Sponsor

Novartis

Generic Drug Name

Aliskiren

Therapeutic Area of Trial

Hypertension

Approved Indication

Indicated for the treatment of essential hypertension

Study Number

CSPP100A2110

Title

A randomized, single-blind, parallel group, multiple oral dose study to evaluate the effect of a light meal on the pharmacokinetics and pharmacodynamics of aliskiren using market 300 mg tablet formulation in subjects with mild to moderate hypertension

Phase of Development

Phase IV

Study Start/End Dates

09-Jun-2009 to 17-Dec-2009

Study Design/Methodology

This was a randomized, single-blind, parallel-group, multiple-dose study in patients with mild to moderate hypertension. One hundred and twenty two patients were randomized to receive aliskiren 300mg either with or without a light breakfast for a period of 4 weeks.
The study consisted of a 14-day screening/conditional washout period, a 2-week placebo run-in period, a 4-week treatment period and a study completion evaluation 7 days after last study drug administration.
Patients who were eligible for the study at screening and had discontinued any prior hypertensive medication were entered into the single-blind placebo run-in period in order to establish a baseline blood pressure and eligibility for randomization based upon the inclusion and exclusion criteria defined in this protocol. Placebo was taken daily in the morning without regard to food intake.

Centres

Eight centers, all in India

Publication

N/A to date

Objectives

Primary objective

- To evaluate the effect of light meals on the pharmacokinetics (AUC(0-τ) & Cmax) and pharmacodynamics (PRA) of the SPP100 300 mg commercial formulation in subjects with mild to moderate hypertension.

Secondary objective(s)

- To evaluate the effect of light meals on other pharmacodynamic parameters (PRC, Ang II) of the SPP100 300 mg commercial formulation in subjects with mild to moderate hypertension
- To evaluate the safety and tolerability following multiple oral doses of the SPP100 300 mg market tablet in subjects with mild to moderate essential hypertension.

Test Product (s), Dose(s), and Mode(s) of Administration

- Oral aliskiren 300 mg Final Market Image (FMI) tablets once each morning for 28 days
- Placebo (aliskiren 300 mg matching) tablets once each morning for 2 weeks during placebo run-in period

Reference Product(s), Dose(s), and Mode(s) of Administration

None

Criteria for Evaluation

Pharmacokinetic/ Pharmacodynamic

PK parameters AUC0-tau, Cmax, Tmax and CL/F (on Day 28) for aliskiren were used to determine the effect of food on aliskiren PK after a single dose and multiple doses. PD assessments included PRA AUE24h and Emax, trough levels of PRA, PRC and Ang II.

Safety

Safety assessments consisted of collecting all adverse events (AEs), serious adverse events (SAEs), with their severity and relationship to study drug. They included the regular monitoring of hematology, blood chemistry and urine performed at the study center laboratory and regular assessments of vital signs, ECG, physical condition and body weight

Bioanalytics

Blood samples (3 mL) were taken for pharmacokinetic evaluation of aliskiren as follows: Predose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 hours post dose on Days 1 and 28. Blood samples (6 mL) were collected to assess PRA on Day -1, at 2, 4, 8 and 12 hours post-dose on Day 1 and on Day 28 when a 24 hour post dose sample was also taken. In addition, separate blood samples were collected on Day -1 and at 24 hours post dose on Day 1 and Day 28 for the assessment of PRC (4 mL sample) and Ang II (10 mL sample).

Statistical Methods

All data collected in this study were listed by treatment group and subject. In addition demographic data, plasma concentrations, pharmacokinetic and pharmacodynamic parameters and safety data were summarized by treatment using n, mean, SD, median and range or frequency tables as appropriate to the data.

Pharmacokinetics/Pharmacodynamics

Two analysis data sets were defined for both PK and PD. The first consisted of all patients with evaluable data but excluding all patients from one site and with major protocol deviations. The second analysis data set that was used for sensitivity analysis consisted of the primary analysis data set plus the data from patients who did not have major protocol deviations.

The primary PK parameters were AUC0-tau and Cmax on Day 28, which were log-transformed (base e) and statistically analyzed using an ANOVA model with food state (fed or fasted) as a factor. An estimate of the treatment difference together with its 90% confidence interval was obtained based upon the log-transformed observations. The estimates and confidence intervals were then “backtransformed” to the original scale, giving the ratios of the fed/fasted states together with 90% confidence intervals for the ratios.

The primary PD variable was PRA AUE24h on Day 28. The analysis was performed on the log-transformed (base e) data. An ANCOVA model was fitted for the change from baseline (Day -1) AUE24h on Day 28 with food state (fed or fasted) as a factor, and log-transformed (base e) baseline AUE24h as a covariate. The food effect (treatment difference of fed versus fasted) was tested at a one-sided significance level of 0.05. An estimate of the treatment difference together with its 90% confidence interval was obtained based upon the log-transformed observations. The esti-

mates and confidence intervals were 'back-transformed' to the original scale, giving the ratios of the fed/fasted states together with 90% confidence intervals for the ratios.

Safety

Safety assessments consisted of collecting all adverse events (AEs), serious adverse events (SAEs), with their severity and relationship to study drug, and pregnancies. They included the regular monitoring of hematology, blood chemistry and urine performed at (study center/central laboratory) and regular assessments of vital signs, physical condition and body weight.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria:

- Male or female outpatients, 18 to 65 years of age with mild to moderate hypertension
- They weighed at least 50 kg and had a body mass index (BMI) within the range of 18 to 35 kg/m2. Mild smokers could be included. Female patients had to be of non-child bearing potential.

Exclusion criteria:

- Severe hypertension
- Secondary form of hypertension.
- Type 1 or type 2 diabetes mellitus
- Serum potassium out side laboratory reference range
- Any history of hypertensive encephalopathy or cerebrovascular accident
- Patients who were previously (within 3 months of Visit 1) treated with aliskiren

Number of Subjects

	Aliskiren 300mg fed	Aliskiren 300mg fasted	All patients
Randomised n	64	60	124
Exposed (%)	62 (100)	60 (100)	122 (100)
Completed n (%)	60 (97)	55 (92)	115 (94)
Withdrawn n (%)	2 (3)	5 (8)	7 (6)
Withdrawn due to adverse events n (%)	0 (0)	0 (0)	0 (0)
Withdrawn for other reasons n (%)	2 (3)	5 (8)	7 (6)

Demographic and Background Characteristics

		Aliskiren 300mg fed N = 62	Aliskiren 300mg fasted N = 60	All treatments N = 122
Age (years)	Mean (SD)	44 (9.6)	44 (8.8)	44 (9.2)
	Range	28, 64	23, 63	23, 64
Gender – n (%)	Male	41 (66%)	31 (52%)	72 (59%)
	Female	21 (34%)	29 (48%)	50 (41%)
Race – n (%)	Asian	62 (100%)	60 (100%)	122 (100%)
Weight (kg)	Mean (SD)	65.8 (12.13)	65.2 (11.67)	65.5 (11.86)
	Range	50.0, 96.0	50.0, 96.0	50.0, 96.0
Height (cm)	Mean (SD)	165 (9.5)	162 (9.5)	163 (9.6)
	Range	145, 189	146, 185	145, 189
BMI (kg/m^2)	Mean (SD)	24.2 (3.65)	24.8 (3.55)	24.5 (3.60)
	Range	18.3, 34.5	17.5, 33.1	17.5, 34.5

Primary Objective Result(s)

Pharmacokinetic results

The results of the statistical analysis of PK parameters AUC0-tau and Cmax on Day 28 for the primary analysis data set are shown in Table below for the fed and fasted treatment groups along with the ratio of the geometric means from each group.

PK parameter	Adjusted geometric mean		Ratio of geometric means	
	Fed	Fasted	Estimate	90% CI
N	40	41		
AUC0-tau (hr.ng/mL)	862	2594	0.33	0.27, 0.41
Cmax (ng/mL)	97.1	410	0.24	0.17, 0.32

The estimates of fed:fasted ratios were well below unity (1.0) as were the upper 90% CIs for AUC0-tau and Cmax, all comparisons were highly significant (P<0.001) This shows that the bioavailability of aliskiren is affected when taken with a light meal and is lower than when patients were fasted. There was a 67% reduction in aliskiren total exposure (AUC0-tau) and a 76% reduction in aliskiren exposure (Cmax) at steady state when aliskiren was taken with a light meal. Day 28 analysis results for the secondary analysis data set are similar to the primary analysis data set.

Pharmacodynamic results

The results of the statistical analysis are shown in Table below. The difference noted at baseline did not impact these results as the baseline AUE24h was included as a covariate.

Treatment	N	Geometric mean (ng/mL)		Baseline-adjusted* geometric mean of Day 28 to baseline ratio	Geometric mean ratio of Fed/Fasted	
		Baseline	Day 28		Estimate	90% CI
Fed	39	6.35	2.83	0.38	1.07	0.95, 1.21
Fasted	40	9.54	2.84	0.35		

*Analysis was of change from baseline with baseline as covariate

The baseline adjusted geometric mean PRA AUE24h was reduced by 62% and 65%, respectively, for the fed and fasted treatment groups. The estimated ratio of fed versus fasted of the geometric mean ratio of Day 28 versus baseline is very close to 1.0 and the confidence intervals include 1 (P=0.35) indicating no evidence of a change in the AUE24h between the fed and the fasted treatment groups.

Secondary Objective Result(s)

Pharmacodynamic results:

	Treatment	N	Geometric mean		Baseline-adjusted geometric mean of Day 28 to baseline ratio	Geometric mean ratio of Fed/Fasted	
			Baseline	Day 28		Estimate	90% CI
Trough PRA (ng/mL/h)	Fed	39	0.30	0.12	0.38	1.04	0.88, 1.23
	Fasted	38	0.35	0.12	0.36		
Trough PRC (ng/L)	Fed	38	2.99	20.19	6.38	0.62	0.42, 0.91
	Fasted	38	3.67	41.62	11.16		
Trough Ang II (pmol/L)	Fed	40	4.82	4.36	0.90	1.06	0.91, 1.25
	Fasted	41	4.91	4.16	0.85		

N values vary due to missing values

Safety Results

Adverse Events by System Organ Class

	Aliskiren 300 mg		
	Fed	**Fasted**	**All**
	N=62	**N=60**	**N=122**
Patients with at least one AE	4 (7%)	7 (12%)	11 (9%)
Primary system organ class			
Investigations	0	3 (5%)	3 (2.5%)
General disorders & administration site conditions	1 (2%)	1 (2%)	2 (2%)
Nervous system disorders	2 (3%)	0	2 (2%)
Blood and lymphatic system disorders	0	1 (2%)	1 (1%)
Gastrointestinal disorders	0	1 (2%)	1 (1%)
Infections and Infestations	0	1 (2%)	1 (1%)
Metabolism and nutrition disorders	1 (2%)	0	1 (1%)

AEs by SOC are presented in descending order of frequency in total group.

10 Most Frequently Reported AEs with Severity Overall by Preferred Term n (%)

		Aliskiren 300 mg		
		Fed	Fasted	All
		N=62	N=60	N=122
Patients with at least one AE		4 (7%)	7 (12%)	11 (9%)
Preferred term	**Severity**			
Headache	Mild	2 (3%)	0	2 (2%)
Blood creatine phosphokinase increased	Mild	0	1 (2%)	1 (1%)
Blood glucose increased	Mild	0	1 (2%)	1 (1%)
Catheter site pain	Moderate	0	1 (2%)	1 (1%)
Catheter site related reaction	Moderate	1 (2%)	0	1 (1%)
Glycosylated haemoglobin increased	Mild	0	1 (2%)	1 (1%)
Hyperglycaemia	Mild	1 (2%)	0	1 (1%)
Leukocytosis	Mild	0	1 (2%)	1 (1%)
Lipase increased	Moderate	0	1 (2%)	1 (1%)
Neutrophilia	Mild	0	1 (2%)	1 (1%)
Urinary tract infection	Moderate	0	1 (2%)	1 (1%)
Vomiting	Mild	0	1 (2%)	1 (1%)

Serious Adverse Events and Deaths

None occurred

Date of Clinical Trial Report

30-May-2010

Date Inclusion on Novartis Clinical Trial Results Database

20 December 2010

Date of Latest Update

17-Dec-2010