Clinical trial results:
An open label, randomized, three period, single-dose, crossover study to determine the bioavailability of 300 mg aliskiren mini-tablets relative to the 300 mg aliskiren market tablet under fasted condition and to evaluate the effect of food on the pharmacokinetics of 300 mg aliskiren mini-tablets in healthy subjects

Summary

EudraCT number	2012-000855-15
Trial protocol	Outside EU/EEA
Global end of trial date	22 February 2010

Results information

Result version number	v1 (current)
This version publication date	25 October 2018
First version publication date	25 October 2018

Trial information

Trial identification

Sponsor protocol code	CSPP100A2109

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	Clinical Disclosure Office, Clinical Disclosure Office, +41 613241111,
Scientific contact	Clinical Disclosure Office, 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)	EMEA-000362-PIP08-04
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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 February 2010
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 February 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to determine the bioavailability of a single oral dose of 300 milligrams (mg) aliskiren mini-tablets relative to the 300 mg aliskiren market tablet under fasted condition in healthy subjects and to evaluate the effect of food on the pharmacokinetics of a single oral dose of 300 mg aliskiren mini-tablets in healthy subjects.

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	31 December 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	India: 69
Worldwide total number of subjects	69
EEA total number of subjects	0

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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	69
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at one center in India.

Pre-assignment

Screening details:

A total of 69 subjects were enrolled in the study.

Period 1

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

Blinding implementation details:

The study was open-label study, hence no blinding was performed.

Arms

Are arms mutually exclusive?	Yes
Arm title	Mini (fasted) then FMI (fasted) then Mini tablet (fed)

Arm description:

Subjects were orally administered with single dose of aliskiren equivalent to 300 mg mini-tablets followed by single dose of aliskiren 300 mg final market image (FMI) tablets under fasted conditions and finally with single dose of aliskiren equivalent to 300 mg mini-tablets under fed condition. A washout interval of least 14 days (maximum 21 days) was maintained between two treatments.

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

Dosage and administration details:

Subjects after having an overnight fast of at least 10 hours (h) were orally administered with single dose of aliskiren equivalent to 300 mg mini-tablets administered with a teaspoon of low fat vanilla ice cream followed by single dose of aliskiren 300 mg FMI tablets, administered with 240 milliliters (mL) of water under fasted condition. Subjects continued to fast till 4 h post dose, during which they were served a standard lunch. Finally subjects received a single dose of aliskiren equivalent to 300 mg mini-tablets, administered with a teaspoon of low fat vanilla ice cream followed by 240 mL of water under fed condition. Dosing of which, was done 30 minutes after start of a USFDA recommended standard high-fat breakfast. Throughout water was not allowed 1 h before and 1 h after dose except that taken with the study medication. Water was then made available as and when needed. A washout interval of least 14 days (maximum 21 days) was maintained between two treatments.

Arm title	FMI (fasted) then Mini (fed) then Mini tablet (fasted)

Arm description:

Subjects were orally administered with single dose of aliskiren 300 mg FMI tablets under fasted conditions followed by single dose of aliskiren equivalent to 300 mg mini-tablets under fed condition and finally with single dose of aliskiren equivalent to 300 mg mini-tablets tablets under fasted conditions. A washout interval of least 14 days (maximum 21 days) was maintained between two treatments.

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

Dosage and administration details:

Subjects after having an overnight fast of at least 10 h were orally administered with single dose of aliskiren 300 mg FMI tablets, administered with 240 mL of water under fasted condition followed by a single dose of aliskiren equivalent to 300 mg mini-tablets, administered with a teaspoon of low fat vanilla ice cream followed by 240 mL of water under fed condition. Dosing was done 30 minutes after start of a USFDA recommended standard high-fat breakfast. Finally subjects received a single dose of aliskiren equivalent to 300 mg mini-tablets administered with a teaspoon of low fat vanilla ice cream followed by 240 mL of water under fasted condition. Subjects continued to fast till 4 h post dose and were served a standard lunch. Throughout water was not allowed 1 h before and 1 h after dose except that taken with the study medication. Water was then made available as and when needed. A washout interval of least 14 days (maximum 21 days) was maintained between two treatments.

Arm title	Mini (fed) then Mini (fasted) then FMI tablet (fasted)

Arm description:

Subjects were orally administered with single dose of aliskiren equivalent to 300 mg mini-tablets under fed condition followed by single dose of aliskiren equivalent to 300 mg mini-tablets tablets under fasted conditions and finally with single dose of aliskiren 300 mg FMI tablets under fasted conditions. A washout interval of least 14 days (maximum 21 days) was maintained between two treatments.

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

Dosage and administration details:

Subjects after having an overnight fast were orally administered with single dose of aliskiren equivalent to 300 mg mini-tablets, administered with a teaspoon of low fat vanilla ice cream followed by 240 mL of water under fed condition. Dosing was done 30 minutes after start of a USFDA recommended standard high-fat breakfast followed by single dose of aliskiren equivalent to 300 mg mini-tablets administered with a teaspoon of low fat vanilla ice cream followed by 240 mL of water under fasted condition. Finally subjects received a single dose of aliskiren 300 mg FMI tablets, administered with 240 mL of water under fasted condition. Subjects continued to fast till 4 h post dose, during which they were served a standard lunch. Throughout water was not allowed 1 h before and 1 h after dose except that taken with the study medication. Water was then made available as and when needed. A washout interval of least 14 days (maximum 21 days) was maintained between two treatments.

Number of subjects in period 1	Mini (fasted) then FMI (fasted) then Mini tablet (fed)	FMI (fasted) then Mini (fed) then Mini tablet (fasted)	Mini (fed) then Mini (fasted) then FMI tablet (fasted)
Started	23	23	23
Completed	18	19	18
Not completed	5	4	5
Administrative problems	3	1	2
Lost to follow-up	1	1	1
Adverse Event (s)	1	2	2

Baseline characteristics

Reporting groups	
Reporting group title	Mini (fasted) then FMI (fasted) then Mini tablet (fed)
Reporting group description:	
Subjects were orally administered with single dose of aliskiren equivalent to 300 mg mini-tablets followed by single dose of aliskiren 300 mg final market image (FMI) tablets under fasted conditions and finally with single dose of aliskiren equivalent to 300 mg mini-tablets under fed condition. A washout interval of least 14 days (maximum 21 days) was maintained between two treatments.	
Reporting group title	FMI (fasted) then Mini (fed) then Mini tablet (fasted)
Reporting group description:	
Subjects were orally administered with single dose of aliskiren 300 mg FMI tablets under fasted conditions followed by single dose of aliskiren equivalent to 300 mg mini-tablets under fed condition and finally with single dose of aliskiren equivalent to 300 mg mini-tablets tablets under fasted conditions. A washout interval of least 14 days (maximum 21 days) was maintained between two treatments.	
Reporting group title	Mini (fed) then Mini (fasted) then FMI tablet (fasted)
Reporting group description:	
Subjects were orally administered with single dose of aliskiren equivalent to 300 mg mini-tablets under fed condition followed by single dose of aliskiren equivalent to 300 mg mini-tablets tablets under fasted conditions and finally with single dose of aliskiren 300 mg FMI tablets under fasted conditions. A washout interval of least 14 days (maximum 21 days) was maintained between two treatments.	

Reporting group values	Mini (fasted) then FMI (fasted) then Mini tablet (fed)	FMI (fasted) then Mini (fed) then Mini tablet (fasted)	Mini (fed) then Mini (fasted) then FMI tablet (fasted)
Number of subjects	23	23	23
Age categorical Units: Subjects			
Adults (18-64 years)	23	23	23
Age continuous Units: years			
arithmetic mean	26.8	25.8	27.7
standard deviation	± 5.93	± 4.29	± 5.57
Gender categorical Units: Subjects			
Male	23	23	23

Reporting group values	Total		
Number of subjects	69		
Age categorical Units: Subjects			
Adults (18-64 years)	69		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Male	69		

End points

End points reporting groups

Reporting group title	Mini (fasted) then FMI (fasted) then Mini tablet (fed)

Reporting group description:

Subjects were orally administered with single dose of aliskiren equivalent to 300 mg mini-tablets followed by single dose of aliskiren 300 mg final market image (FMI) tablets under fasted conditions and finally with single dose of aliskiren equivalent to 300 mg mini-tablets under fed condition. A washout interval of least 14 days (maximum 21 days) was maintained between two treatments.

Reporting group title	FMI (fasted) then Mini (fed) then Mini tablet (fasted)

Reporting group description:

Subjects were orally administered with single dose of aliskiren 300 mg FMI tablets under fasted conditions followed by single dose of aliskiren equivalent to 300 mg mini-tablets under fed condition and finally with single dose of aliskiren equivalent to 300 mg mini-tablets tablets under fasted conditions. A washout interval of least 14 days (maximum 21 days) was maintained between two treatments.

Reporting group title	Mini (fed) then Mini (fasted) then FMI tablet (fasted)

Reporting group description:

Subjects were orally administered with single dose of aliskiren equivalent to 300 mg mini-tablets under fed condition followed by single dose of aliskiren equivalent to 300 mg mini-tablets tablets under fasted conditions and finally with single dose of aliskiren 300 mg FMI tablets under fasted conditions. A washout interval of least 14 days (maximum 21 days) was maintained between two treatments.

Subject analysis set title	Mini tablet (fasted)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects after having an overnight fast of at least 10 h were orally administered with single dose of aliskiren equivalent to 300 mg mini-tablets administered with a teaspoon of low fat vanilla ice cream followed by 240 mL of water under fasted condition. Subjects continued to fast till 4 h post dose, during which they were served a standard lunch. Water was not allowed 1 h before and 1 h after dose except that taken with the study medication. Water was then made available as and when needed.

Subject analysis set title	FMI tablet (fasted)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects after having an overnight fast of at least 10 h were orally administered with single dose of aliskiren 300 mg FMI tablets, administered with 240 mL of water under fasted condition. Subjects continued to fast till 4 h post dose, during which they were served a standard lunch. Water was not allowed 1 h before and 1 h after dose except that taken with the study medication. Water was then made available as and when needed.

Subject analysis set title	Mini tablet (fed)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects after having an overnight fast were orally administered with single dose of aliskiren equivalent to 300 mg mini-tablets, administered with a teaspoon of low fat vanilla ice cream followed by 240 mL of water under fed condition. Dosing was done 30 minutes after start of a USFDA recommended standard high-fat breakfast. Water was not allowed 1 h before and 1 h after dose except that taken with the study medication. Water was then made available as and when needed.

Primary: Area under the curve from time zero to the last measurable concentration sampling time (AUClast) of aliskiren

End point title	Area under the curve from time zero to the last measurable concentration sampling time (AUClast) of aliskiren

End point description:

AUClast was defined as the area under the plasma concentration-time curve up to the last measurable concentration time point and was calculated as the sum of linear trapezoids using non-compartmental analysis were determined using WinNonlin Pro (Version 5.0.1). Plasma concentrations of aliskiren was analyzed using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay with a lower limit of quantification (LLOQ) of 0.5 nanogram (ng)/mL. The analysis was performed on pharmacokinetic (PK) analysis set (PAS) defined as all subjects who completed at least one treatment period with evaluable aliskiren PK data.

End point type	Primary

End point timeframe:

Pre-dose, 0.25 h, 0.5 h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 12h at Day 1; Day 2, Day 3, Day 4, Day 5, Day 7 and Day 8 post dose

End point values	Mini tablet (fasted)	FMI tablet (fasted)	Mini tablet (fed)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	60	61	62	
Units: ng.hr/mL				
geometric mean (geometric coefficient of variation)	2872 (± 39.12)	2809 (± 44.35)	447.3 (± 46.28)	

Statistical analyses

Statistical analysis title	Bioavailability: AUClast of aliskiren

Statistical analysis description:

Comparison of AUClast for Mini tablet fasted with FMI tablet fasted was evaluated to determine the bioavailability of a single oral dose of 300 mg mini-tablets relative to the 300 mg FMI tablet under fasted condition. The number of subjects analyzed for this end point were 60 and 61 respectively, but since this is a cross-over study, the subjects analyzed feature as 121 below, which is the total of the two arms that are being compared [Mini tablet fasted (N=60) and FMI tablet fasted (N=61)].

Comparison groups	Mini tablet (fasted) v FMI tablet (fasted)
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Geometric mean ratio
Point estimate	1.02
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.92
upper limit	1.14

Statistical analysis title	Food effect: AUClast of aliskiren

Statistical analysis description:

Comparison of AUClast for Mini tablet fed with Mini tablet fasted was evaluated to determine the effect of food on the pharmacokinetics of a single oral dose of 300 mg mini-tablets. The number of subjects analyzed for this end point were 62 and 60 respectively, but since this is a cross-over study, the subjects analyzed feature as 122 below, which is the total of the two arms that are being compared [Mini tablet fed (N=62) and Mini tablet fasted (N=60)].

Comparison groups	Mini tablet (fed) v Mini tablet (fasted)

Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Geometric mean ratio
Point estimate	0.16
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.14
upper limit	0.18

Primary: Area under the concentration-time curve to infinity (AUCinf) of aliskiren

End point title	Area under the concentration-time curve to infinity (AUCinf) of aliskiren

End point description:

AUCinf was defined as the area under the curve from time zero to infinity. AUCinf was calculated using non-compartmental methods using WinNonlin Pro (Version 5.0.1) by adding area under the curve from time zero to the last measurable concentration sampling time (AUClast) and the value obtained from dividing the last measurable plasma concentration (Clast) by terminal elimination rate constant (ke). Plasma concentrations of aliskiren was analyzed using a validated LC-MS/MS assay with LLOQ of 0.5 ng/mL. The analysis was performed on PAS population.

End point type	Primary

End point timeframe:

Pre-dose, 0.25 h, 0.5 h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 12h at Day 1; Day 2, Day 3, Day 4, Day 5, Day 7 and Day 8 post dose

End point values	Mini tablet (fasted)	FMI tablet (fasted)	Mini tablet (fed)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	60	61	62	
Units: ng.hr/mL				
geometric mean (geometric coefficient of variation)	3115 (± 37.98)	3050 (± 42.94)	504.7 (± 45.76)	

Statistical analyses

Statistical analysis title	Bioavailability: AUCinf of aliskiren

Statistical analysis description:

Comparison of AUCinf for Mini tablet fasted with FMI tablet fasted was evaluated to determine the bioavailability of a single oral dose of 300 mg mini-tablets relative to the 300 mg FMI tablet under fasted condition. The number of subjects analyzed for this end point were 60 and 61 respectively, but since this is a cross-over study,the subjects analyzed feature as 121 below, which is the total of the two arms that are being compared [Mini tablet fasted (N=60) and FMI tablet fasted (N=61)].

Comparison groups	Mini tablet (fasted) v FMI tablet (fasted)

Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Geometric mean ratio
Point estimate	1.01
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.91
upper limit	1.12

Statistical analysis title	Food effect: AUCinf of aliskiren

Statistical analysis description:

Comparison of AUClast for Mini tablet fed with Mini tablet fasted was evaluated to determine the effect of food on the pharmacokinetics of a single oral dose of 300 mg mini-tablets. The number of subjects analyzed for this end point were 62 and 60 respectively, but since this is a cross-over study, the subjects analyzed feature as 122 below, which is the total of the two arms that are being compared [Mini tablet fed (N=62) and Mini tablet fasted (N=60)].

Comparison groups	Mini tablet (fasted) v Mini tablet (fed)
Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Geometric mean ratio
Point estimate	0.17
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.15
upper limit	0.19

Primary: Maximum plasma concentration (Cmax) of aliskiren

End point title	Maximum plasma concentration (Cmax) of aliskiren

End point description:

Cmax was defined as the maximum (peak) observed drug concentration in blood after single dose administration. Cmax was directly determined from the raw plasma concentration-time data using WinNonLin Professional version 5.2. Plasma concentrations of aliskiren was analyzed using a validated LC-MS/MS assay with LLOQ of 0.5 ng/mL. The analysis was performed on PAS population.

End point type	Primary

End point timeframe:

Pre-dose, 0.25 h, 0.5 h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 12h at Day 1; Day 2, Day 3, Day 4, Day 5, Day 7 and Day 8 post dose

End point values	Mini tablet (fasted)	FMI tablet (fasted)	Mini tablet (fed)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	60	61	62	
Units: ng/mL				
geometric mean (geometric coefficient of variation)	414.4 (± 50.22)	390.9 (± 53.02)	19.29 (± 50.98)	

Statistical analyses

Statistical analysis title	Bioavailability: Cmax of aliskiren

Statistical analysis description:

Comparison of Cmax for Mini tablet fasted with FMI tablet fasted was evaluated to determine the bioavailability of a single oral dose of 300 mg mini-tablets relative to the 300 mg FMI tablet under fasted condition. The number of subjects analyzed for this end point were 60 and 61 respectively, but since this is a cross-over study,the subjects analyzed feature as 121 below, which is the total of the two arms that are being compared [Mini tablet fasted (N=60) and FMI tablet fasted (N=61)].

Comparison groups	Mini tablet (fasted) v FMI tablet (fasted)
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Geometric mean ratio
Point estimate	1.06
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.94
upper limit	1.21

Statistical analysis title	Food effect: Cmax of aliskiren

Statistical analysis description:

Comparison of Cmax for Mini tablet fed with Mini tablet fasted was evaluated to determine the effect of food on the pharmacokinetics of a single oral dose of 300 mg mini-tablets. The number of subjects analyzed for this end point were 62 and 60 respectively, but since this is a cross-over study, the subjects analyzed feature as 122 below, which is the total of the two arms that are being compared [Mini tablet fed (N=62) and Mini tablet fasted (N=60)].

Comparison groups	Mini tablet (fasted) v Mini tablet (fed)
Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Geometric mean ratio
Point estimate	0.05
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.04
upper limit	0.05

Primary: Time to reach maximum (peak) drug concentration (Tmax) of aliskiren

End point title	Time to reach maximum (peak) drug concentration (Tmax) of aliskiren[1]

End point description:

Tmax was defined as the time to reach maximum (peak) drug concentration after single dose administration. Tmax was directly determined from the raw plasma concentration-time data using WinNonLin Professional version 5.2. Plasma concentrations of aliskiren was analyzed using a validated LC-MS/MS assay with LLOQ of 0.5 ng/mL. The analysis was performed on PAS population.

End point type	Primary

End point timeframe:

Pre-dose, 0.25 h, 0.5 h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 12h at Day 1; Day 2, Day 3, Day 4, Day 5, Day 7 and Day 8 post dose

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	Mini tablet (fasted)	FMI tablet (fasted)	Mini tablet (fed)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	60	61	62	
Units: hours				
median (full range (min-max))	1 (0.5 to 6)	2 (0.3 to 6)	1.5 (0.3 to 12)	

Statistical analyses

No statistical analyses for this end point

Primary: The elimination half-life associated with the terminal slope (λz) of a semilogarithmic concentration-time curve (T1/2) of aliskiren

End point title	The elimination half-life associated with the terminal slope (λz) of a semilogarithmic concentration-time curve (T1/2) of aliskiren[2]

End point description:

T1/2 was defined as the elimination half-life associated with the terminal slope of a semi logarithmic concentration-time curve. T1/2 was calculated using non-compartmental methods using WinNonlin Pro (Version 5.0.1) calculated as Ln2/ke. Plasma concentrations of aliskiren was analyzed using a validated LC-MS/MS assay with LLOQ of 0.5 ng/mL. The analysis was performed on PAS population.

End point type	Primary

End point timeframe:

Pre-dose, 0.25 h, 0.5 h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 12h at Day 1; Day 2, Day 3, Day 4, Day 5, Day 7 and Day 8 post dose

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	Mini tablet (fasted)	FMI tablet (fasted)	Mini tablet (fed)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	58	60	52	
Units: hour				
median (full range (min-max))	64.51 (39.9 to 99)	67.36 (22.9 to 102)	61.97 (15.8 to 106)	

Statistical analyses

No statistical analyses for this end point

Primary: The apparent total body clearance of drug from the plasma (CL/F) of aliskiren

End point title	The apparent total body clearance of drug from the plasma (CL/F) of aliskiren[3]

End point description:

CL/F was defined as the apparent clearance of a drug from the blood after oral administration. CL/F was analyzed using non-compartmental methods using WinNonlin Pro (Version 5.0.1). Plasma concentrations of aliskiren was analyzed using a validated LC-MS/MS assay with LLOQ of 0.5 ng/mL. The analysis was performed on PAS population.

End point type	Primary

End point timeframe:

Pre-dose, 0.25 h, 0.5 h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 12h at Day 1; Day 2, Day 3, Day 4, Day 5, Day 7 and Day 8 post dose

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	Mini tablet (fasted)	FMI tablet (fasted)	Mini tablet (fed)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	58	60	52	
Units: mL/h				
geometric mean (geometric coefficient of variation)	96320 (± 37.98)	98360 (± 42.94)	594400 (± 45.76)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with Adverse Events (AEs), Serious Adverse Events (SAEs), AE leading to discontinuation and who died

End point title	Number of subjects with Adverse Events (AEs), Serious Adverse Events (SAEs), AE leading to discontinuation and who died

End point description:

AEs are defined as any unfavorable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome or disease which either occurs during study, having been absent at baseline, or, if present at baseline, appears to worsen. Serious adverse events are any untoward medical occurrences that result in death, are life threatening, require (or prolong) hospitalization, cause

persistent or significant disability/incapacity, result in congenital anomalies or birth defects, or are other conditions which in judgment of investigators represent significant hazards. The analysis was performed on safety set population defined as all subjects who received at least one dose of the study drug.

End point type	Secondary

End point timeframe:

From Day 1 to 30 days after the last subject treatment (approximately 30 days)

End point values	Mini tablet (fasted)	FMI tablet (fasted)	Mini tablet (fed)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	60	61	62	
Units: Subjects				
AEs	12	11	21	
SAEs	0	0	0	
AEs leading to discontinuation	0	1	4	
Deaths	0	0	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious Adverse Events are monitored from date of First Subject First Visit (FSFV) until Last Subject Last Visit (LSLV). All other adverse events are monitored from First Subject First Treatment until LSLV.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.1

Reporting groups

Reporting group title	Mini-tablets fed

Reporting group description:

Subjects after having an overnight fast were orally administered with single dose of aliskiren equivalent to 300 mg mini-tablets, administered with a teaspoon of low fat vanilla ice cream followed by 240 mL of water under fed condition. Dosing was done 30 minutes after start of a USFDA recommended standard high-fat breakfast. Water was not allowed 1 h before and 1 h after dose except that taken with the study medication. Water was then made available as and when needed.

Reporting group title	Market-tablet fasted

Reporting group description:

Subjects after having an overnight fast of at least 10 h were orally administered with single dose of aliskiren 300 mg FMI tablets, administered with 240 mL of water under fasted condition. Subjects continued to fast till 4 h post dose, during which they were served a standard lunch. Water was not allowed 1 h before and 1 h after dose except that taken with the study medication. Water was then made available as and when needed.

Reporting group title	All Subjects

Reporting group description:

Subjects after having an overnight fast of at least 10 h were orally administered with aliskiren, administered with 240 mL of water under fasted condition. Water was not allowed 1 h before and 1 h after dose except that taken with the study medication. Water was then made available as and when needed.

Reporting group title	Mini-tablets fasted

Reporting group description:

Subjects after having an overnight fast of at least 10 h were orally administered with single dose of aliskiren equivalent to 300 mg mini-tablets administered with a teaspoon of low fat vanilla ice cream followed by 240 mL of water under fasted condition. Subjects continued to fast till 4 h post dose, during which they were served a standard lunch. Water was not allowed 1 h before and 1 h after dose except that taken with the study medication. Water was then made available as and when needed.

Serious adverse events	Mini-tablets fed	Market-tablet fasted	All Subjects
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 62 (0.00%)	0 / 61 (0.00%)	0 / 69 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Mini-tablets fasted		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 60 (0.00%)		

number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Mini-tablets fed	Market-tablet fasted	All Subjects
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 62 (24.19%)	5 / 61 (8.20%)	23 / 69 (33.33%)
Investigations			
Blood creatinine increased			
subjects affected / exposed	2 / 62 (3.23%)	1 / 61 (1.64%)	4 / 69 (5.80%)
occurrences (all)	2	1	4
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 62 (4.84%)	0 / 61 (0.00%)	6 / 69 (8.70%)
occurrences (all)	3	0	6
Headache			
subjects affected / exposed	4 / 62 (6.45%)	3 / 61 (4.92%)	7 / 69 (10.14%)
occurrences (all)	4	3	9
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 62 (4.84%)	1 / 61 (1.64%)	5 / 69 (7.25%)
occurrences (all)	3	1	6
Nausea			
subjects affected / exposed	2 / 62 (3.23%)	0 / 61 (0.00%)	4 / 69 (5.80%)
occurrences (all)	2	0	4
Vomiting			
subjects affected / exposed	3 / 62 (4.84%)	1 / 61 (1.64%)	6 / 69 (8.70%)
occurrences (all)	3	1	6

Non-serious adverse events	Mini-tablets fasted		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 60 (13.33%)		
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		

Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 60 (5.00%)		
occurrences (all)	3		
Headache			
subjects affected / exposed	2 / 60 (3.33%)		
occurrences (all)	2		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	2 / 60 (3.33%)		
occurrences (all)	2		
Vomiting			
subjects affected / exposed	2 / 60 (3.33%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported