Sponsor

Novartis

Generic Drug Name

Aliskiren

Therapeutic Area of Trial

Hypertension

Approved Indication

Hypertension

Study Number

CSPP100A1104

Title

A multiple center, randomized, double blind, parallel group, multiple oral dose study to evaluate the pharmacokinetic and pharmacodynamic profiles of 150 mg and 300 mg of SPP100 in Japanese patients with mild to moderate essential hypertension

Phase of Development

Phase III

Study Start/End Dates

04 Jan 2007 to 21 Jun 2007

Study Design/Methodology

This study was a multiple center, randomized, double blind, parallel group study. A 4-week placebo run-in period was followed by a 4-week treatment period (SPP 100 at doses of 150 mg or 300 mg) and a 1-week follow-up period. . Study drugs were administered once daily between 6:00 and 10:00 a.m. every morning, 30 minutes after the start of breakfast

Centres

2 centers in 1 country: Japan (2)

Publication

Objectives

Primary objective

- To evaluate the pharmacokinetic profile of SPP100 administered orally 30 min after meal in Japanese patients with essential hypertension

Secondary objectives

- To evaluate the effect of renin inhibition by SPP100 administered orally 30 min after meal in Japanese patients with essential hypertension by comparing the RAS profile during a 4 week treatment period with SPP100 to that during the run-in period
- To evaluate the relationship among steady state pharmacokinetics, change in RAS biomarkers and blood pressure lowering effect of SPP100 administered orally 30 min after meal in Japanese patients with essential hypertension
- To evaluate the safety of SPP100 orally administered 30 min after meal in Japanese patients with essential hypertension

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

Oral tablet of SPP100 once daily at around 8:00 a.m. (between 6:00 and 10:00 a.m.) every morning, 30 minutes after start of breakfast.

- SPP100 150 mg: one tablet of SPP100 150 mg tablet and one tablet of SPP100 matching placebo.
- SPP100 300 mg: two tablets of SPP100 150 mg tablet

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

Oral tablet of SPP100 matching placebo once daily at around 8:00 a.m. (between 6:00 and 10:00 a.m.) every morning, 30 minutes after start of breakfast.

Criteria for Evaluation

Pharmacokinetic evaluation

- Plasma SPP100 concentrations on Day 1, 2, 14, 28, 29 and 35

Pharmacodynamic evaluation

- RAS biomarkers: plasma renin activity [PRA], plasma active renin concentration [PRC], plasma angiotensin I concentration [Ang I], plasma angiotensin II concentration [Ang II], and plasma aldosterone concentration [Ald]) on Day -2, -1, 1, 2, 14, 28, 29 and 35
- Blood pressure and pulse rate on Day -2, -1, 1, 2, 14, 28, 29 and 35

Exploratory pharmacodynamic evaluation

- Catecholamines (adrenaline, noradrenaline, dopamine) on Day -2, -1, 1, 2, 28 and 29
- Plasma and urine angiotensinogen concentration on Day 1 and Day 29
- Plasma oxidated albumin on Day 1 and Day 29

Safety

- Body measurements
- ECG evaluations
- Postural hypotension
- Standard clinical laboratory evaluations
- Adverse events and serious adverse events

Statistical Methods

Pharmacokinetic evaluation:

All completed patients with quantifiable PK measurements were included in the PK data analysis. PK parameters (AUC_{0-t}, AUC_{0-inf}, $AUC_{0-\tau,ss}$, C_{max}, C_{min}, $C_{av,ss}$, CL/F, λ_z, t_{max}, $t_{1/2}$, V_z/F) were determined using non-compartmental methods. PK parameters were summarized using plots and descriptive statistics.

Pharmacodynamic evaluation:

The primary analysis was planned to be of a per-protocol population of eligible patients with evaluable PD data.

PD data were listed, and summarized using descriptive statistics, including changes from the mean value of the run-in period (mean for each time point in Day -2 and Day -1). For adrenaline, noradrenaline and dopamine changes between the 5 and 20 hour assessments were also included.

Blood pressure and RAS biomarkers were summarized by means of AUE, ΔAUE (difference of AUE between baseline and the treatment), E_{max}, ΔE_{max} (maximal change from time-matched baseline value), t_{max} and trough level. These summary measures were listed and summarized using descriptive statistics and plots.

AUE, E_{max} and trough levels of RAS assessments and BP at Day 28 were compared between the two treatment groups using Analysis of Covariance. Changes from baseline within each treatment group were assessed using paired t-tests. Differences in t_{max} were analyzed non-parametric rank based tests.

Scatter plots and correlation statistics were produced to assess the relationship between various PD parameters, and between PK and PD parameters, at baseline and Day 28.

Safety evaluation:

All patients who received at least one treatment were to be included in the safety and tolerability evaluation. Safety data were reported using listings, plots and descriptive statistics.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria:

Patients were included who met the following criteria:

1. Age: Patients aged 20 to 80 years (at the time of obtaining informed consent)
2. Gender: Male or female
3. Blood pressure:
    1) Mean (based on 3 recordings at 1-2 minutes interval) sitting diastolic blood pressure values at Visits 2 and Visit 3 (Day -14 and Day -3) should meet the following criteria:
    Visit 2 (Day -14) : ≥ 90 mmHg and < 110 mmHg
    Visit 3 (Day -3) : ≥ 95 mmHg and < 110 mmHg
    2) The difference in mean sitting diastolic blood pressure at Visits 2 and Visit 3 (Day -14 and Day -3) is within 10 mmHg.
4. Treatment status: Out patient
5. Body weight: no less than 50 kg.
6. Able to communicate well with the investigator, to understand and comply with the requirements of the study. Understand and sign the written informed consent.

Exclusion criteria:

Patients meeting any of the following criteria were excluded from entry into or continuation in the study.

1. Pregnant women, lactating mothers, women suspected of being pregnant, or women who wish to be pregnant Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test (> 5 mIU/mL).
2. Patients with mean sitting SBP ≥ 180 mmHg and/or mean sitting DBP ≥ 110 mmHg at Visit 1, 2 or 3 (Day -28, -14 or -3)
3. Patients with or suspected of having secondary hypertension (due to aortic coarctation, pri-

mary aldosteronism, coarctation of renal artery, renal hypertension [renal vascular or renal parenchymal], pheochromocytoma, etc.)

4. Patients suspected of having malignant hypertension
5. Patients with any of the following severe diseases or signs:
    1) Cardiac disease: Patients with congestive heart failure, myocardial infarction (onset within 52 weeks prior to Visit 1 [Day -28]); patients who have undergone PCI (PTCA) or coronary bypass surgery within 24 weeks prior to Visit 1 (Day -28); or patients with angina pectoris, arrhythmia requiring therapeutic intervention or accompanied by clinical symptoms, second or third degree atrioventricular block, chronic atrial fibrillation, clinically significant valvular heart disease
    2) Renal disease: Patients who have a serum creatinine (SCr) > 1.5 x ULN by laboratory tests at Visit 1 (Day -28), or patients with severe renal disorder
    3) Hepatic disease: Patients found to have AST (GOT) > 2 x ULN or ALT (GPT) > 2 x ULN by laboratory tests at Visit 1 (Day -28), or patients with severe hepatic disorder (e.g., hepatic failure, liver cirrhosis)
    4) Cerebrovascular disorder: Patients with cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage, or transient cerebral ischemic attack accompanied by clinical symptoms (including the history of onset within 52 weeks prior to Visit 1 [Day -28])
6. Patients with a clinically significant allergy (including asthmatic patients currently receiving drug therapy, patients with allergy to multiple drugs, or anaphylactic reaction due to drug allergy)
7. Patients with pancreatitis or with a history of pancreatitis
8. Patients on treatment of duodenal or gastric ulcer (including maintenance therapy for preventing recurrence), or patients who have had duodenal or gastric ulcer within 12 weeks prior to Visit 1 (Day -28) or patients with a history of gastrointestinal surgery or gastrointestinal disease which could interfere with drug absorption
9. Patients with overt dehydration or with electrolyte abnormality of clinical concern
10. Patients with type I diabetes mellitus, patients with type II diabetes mellitus under insulin therapy, or patients with poor-glucose-control type II diabetes mellitus (HbA1C: > 8% at Visit 1 [Day -28])
11. Patients with a history of malignant tumors including leukemia and lymphoma, treated or untreated, within the past 5 years whether or not there is evidence of local recurrence or metastases (except for localized basal cell carcinoma of the skin).
12. Patients with a history of autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus.
13. Patients with anemia with clinical symptoms
14. Patient with fecal occult blood positive at Visit 1 (Day -28), unless gastrointestinal bleeding can be ruled out by future medical evaluation.
15. Patients with hypothyroidism (TSH > 5.00 μIU/mL at Visit 1 [Day -28])
16. Patients who previously entered a SPP100 study and who received investigational drug (including placebo).
17. Patients who have received other investigational drug (including placebo) within 12 weeks prior to Visit 1 (Day -28).

18. Patients with a history of hypersensitivity to SPP100 or the drugs with similar chemical structures
19. Alcoholic patients
20. Patients who have history of drug abuse within 52 weeks prior to Visit 1 (Day -28)
21. Any person who is involved in the execution of the protocol will not be eligible for enrollment in the study.
22. Patients who are considered unlikely to comply with the requirements specified in the protocol by the investigator or subinvestigator.
23. Donation or loss of 400 mL or more of blood within 3 months prior to participation, donation or loss of 200 mL or more of blood within 1 month prior to participation, or donation of component blood within 2 weeks prior to participation.
24. History and complication of immunodeficiency diseases, including a positive HIV test result.
25. A positive Hepatitis B surface antigen (HBsAg), Hepatitis C or syphilis test result.

Number of Subjects

	SPP100 150 mg	SPP100 300 mg	Placebo	Total
Patients				
Screened	-	-		131
Entered run-in period	-	-	79	79
Discontinued during run-in period	-	-	14	46
Randomized	17	16	-	33
Completed	17	16	-	33
Discontinued during treatment period	0	0	-	0
Main cause of discontinuation during run-in period				
Abnormal test procedure result(s)*	-	-	21	21
Abnormal laboratory value(s)**	-	-	15	15
Subject withdrew consent	-	-	5	5
Subject's condition no longer requires study drug	-	-	2	2
Administrative problems	-	-	2	2
Adverse event(s)	-	-	1	1

* Abnormal test procedure result(s): any abnormal signs, symptoms or test results other than laboratory test results, including deviation from inclusion criteria or meeting exclusion criteria for BP results.
** Abnormal laboratory value(s): any abnormal laboratory test results, including meeting the exclusion criteria for laboratory test results.

Demographic and Background Characteristics

Demographic summary

	SPP100 150 mg	SPP100 300 mg
N	17	16
Females : males	11 : 6	11 : 5

Mean age, years (SD)	61.8 (9.02)	60.7 (7.49)
Mean weight, kg (SD)	64.22 (7.974)	67.37 (9.633)
Race Oriental n (%)	 17 (100.0)	 16 (100.0)
Mean sitting DBP, mmHg (SD)	93.8 (8.19)	94.7 (9.50)
Mean sitting SBP, mmHg (SD)	149.5 (17.09)	150.6 (13.32)

Pharmacokinetic Results

Summary statistics of key PK parameters of plasma SPP100

PK parameters	Statistics	SPP100 150 mg	SPP100 300 mg
Day 1			
C_{max} (ng/mL)	Mean ± SD	30.54 ± 38.221	97.23 ± 132.412
AUC_{0-t} (ng·h/mL)	Mean ± SD	112.67 ± 98.719	354.52 ± 371.289
t_{max} (h)	Median	1	2.5
Trough level (ng/mL)	Mean ± SD	1.82 ± 1.182	4.13 ± 1.812
Day 28			
$C_{max,ss}$ (ng/mL)	Mean ± SD	22.88 ± 16.972	91.83 ± 96.573
$AUC_{0-\tau,ss}$ (ng·h/mL)	Mean ± SD	225.74 ± 135.633	679.26 ± 378.698
$t_{max,ss}$ (h)	Median	2	1
Trough level (ng/mL)	Mean ± SD	6.98 ± 4.755	18.90 ± 10.459

Trough level was the concentration at 24 hours after the treatment.

Pharmacodynamic Results

Summary statistics of change from baseline to Day 28 in key PD parameters (absolute values of increase in PRC, absolute values of decrease in all other parameters)

PD parameters	Statistics	SPP100 150 mg	SPP100 300 mg
PRA			
ΔE_{max} (ng/mL/h)	Mean ± SD	0.582 ± 0.4653	0.572 ± 0.2805
ΔAUE (ng/mL)	Mean ± SD	8.558 ± 9.6940	8.877 ± 4.8774
PRC			
ΔE_{max} (pg/mL)	Mean ± SD	28.988 ± 23.3007	54.131 ± 58.5017
ΔAUE (pg·h/mL)	Mean ± SD	444.672 ± 351.4139	731.870 ± 748.5582
Ang I			
ΔE_{max} (pg/mL)	Mean ± SD	30.221 ± 19.7175	33.891 ± 16.8842
ΔAUE (pg·h/mL)	Mean ± SD	354.868 ± 370.0604	444.789 ± 360.9384
Ang II			
ΔE_{max} (pg/mL)	Mean ± SD	3.294 ± 1.7505	2.969 ± 1.9704
ΔAUE (pg·h/mL)	Mean ± SD	10.103 ± 35.8634	14.656 ± 41.5114
AId			
ΔE_{max} (pg/mL)	Mean ± SD	30.576 ± 19.4966	30.800 ± 20.5846
ΔAUE (pg·h/mL)	Mean ± SD	132.724 ± 359.9706	227.481 ± 283.0964
Supine DBP			
ΔE_{max} (mmHg)	Mean ± SD	11.166 ± 7.2163	12.313 ± 5.0950
ΔAUE (mmHg·h)	Mean ± SD	86.909 ± 160.0997	118.026 ± 105.8416

Supine SBP			
ΔE_{max} (mmHg)	Mean ± SD	15.000 ± 7.7698	16.230 ± 6.2430
ΔAUE (mmHg·h)	Mean ± SD	76.045 ± 258.1573	183.044 ± 157.3448

Values represent absolute changes between run-in (pretreatment baseline) and day 28 of treatment:

ΔE_{max} for PRC = maximum ($E_{(t, Day\ 28)} - E_{(t, mean\ of\ run\text{-}in)}$); ΔE_{max} for all other parameters = maximum ($E_{(t, mean\ of\ run\text{-}in)} - E_{(t, Day\ 28)}$)

ΔAUE for PRC = $\int_{0\text{-}t} (E_{(t, Day\ 28)} - E_{(t, mean\ of\ run\text{-}in)})$: ΔAUE for all other parameters = $\int_{0\text{-}t} (E_{(t, mean\ of\ run\text{-}in)} - E_{(t, Day\ 28)})$

Exploratory Pharmacodynamic Results

Angiotensinogen: No notable changes in mean levels of plasma and urine angiotensinogen were observed after SPP100 treatment.

Catecholamine: No notable changes with SPP100 treatment were observed. The RAS inhibition by SPP100 does not affect on plasma catecholamines during daytime and nighttime.

Oxidated albumin: No notable changes were observed in mean plasma oxidated albumin levels after SPP100 treatment.

Safety Results

Adverse events overall in the treatment period by body system – n (%) of patients

Body system	SPP100 150 mg N=17 n (%)	SPP100 300 mg N=16 n (%)	Total N=33 n (%)
Any body system	5 (29.4)	7 (43.8)	12 (36.4)
Blood and lymphatic system disorders	1 (5.9)	1 (6.3)	2 (6.1)
Cardiac disorders	0 (0.0)	1 (6.3)	1 (3.0)
Eye disorders	1 (5.9)	0 (0.0)	1 (3.0)
Gastrointestinal disorders	1 (5.9)	1 (6.3)	2 (6.1)
General disorders and administration site conditions	0 (0.0)	1 (6.3)	1 (3.0)
Infections and infestations	0 (0.0)	1 (6.3)	1 (3.0)
Injury, poisoning and procedural complications	1 (5.9)	0 (0.0)	1 (3.0)
Metabolism and nutrition disorders	1 (5.9)	0 (0.0)	1 (3.0)
Musculoskeletal and connective tissue disorders	1 (5.9)	2 (12.5)	3 (9.1)
Nervous system disorders	2 (11.8)	3 (18.8)	5 (15.2)
Respiratory, thoracic and mediastinal disorders	2 (11.8)	0 (0.0)	2 (6.1)
Vascular disorders	1 (5.9)	0 (0.0)	1 (3.0)

Serious Adverse Events and Deaths

No patients experienced any serious adverse events.

Date of Clinical Trial Report 05 Dec 2007
Date Inclusion on Novartis Clinical Trial Results Database 19 May 2008
Date of Latest Update