting group description:

Subjects received single dose of oral mini-tablets (3.125 mg) of aliskiren at 6 mg/kg body weight daily for a total of 8 days.

Reporting group values	Aliskiren 2 mg/kg	Aliskiren 6 mg/kg	Total
Number of subjects	19	20	39
Age categorical			
Units: Subjects			
6–11 years	10	10	20
12–17 years	9	10	19
Age continuous			
Units: years			
arithmetic mean	12.2	11.8	
standard deviation	± 3.12	± 3.78	-
Gender categorical			
Units: Subjects			
Female	10	8	18
Male	9	12	21

End points

End points reporting groups

Reporting group title	Aliskiren 2 mg/kg
Reporting group description: Subjects received single dose of oral mini-tablets (3.125 milligram [mg]) of aliskiren at 2 milligram/kilogram (mg/kg) body weight daily for a total of 8 days.	
Reporting group title	Aliskiren 6 mg/kg
Reporting group description: Subjects received single dose of oral mini-tablets (3.125 mg) of aliskiren at 6 mg/kg body weight daily for a total of 8 days.	

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) ^[1]
End point description: An AE was defined as any unfavorable 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 in safety population (SAF), defined as all the randomized subjects who received at least one dose of study drug.	
End point type	Primary
End point timeframe: Day 1 up to Day 12	

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 primary outcome measure.

End point values	Aliskiren 2 mg/kg	Aliskiren 6 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	20		
Units: Number of subjects				
AEs	10	8		
SAEs	0	1		

Statistical analyses

No statistical analyses for this end point

Primary: Maximum plasma concentration (C_{max}) of aliskiren

End point title	Maximum plasma concentration (C _{max}) of aliskiren
End point description: Maximum observed plasma concentration following drug administration was determined from the raw plasma concentration-time data. The analysis was performed in pharmacokinetic (PK) population which included all subjects who had evaluable aliskiren concentration data with no protocol deviations that	

presumably affected PK results. The 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively.

End point type	Primary
End point timeframe:	
Pre-dose (0), 0.5, 1, 1.5, 2, 3, 4, 6, 10, and 24 hours post-dose on Day 1 and at 48, 72 and 96 hours post dose on Day 8	

End point values	Aliskiren 2 mg/kg	Aliskiren 6 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	20		
Units: nanograms/millilitres				
arithmetic mean (standard deviation)				
Day 1: 6-11 years old (n=10, 10)	76.8 (± 78.21)	393.3 (± 377.37)		
Day 8: 6-11 years old (n=9, 10)	82.2 (± 97.85)	397.1 (± 187.06)		
Day 1: 12-17 years old (n=9, 10)	136.5 (± 132.57)	424.3 (± 188.79)		
Day 8: 12-17 years old (n=9, 10)	278.7 (± 357.54)	485.7 (± 300.58)		

Statistical analyses

Statistical analysis title	Cmax of aliskiren following single dose on Day 1
Statistical analysis description:	
Regression modelling was performed to evaluate the effect of age on the single dose Cmax of aliskiren.	
Comparison groups	Aliskiren 2 mg/kg v Aliskiren 6 mg/kg
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.476
Method	ANCOVA
Parameter estimate	Slope
Point estimate	1.04
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.95
upper limit	1.13

Statistical analysis title	Cmax of aliskiren at steady state on Day 8
Statistical analysis description:	
Regression modelling was performed to evaluate the effect of age on the steady state Cmax of aliskiren.	
Comparison groups	Aliskiren 2 mg/kg v Aliskiren 6 mg/kg

Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.534
Method	ANCOVA
Parameter estimate	Slope
Point estimate	1.03
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.94
upper limit	1.13

Primary: Area under the plasma concentration-time curve in one dosing interval (AUC0-24) of aliskiren

End point title	Area under the plasma concentration-time curve in one dosing interval (AUC0-24) of aliskiren
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End point description:

Area under the plasma concentration-time curve in one dosing interval (24 h) was estimated from the raw plasma concentration time data. The analysis was performed in PK population. The 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively.

