Sponsor

Novartis

Note: This study was conducted by Speedel Pharma Ltd., NCT00561171

Generic Drug Name

SPP635

Therapeutic Area of Trial

Diabetes Mellitus Type II with Mild to Moderate Hypertension

Approved Indication

Investigational

Study Number

CSPP635CRD05

Title

A Phase IIa, Double-Blind, Randomized, Parallel-Design, Four-week Study to Investigate the Efficacy and Safety of Two Different Doses of the Renin-inhibitor SPP635 Once Daily in Type II Diabetic Patients With Mild to Moderate Hypertension and Albuminuria

Phase of Development

Phase IIa

Study Start/End Dates

23 Nov 2007 to 29 Sep 2008

Study Design/Methodology

This was a phase IIa, double-blind, randomized, parallel-design, four-week study to investigate the efficacy, safety and tolerability of two different doses of SPP635 (200 mg and 450 mg once daily) in type II diabetic patients with mild to moderate hypertension and albuminuria.

The total study duration for patients completing the entire study was approximately 7-10 weeks:

- Screening phase: eligibility of patients was checked within two weeks
- Wash-out phase: angiotensin converting enzyme inhibitors (ACEi)/angiotensin receptor blockers (ARB) were washed out for 7-21 days

- Treatment phase: patients received study medication for 28 days
- Follow-up phase: patients were observed 7-10 days after last treatment. After the follow-up phase, patients resumed antihypertensive treatment at the discretion of the investigator/general practitioner (GP)

All treatments other than ACEi/ARB (which were to be washed-out) with an effect on BP and all anti-diabetic treatments were to be kept at a stable dose throughout study.

Centres

14 centers in 2 countries: Ireland (5) and Hungary (9).

Publication

Ongoing

Objectives

Primary objective(s)

- To assess the effect of 200 and 450 mg SPP635 once daily on (systolic and diastolic) ambulatory blood pressure (ABPM) compared to baseline, split into daytime blood pressure (BP), night-time BP and 24-hour BP

Secondary objective(s)

- To assess the effect of 200 and 450 mg SPP635 once daily on albuminuria versus baseline investigated as 24-hour urinary albumin excretion and urinary albumin:creatinine ratio (ACR)
- To assess the effect of 200 and 450 mg SPP635 once daily on trough sitting office BP (systolic and diastolic) compared to baseline
- To assess the effect of 200 and 450 mg SPP635 once daily on plasma renin activity (PRA)
- To assess plasma levels of SPP635
- To assess the safety and tolerability of 200 and 450 mg SPP635 once daily.

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

SPP635 (or matched placebo) was provided as hard gelatin capsules for oral use. For both dosages, 3 capsules per day were taken:

- 450 mg once daily dose was taken as 3 capsules containing 150 mg SPP635.
- 200 mg once daily dose was taken as 2 capsules containing 100 mg SPP635 plus 1 capsule of matching placebo.

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

Not applicable

Criteria for Evaluation

Primary variables

- Change of BP measured by ABPM (systolic and diastolic) at baseline and after 4 weeks of treatment or after early discontinuation; split into daytime, night-time and 24h BP

Secondary variables

- Change of BP measured by sitting office BP (systolic and diastolic) at screening, baseline, after 2 weeks of treatment, after 4 weeks of treatment or after early discontinuation and at follow-up
- Effect on albuminuria assessed by 24 hour urinary albumin excretion and ACR at baseline and after 4 weeks of treatment or after early discontinuation

Safety and tolerability

Safety assessments consisted of monitoring and recording all adverse events (AEs), serious adverse events (SAEs), with their severity and relationship to study drug; pregnancies; the regular monitoring of hematology, blood chemistry and urine values; and regular assessments of vital signs and physical condition.

Pharmacology

- Assessment of PRA at baseline, after 2 weeks of treatment, after 4 weeks of treatment or after early discontinuation and at follow-up.
- Plasma concentration of SPP635 at PK baseline at Day 1, after 2 weeks of treatment, after 4 weeks of treatment or after early discontinuation.

Other

Not applicable

Statistical Methods

For sample size, no formal calculations were performed. Enrollment of max. 50 patients was planned in order to achieve at least 40 evaluable patients. Twenty-five patients were to be randomized to receive 200 mg SPP635 and 25 patients to receive 450 mg SPP635. This sample size was deemed sufficient for an exploratory study.

Descriptive statistics were used with graphical representation (as appropriate). Comparisons (pair-wise differences) between baseline values and values obtained following treatment for 2 weeks (if scheduled), and 4 weeks were performed within each treatment group and the changes from baseline were compared between treatment groups. PK/pharmacodynamic relationship was

assessed using PK trough levels, and PRA levels and BP (ABPM for each daytime, night-time, and 24 hour, both systolic and diastolic; sitting office BP separate assessments for systolic and diastolic BP), and for 24 hour urinary albumin excretion and urinary ACR.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria:

1. Men or women, aged 8 to 75 years, inclusive
2. Female patients, either postmenopausal for ≥ 2 years or surgically sterile or of child-bearing potential and using double contraception, with at least one method being a barrier contraceptive
3. Written informed consent prior to study participation
4. Type II diabetes mellitus with stable anti-diabetic treatment for at least
5. 3 months prior to screening
6. Glycosylated subfraction of hemoglobin A (HbA1c) of ≥ 6.5 %
7. Patients with history of hypertension treated with stable dose(s) of antihypertensive drug(s) for at least 3 months prior to screening. At least one of the antihypertensive drugs had to be an ACEi or ARB
8. Mean sitting systolic office BP (SBP) ≤ 150 mm Hg at screening
9. Albuminuria as indicated by mean urinary ACR of ≥ 2.5 mg/mmol (males) or ≥ 3.5 mg/mmol (females) at screening
10. (after Amendment 3) Albuminuria as indicated by mean urinary ACR of ≥ 2.5 mg/mmol (males) or ≥ 3.5 mg/mmol (females) at screening or by 24h albuminuria of ≥ 30 mg at baseline
11. Ability to communicate with the investigator and comply with the study requirements
12. At baseline, after wash-out a mean sitting SBP ≥ 8 mm Hg higher than at screening but ≤ 179 mm Hg

Exclusion Criteria:

1. Pregnant or lactating women
2. Participation in any clinical trial within 8 weeks (or longer as required by local regulation) prior to dosing
3. Donation of any blood or plasma in the past month or, inclusive of this study, donation in excess of 500 mL of blood within the three months preceding the start of the study treatment period
4. Significant illness within 2 weeks prior to screening
5. Any history of malignancy except basal cell cancer of the skin
6. Heart failure, stroke, myocardial infarction, transient ischemic attack, or hypertensive encephalopathy within the past 6 months
7. Current or past history of clinically significant electrocardiogram (ECG) abnormalities such as permanent second degree atrioventricular (AV) block or higher, unstable angina, percutaneous transluminal coronary angioplasty (PTCA), coronary artery bypass graft (CABG) or cerebrovascular accident in the last three months

8. Any history or presence of kidney damage as indicated by a mean urinary ACR of ≥ 34 mg/mmol at screening
9. Known hypersensitivity to SPP635 or chemically related compounds
10. Treatment with Aliskiren
11. History of drug or alcohol abuse within the 12 months prior to dosing or evidence of such abuse

Number of Subjects

	SPP635 200 mg	**SPP635 450 mg**
Planned N	max. 25	max. 25
Randomised n	22	23
Intent-to-treat population (ITT) n (%)	22 (100%)	23 (100%)
Completed n (%)	21 (95.5%)	21 (91.3%)
Withdrawn n (%)	1 (4.5%)	2 (8.7%)
Withdrawn due to adverse events n (%)	1 (4.5%)	2 (8.7%)
Withdrawn due to lack of efficacy n (%)	0	0
Withdrawn for other reasons n (%)	0	0

Demographic and Background Characteristics

	SPP635 200 mg	**SPP635 450 mg**
N (Safety set)	22	23
Male	19 (86.4)	20 (87.0)
Female	3 (13.6)	3 (13.0)
Ethnic Origin: Caucasian	22 (100.0)	23 (100.0)
Age [years]	61.3 ± 8.1	63.2 ± 10.7
Height [cm]	170.7 ± 7.0	171.5 ± 8.2
Weight [kg]	97.0 ± 18.5	94.9 ± 18.3
Body Mass Index [kg/m²]	33.3 ± 5.7	32.2 ± 5.4

Primary Objective Result(s)

Change of BP measured by ABPM at baseline and after 4 weeks, split into daytime, night-time and 24-hours BP

Mean ABPM [mm Hg] Absolute change from baseline (mean ± SD)	**SPP635 200 mg (N=22)**	**SPP635 450 mg (N=19)**	**Total (N=41)**
SBP-daytime	-7.3 ± 5.32 p < 0.0001	-7.2 ± 7.13 p < 0.0001	-7.3 ± 6.14
DBP-daytime	-4.9 ± 4.06 p < 0.0001	-6.1 ± 3.47 p < 0.0001	-5.4 ± 3.81
SBP-night-time	-5.1 ± 8.89 p = 0.0089	-6.8 ± 10.14 p = 0.0023	-5.9 ± 9.41
DBP-night-time	-2.6 ± 6.54 p = 0.0392	-3.4 ± 8.33 p = 0.0282	-3.0 ± 7.34
SBP-24 hours	-6.4 ± 4.73 p < 0.0001	-6.6 ± 7.14 p < 0.0001	-6.5 ± 5.89
DBP-24 hours	-4.1 ± 3.13 p < 0.0001	-5.0 ± 4.31 p < 0.0001	-4.5 ± 3.70

Secondary Objective Result(s)

Office Blood Pressure

Change of sitting office BP at screening, baseline, after 2 weeks, after 4 weeks or after early discontinuation

Office BP [mm Hg] Absolute change from baseline (mean ± SD)	**SPP635 200 mg (N=22)**	**SPP635 450 mg (N=23)**	**Total (N=45)**
SBP	0.3 ± 13.75 p = 0.5177	-8.7 ± 11.63 p = 0.0013	-4.3 ± 13.36
DBP	-0.1 ± 8.96 p = 0.5482	-4.4 ± 6.46 p = 0.0004	-2.3 ± 7.99

UAER/ACR

UAER [mg/24h]	**SPP635 200 mg (N=22)**	**SPP635 450 mg (N=23)**	**Total (N=45)**
arithmetic mean ± standard deviation (median)			
Absolute values			
	(N=22)	**(N=23)**	**(N=45)**
Baseline	406.19 ± 676.88 (184.80)	352.91 ± 308.08 (214.20)	378.96 ± 517.83 (203.00)
	(N=22)	**(N=21)**	**(N=43)**
EOT/Early Termination	267.92 ± 411.12 (168.85)	194.40 ± 205.03 (145.80)	232.02 ± 325.44 (158.40)
Absolute change from baseline to EOT/Early Termination	-138.27 ± 284.12 (-67.80)	-152.29 ± 252.28 (-91.40)	-145.11 ± 265.93 (-84.60)
Relative change from baseline to EOT/Early Termination	0.8 / 3.33[a] (0.70)	0.5 / 2.09[a] (0.59)	0.6 / 2.80[a] (0.62)
Natural logarithm			
	(N=22)	**(N=23)**	**(N=45)**
Baseline	5.22 ± 1.44 (5.25)	5.57 ± 0.78 (5.40)	5.40 ± 1.15 (5.30)
	(N=22)	**(N=21)**	**(N=43)**
EOT/Early Termination	5.03 ± 1.04 (5.15)	4.81 ± 1.08 (5.00)	4.93 ± 1.05 (5.10)
Absolute change from baseline	-0.19 ± 1.21 (-0.35)	-0.73 ± 0.72 (-0.50)	-0.45 ± 1.03 (-0.50)
p-value	p = 0.1845[b]	p = 0.0017[b]	p = 0.1534[c]
Natural logarithm - Male patients			
	(N=19)	**(N=20)**	**(N=39)**
Absolute change from baseline	-0.22 ± 1.27 (-0.40)	-0.72 ± 0.74 (-0.55)	-0.46 ± 1.07 (-0.50)
p-value	p = 0.2331[b]	p = 0.0059[b]	p = 0.2364[c]
Natural logarithm - Female patients			
	(N=3)	**(N=3)**	**(N=6)**
Absolute change from baseline	-0.03 ± 0.90 (-0.10)	-0.77 ± 0.74 (-0.50)	-0.40 ± 0.84 (-0.35)
p-value	p = 0.6055[b]	p = 0.6884[b]	p = 0.8689[c]

EOT = end of treatment, UAER = Urinary Albumin Excretion Rate

[a] geometric mean, geometric standard deviation

[b] t-test within treatment group. A p-value < 0.05 indicates a significant change from baseline
[c] t-test between treatment groups. A p-value < 0.05 indicates a difference between treatment groups
[d] relative change is defined as value at EOT/early termination divided by baseline value

PK Results:

Plasma concentration (ng/mL) [b]	**SPP635 200 mg (N=22)**	**SPP635 450 mg (N=23)**	**Total (N=45)**
arithmetic mean ± standard deviation (median)			
	(N=17)	**(N=12)**	**(N=29)**
PK baseline	35.00 ± 23.59 (29.12) [29.59, 1.78] [a]	73.43 ± 66.24 (55.87) [58.71, 1.88] [a]	50.91 ± 49.12 (37.73) [39.29, 1.98] [a]
	(N=22)	**(N=22)**	**(N=44)**
Interim visit	77.92 ± 111.82 (51.80) [52.57, 2.18] [a]	138.57 ± 124.00 (110.53) [86.32, 3.28] [a]	108.24 ± 120.65 (69.03) [67.36, 2.78] [a]
	(N=22)	**(N=22)**	**(N=44)**
EOT/Early Termination	52.93 ± 58.64 (40.74) [38.53, 2.15] [a]	132.71 ± 91.09 (108.98) [102.80, 2.17] [a]	92.82 ± 85.79 (56.84) [62.94, 2.48] [a]
	(N=22)	**(N=21)**	**(N=43)**
Follow-up	0.56 ± 1.79 (0.00) [0.17, 3.52] [a]	1.61 ± 2.45 (1.11) [0.58, 5.17] [a]	1.08 ± 2.18 (0.00) [0.31, 4.78] [a]

LLOQ = lower limit of quantification, PK = pharmacokinetics, SD = standard deviation
[a] geometric mean, geometric SD
[b] For the calculation of geometric mean and geometric SD measurements below LLOQ were substituted by 0.1, for the calculation of other parameters they were substituted by 0.

PD Results:

	SPP635 200 mg (N=22)	**SPP635 450 mg (N=23)**	**Total (N=45)**
arithmetic mean ± standard deviation (median)			
PRA (ng/mL/h)			
	(N=21)	**(N=23)**	**(N=44)**
Baseline	1.67 ± 2.84 (0.60)	1.20 ± 1.17 (0.62)	1.42 ± 2.12 (0.62)
	(N=16)	**(N=12)**	**(N=28)**
PK baseline	0.54 ± 0.74 (0.26)	0.41 ± 0.46 (0.22)	0.48 ± 0.63 (0.26)
	(N=21)	**(N=21)**	**(N=42)**
Interim visit	0.47 ± 0.58 (0.30)	0.80 ± 2.15 (0.25)	0.63 ± 1.56 (0.29)
	(N=22)	**(N=23)**	**(N=45)**
EOT/Early Termination	0.51 ± 0.50 (0.42)	0.43 ± 0.34 (0.40)	0.47 ± 0.42 (0.40)
	(N=22)	**(N=21)**	**(N=43)**
Follow-up	2.44 ± 3.17 (1.52)	2.70 ± 3.20 (1.71)	2.57 ± 3.15 (1.55)

Renin inhibition (%)[a]			
	(N=16)	**(N=12)**	**(N=28)**
PK baseline	59.29 ± 26.60 (58.15)	46.93 ± 105.08 (76.45)	53.99 ± 70.22 (71.65)
	(N=20)	**(N=21)**	**(N=41)**
Interim visit	47.63 ± 50.00 (63.60)	51.87 ± 54.53 (61.50)	49.80 ±51.76 (62.50)
	(N=21)	**(N=23)**	**(N=44)**
EOT/Early Termination	36.69 ± 60.84 (48.80)	52.32 ± 37.87 (63.90)	44.86 ± 50.18 (59.30)
	(N=21)	**(N=21)**	**(N=42)**
Follow-up	-285.23 ± 1007.51 (-37.20)	-296.28 ± 544.84 (-113.0)	-290.75 ± 800.00 (-82.60)

LLOQ = lower limit of quantification, PRA = plasma renin activity
[a] For the calculation of measurements below LLOQ, half of the limit was used for the summaries. If a value was above the upper limit, then the limit multiplied by 1.5 was used.

Safety Results

Adverse Events by System Organ Class

TEAEs	SPP635 200 mg (N=22)	SPP635 450 mg (N=23)	Total (N=45)
SOC/PT[a]	**n (%)/number of AEs**	**n (%)/number of AEs**	**n (%)/number of AEs**
Number of patients with TEAEs	**8 (36.4)/10**	**7 (30.4)/14**	**15 (33.3)/24**
Nervous system disorders	**2 (9.1)/2**	**3 (13.0)/4**	**5 (11.1)/6**
Headache	2 (9.1)/2	1 (4.3)/1	3 (6.7)/3
Dizziness	0	1 (4.3)/1	1 (2.2)/1
Hypoaesthesia	0	1 (4.3)/1	1 (2.2)/1
Tension headache	0	1 (4.3)/1	1 (2.2)/1
General disorders and administration site disorders	**1 (4.5)/1**	**2 (8.7)/2**	**3 (6.7)/3**
Asthenia	0	1 (4.3)/1	1 (2.2)/1
Chest discomfort	0	1 (4.3)/1	1 (2.2)/1
Peripheral coldness	1 (4.5)/1	0	1 (2.2)/1
Investigations	**1 (4.5)/1**	**2 (8.7)/4**	**3 (6.7)/3**
Gamma/Glutamyltransferase increased	0	2 (8.7)/2	2 (4.4)/2
Blood triglycerides increased	0	1 (4.3)/1	1 (2.2)/1
Electrocardiogram QT prolonged	1 (4.5)/1	0	1 (2.2)/1
Electrocardiogram ST segment depression	0	1 (4.3)/1	1 (2.2)/1
Gastrointestinal disorders	**1 (4.5)/1**	**1 (4.3)/1**	**2 (4.4)/2**
Eructation	1 (4.5)/1	0	1 (2.2)/1
Nausea	0	1 (4.3)/1	1 (2.2)/1
Vascular disorders	**1 (4.5)/1**	**1 (4.3)/1**	**2 (4.4)/2**
Hypertension	1 (4.5)/1	0	1 (2.2)/1
Hypotension	0	1 (4.3)/1	1 (2.2)/1
Blood and lymphatic disorders	**0**	**1 (4.3)/1**	**1 (2.2)/1**
Anaemia	0	1 (4.3)/1	1 (2.2)/1
Eye disorders	**1 (4.5)/1**	**0**	**1 (2.2)/1**
Visual disturbance	1 (4.5)/1	0	1 (2.2)/1
Infections and infestations	**1 (4.5)/1**	**0**	**1 (2.2)/1**
Ear infection	1 (4.5)/1	0	1 (2.2)/1
Metabolism and nutrition disorders	**0**	**1 (4.3)/1**	**1 (2.2)/1**
Polydipsia	0	1 (4.3)/1	1 (2.2)/1
Musculoskeletal and connective tissue disorders	**1 (4.5)/1**	**0**	**1 (2.2)/1**
Periostitis	1 (4.5)/1	0	1 (2.2)/1
Respiratory, thoracic and mediastinal disorders	**1 (4.5)/1**	**0**	**1 (2.2)/1**
Dysphonia	1 (4.5)/1	0	1 (2.2)/1

TEAE = Treatment Emergent Adverse Event

PT = Preferred Term

MedDRA = Medical Dictionary for Regulatory Activities

SOC = System Organ Class

[a]All terms were coded acc. to MedDRA 10.1. SOCs presented in bold, PT in normal font. Subjects were counted only once within each SOC and each PT.

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

Treatment Emergent Adverse Events	SPP635 200 mg (N=22)	SPP635 450 mg (N=23)	Total (N=45)
Preferred Term	**n (%)/number of AEs**	**n (%)/number of AEs**	**n (%)/number of AEs**
Headache	2 (9.1)/2	1 (4.3)/1	3 (6.7)/3
Dizziness	0	1 (4.3)/1	1 (2.2)/1
Hypoaesthesia	0	1 (4.3)/1	1 (2.2)/1
Tension headache	0	1 (4.3)/1	1 (2.2)/1
Asthenia	0	1 (4.3)/1	1 (2.2)/1
Chest discomfort	0	1 (4.3)/1	1 (2.2)/1
Peripheral coldness	1 (4.5)/1	0	1 (2.2)/1
Gamma/Glutamyltransferase increased	0	2 (8.7)/2	2 (4.4)/2
Blood triglycerides increased	0	1 (4.3)/1	1 (2.2)/1
Electrocardiogram QT prolonged	1 (4.5)/1	0	1 (2.2)/1
Electrocardiogram ST segment depression	0	1 (4.3)/1	1 (2.2)/1
Eructation	1 (4.5)/1	0	1 (2.2)/1
Nausea	0	1 (4.3)/1	1 (2.2)/1
Hypertension	1 (4.5)/1	0	1 (2.2)/1
Hypotension	0	1 (4.3)/1	1 (2.2)/1
Anaemia	0	1 (4.3)/1	1 (2.2)/1
Visual disturbance	1 (4.5)/1	0	1 (2.2)/1
Ear infection	1 (4.5)/1	0	1 (2.2)/1
Polydipsia	0	1 (4.3)/1	1 (2.2)/1
Periostitis	1 (4.5)/1	0	1 (2.2)/1
Dysphonia	1 (4.5)/1	0	1 (2.2)/1

Serious Adverse Events and Deaths

No treatment-emergent SAEs were observed during this study.

Other Relevant Findings

None

Date of Clinical Trial Report

23 March 2009

Date Inclusion on Novartis Clinical Trial Results Database

25 September 2009

Date of Latest Update

30 September 2009