End point type	Primary
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End point timeframe:

Pre-dose (0), 0.5, 1, 1.5, 2, 3, 4, 6, 10, and 24 hours post-dose on Day 1 and at 48, 72 and 96 hours post dose on Day 8

End point values	Aliskiren 2 mg/kg	Aliskiren 6 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	20		
Units: hours*nanograms/millitres				
arithmetic mean (standard deviation)				
Day 1: 6-11 years old (n=10, 10)	278.3 (± 237.29)	1231 (± 728.46)		
Day 8: 6-11 years old (n=9, 10)	403.6 (± 326.76)	1959.9 (± 821.43)		
Day 1: 12-17 years old (n=9, 10)	390.9 (± 264.5)	1808.7 (± 806.78)		
Day 8: 12-17 years old (n=9, 10)	847.2 (± 803.44)	2087 (± 999.1)		

Statistical analyses

Statistical analysis title	AUC0-24 of aliskiren following single dose on Day1
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Statistical analysis description:

Regression modelling was performed to evaluate the effect of age on the single dose AUC0-24 of aliskiren.

Comparison groups	Aliskiren 2 mg/kg v Aliskiren 6 mg/kg
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.233
Method	ANCOVA
Parameter estimate	Slope
Point estimate	1.04
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.98
upper limit	1.11

Statistical analysis title	AUC0-24 of aliskiren at steady state on Day 8
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Statistical analysis description:

Regression modelling was performed to evaluate the effect of age on the steady state AUC0-24 of aliskiren.

Comparison groups	Aliskiren 2 mg/kg v Aliskiren 6 mg/kg
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.609
Method	ANCOVA
Parameter estimate	Slope
Point estimate	1.02
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.96
upper limit	1.09

Primary: Apparent plasma clearance (CL/F) of aliskiren

End point title	Apparent plasma clearance (CL/F) of aliskiren
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End point description:

Apparent oral clearance of drug from the plasma (CL/F) was calculated as Dose/AUC0- ∞ , where CL was the clearance of the drug, F was the absolute oral bioavailability and AUC (0 - ∞) was area under the plasma concentration versus time curve (AUC) from time zero to extrapolated infinite time (0 - ∞). The analysis was performed in PK population. The 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively.

End point type	Primary
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End point timeframe:

Pre-dose (0), 0.5, 1, 1.5, 2, 3, 4, 6, 10, and 24 hours post-dose on Day 1 and at 48, 72 and 96 hours post dose on Day 8

End point values	Aliskiren 2 mg/kg	Aliskiren 6 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	20		
Units: millilitres/hours/kilograms				
arithmetic mean (standard deviation)				
6-11 years old (n=9, 10)	9694 (± 8704.71)	3905.4 (± 2628.52)		
12-17 years old (n=9, 10)	5388.1 (± 5580.55)	3539 (± 1587.49)		

Statistical analyses

Statistical analysis title	CL/F of aliskiren following single dose on Day 1
Statistical analysis description:	
Regression modelling was performed to evaluate the effect of age on the single dose CL/F of aliskiren.	
Comparison groups	Aliskiren 2 mg/kg v Aliskiren 6 mg/kg
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.233
Method	ANCOVA
Parameter estimate	Slope
Point estimate	0.96
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.9
upper limit	1.02

Statistical analysis title	CL/F of aliskiren at steady state on Day 8
Statistical analysis description:	
Regression modelling was performed to evaluate the effect of age on the steady state CL/F of aliskiren.	
Comparison groups	Aliskiren 2 mg/kg v Aliskiren 6 mg/kg
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.609
Method	ANCOVA
Parameter estimate	Slope
Point estimate	0.98
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.92
upper limit	1.05

Primary: Time to maximum plasma concentration (Tmax) of aliskiren

End point title	Time to maximum plasma concentration (Tmax) of aliskiren ^[2]
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End point description:

Tmax was defined as the time required to reach maximum observed plasma concentration following drug administration. Tmax was directly determined from the raw plasma concentration-time data. The analysis was performed in PK population. The 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively.

End point type	Primary
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End point timeframe:

Pre-dose (0), 0.5, 1, 1.5, 2, 3, 4, 6, 10, and 24 hours post-dose on Day 1 and at 48, 72 and 96 hours post dose on Day 8

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 primary outcome measure.

End point values	Aliskiren 2 mg/kg	Aliskiren 6 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	20		
Units: hours				
median (full range (min-max))				
Day 1: 6-11 years old (n=10, 10)	1 (0.5 to 4.1)	1.5 (0.5 to 4.1)		
Day 8: 6-11 years old (n=9, 10)	1 (0.5 to 4)	1.5 (0.5 to 6)		
Day 1: 12-17 years old (n=9, 10)	1 (0.5 to 3)	1.8 (0.5 to 4)		
Day 8: 12-17 years old (n=9, 10)	1 (0.5 to 3)	2 (0.5 to 3)		

Statistical analyses

No statistical analyses for this end point

Primary: Terminal elimination half-life (t1/2) of aliskiren

End point title	Terminal elimination half-life (t1/2) of aliskiren ^[3]
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End point description:

Terminal elimination half-life was estimated from the terminal slope of a semilogarithmic concentration-time curve. The analysis was performed in PK population. The 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively.

End point type	Primary
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End point timeframe:

Pre-dose (0), 0.5, 1, 1.5, 2, 3, 4, 6, 10, and 24 hours post-dose on Day 1 and at 48, 72 and 96 hours post dose on Day 8

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 primary outcome measure.

End point values	Aliskiren 2 mg/kg	Aliskiren 6 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	20 ^[4]		
Units: hours				
arithmetic mean (standard deviation)				
6-11 years old (n=9, 10)	38.8 (± 11.69)	45.1 (± 12.27)		
12-17 years old (n=9, 10)	39.2 (± 4.65)	42.9 (± 6.47)		

Notes:

[4] - In 6–11 year old category(6 mg/kg), n =9 as one subject was excluded due to short sample collection.

Statistical analyses

No statistical analyses for this end point

Secondary: Accumulation index based on Cmax (AICmax) of aliskiren

End point title	Accumulation index based on Cmax (AICmax) of aliskiren
End point description: Accumulation index based on Cmax was the ratio of Cmax values on Day 8 and Day 1. The analysis was performed in PK population.	
End point type	Secondary
End point timeframe: Pre-dose (0), 0.5, 1, 1.5, 2, 3, 4, 6, 10, and 24 hours post-dose on Day 1 and at 48, 72 and 96 hours post dose on Day 8	

End point values	Aliskiren 2 mg/kg	Aliskiren 6 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	20		
Units: ratio				
arithmetic mean (standard deviation)				
6-11 years old (n=9, 10)	1.5 (± 1.32)	3.3 (± 6.22)		
12-17 years old (n=9, 10)	2.9 (± 3.4)	1.2 (± 0.68)		

Statistical analyses

No statistical analyses for this end point

Secondary: Accumulation index based on AUC (AIAUC) of aliskiren

End point title	Accumulation index based on AUC (AIAUC) of aliskiren
End point description: Accumulation index based on AUC was the ratio of AUC values on Day 8 and Day 1. The analysis was performed in PK population.	
End point type	Secondary
End point timeframe: Pre-dose (0), 0.5, 1, 1.5, 2, 3, 4, 6, 10, and 24 hours post-dose on Day 1 and at 48, 72 and 96 hours post dose on Day 8	

End point values	Aliskiren 2 mg/kg	Aliskiren 6 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	20		
Units: ratio				
arithmetic mean (standard deviation)				
6-11 years old (n=9, 10)	1.9 (± 1.01)	2.2 (± 1.93)		
12-17 years old (n=9, 10)	2.1 (± 1.29)	1.3 (± 0.64)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in plasma renin activity (PRA) at Days 1, 8 and 9

End point title	Change from baseline in plasma renin activity (PRA) at Days 1, 8 and 9
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End point description:

Pharmacodynamics (PD) of aliskiren was assessed based on the changes in plasma renin activity (PRA) using a high sensitivity PRA assay. Negative change from baseline in PRA indicated improvement. The analysis was performed in Full analysis set (FAS) population, which included all randomized subjects. The 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively.

End point type	Secondary
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End point timeframe:

Baseline to 2 and 10 hours post-dose on Day 1; pre-dose, 2, 10, and 24 hours post-dose on Day 8

End point values	Aliskiren 2 mg/kg	Aliskiren 6 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	20		
Units: nanograms/millilitres/hours				
arithmetic mean (standard deviation)				
Day 1: 2 hour post-dose (n=15, 15)	-1.8 (± 1.62)	-4 (± 6.68)		
Day 1: 10 hour post-dose (n=14, 13)	-1.8 (± 1.73)	-3.8 (± 6.79)		
Day 8: pre-dose (n=14, 15)	-1.3 (± 1.77)	-3.5 (± 5.91)		
Day 8: 2 hour post-dose (n=11, 14)	-1.4 (± 1.6)	-3.6 (± 6.79)		
Day 8: 10 hour post dose (n=13, 15)	-1.7 (± 1.81)	-3.8 (± 6.41)		
Day 8: 24 hour post dose (n=13, 15)	-1.5 (± 1.82)	-3.6 (± 6.46)		

Statistical analyses

Secondary: Change from baseline in mean sitting systolic blood pressure (msSBP) and mean sitting diastolic blood pressure (msDBP) at Day 9

End point title	Change from baseline in mean sitting systolic blood pressure (msSBP) and mean sitting diastolic blood pressure (msDBP) at Day 9
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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 2-3 minute intervals and the average of three sitting systolic or diastolic blood pressure measurements were used as the initial mean sitting systolic office blood pressure (MsSBP) or mean sitting diastolic office blood pressure (MsDBP) for that visit. Change from baseline in MsSBP and MsDBP was evaluated. Negative change from baseline in msSBP and msDBP indicated improvement i.e reduction in BP. The analysis was performed in FAS population. The 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively.

End point type	Secondary
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End point timeframe:

Baseline to Day 9

End point values	Aliskiren 2 mg/kg	Aliskiren 6 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	20		
Units: millimeters of mercury				
arithmetic mean (standard deviation)				
msSBP: 6-11 years old (n=10, 10)	-4.5 (± 14.63)	-7.7 (± 11.76)		
msSBP: 12-17 years old (n=9, 10)	-7.6 (± 9.07)	-7.7 (± 9.38)		
msDBP: 6-11 years old (n=10, 10)	-1.7 (± 4.69)	0 (± 8.87)		
msDBP: 12-17 years old (n=9, 10)	-5.3 (± 8.78)	-5.8 (± 8)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

SAEs are monitored from date of First Subject First Visit (FSFV) until 30 days after Last Subject Last Visit (LSLV) or last treatment. All other adverse events are monitored from First Subject First Treatment (FSFT) until Last Subject Last Visit (LSLV).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	12.1
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Reporting groups

Reporting group title	Aliskiren 2 mg/kg
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Reporting group description:

Subjects received single dose of oral mini-tablets (3.125 mg) of aliskiren at 2 mg/kg body weight daily for a total of 8 days.

Reporting group title	Aliskiren 6 mg/kg
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Reporting group description:

Subjects received single dose of oral mini-tablets (3.125 mg) of aliskiren at 6 mg/kg body weight daily for a total of 8 days.

Serious adverse events	Aliskiren 2 mg/kg	Aliskiren 6 mg/kg	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 19 (0.00%)	1 / 20 (5.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Infections and infestations			
Swine influenza			
subjects affected / exposed	0 / 19 (0.00%)	1 / 20 (5.00%)	
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 2 mg/kg	Aliskiren 6 mg/kg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 19 (52.63%)	7 / 20 (35.00%)	
Investigations			
Blood pressure increased			
subjects affected / exposed	1 / 19 (5.26%)	0 / 20 (0.00%)	
occurrences (all)	1	0	

Body temperature increased subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 20 (0.00%) 0	
Vascular disorders Flushing subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 20 (5.00%) 1	
Hypertension subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 20 (5.00%) 1	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	4 / 19 (21.05%) 5	2 / 20 (10.00%) 2	
Blood and lymphatic system disorders Lymphadenopathy subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 20 (5.00%) 1	
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 20 (0.00%) 0	
Pyrexia subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 20 (5.00%) 1	
Ear and labyrinth disorders Tinnitus subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 2	0 / 20 (0.00%) 0	
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 20 (5.00%) 1	
Abdominal pain upper subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	2 / 20 (10.00%) 2	
Diarrhoea			

subjects affected / exposed	0 / 19 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	1 / 19 (5.26%)	2 / 20 (10.00%)	
occurrences (all)	1	3	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 19 (5.26%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Epistaxis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Pharyngeal inflammation			
subjects affected / exposed	1 / 19 (5.26%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Productive cough			
subjects affected / exposed	1 / 19 (5.26%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	0 / 19 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 19 (5.26%)	0 / 20 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 February 2009	1. Clarified the exclusion criteria of HIV, hepatitis B, and hepatitis tests 2. Modified the blood volume required for PD evaluation 3. Clarified the addition and optional use of heparin to flush the intravenous (i.v.) lock used for PK and PD blood draws.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported