Sponsor

Novartis

Generic Drug Name

Aliskiren

Therapeutic Area of Trial

Cardiovascular

Approved Indication

Investigational Drug

Study Number

CSPP100A2240

Title

A randomized, double-blind, cross-over, 4-period, 4 treatment, within-subject placebo-controlled study to assess the optimal renoprotective dose of Aliskiren in hypertensive type 2 diabetes patients with incipient or overt nephropathy

Phase of Development

Phase II

Study Start/End Dates

11 Oct 2005 to 22 Apr 2008

Study Design/Methodology

This was a randomized, double-blind, cross-over, 4-period, 4-treatment, within-patient, placebo-controlled study. Diabetic patients with hypertension and incipient or overt diabetic nephropathy were enrolled and randomized to 1 of 4 treatment sequences: Aliskiren 150 mg, Aliskiren 300 mg, Aliskiren 600 mg and matching placebo. Each patient entered a four week run-in period, the 32-week treatment period, and an eight week washout period.

Centres

There was 1 center in Denmark.

Publication

None

Objectives

Primary objective(s)

To investigate the antiproteinuric effect of increasing doses of aliskiren versus placebo.

Secondary objective(s)

To assess the effects of multiple-dose administration of aliskiren on glomerular filtration rate (GFR) and blood pressure

To investigate whether there is a change on biomarkers of inflammation and cardiovascular risk.

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

Oral tablets of Aliskiren 150 mg, Aliskiren 300 mg, Aliskiren 600 mg and matching placebo.

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

None

Criteria for Evaluation

Primary variables

The primary pharmadynamic variable was the urinary albumin creatinine ration (UACR). Urinary pharmacodynamic assessments included Glomerular Filtration Rate (GFR), urinary albumin (UALB), urea and creatinine

Secondary variables

Sitting and standing BP were measured and recorded and at all study visits. On Day -1 of Period 1, and on Day 56 of each treatment period, 24-hour ambulatory blood pressure (ABP) measurements were performed every 15 minutes from 0700 h to 2300 h (daytime) and every 30 minutes from 2300 h to 0700 h (nighttime). A daytime mean, a nighttime mean, and a 24-hour mean were calculated from the data collected and these mean values were recorded.

At baseline and on Day 56 of each treatment period, blood samples were obtained for measurement of the following markers of inflammation and cardiovascular risk: Ang I, Ang II, ACE activity, PRA (including high-sensitivity PRA [hsPRA], trapping PRA, and trapping hsPRA), angiotensinogen, fibrinogen, adiponectin, plasma renin concentration (PRC), prorenin, aldosterone, von Willebrand Factor, high-sensitivity C-reactive protein (hsCRP), vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), plasminogen activator inhibitor-1 (PAI-1), and asymmetric dimethylarginine (ADMA).

MSSBP/MSDBP below 150/90 mmHg was considered as target blood pressure for the study.

Safety and tolerability

Safety assessments consisted of monitoring and recording all adverse events (AEs) and serious advser events (SAEs), pregnancies, blood laboratory tests (routine chemistry and haematology) and urine analyses, regular assessments of vital signs, physical examination, body weight, 12-lead ECGs and recording of all concomitant medications/non-drug therapies were obtained.

Statistical Methods

All efficacy variables were analyzed using a mixed model with sequence, treatment, and period as fixed factors and patient (nested in sequence) as a random factor. The following treatment comparisons were estimated:

aliskiren 150 mg vs placebo, aliskiren 300 mg vs placebo, aliskiren 600 mg vs placebo
aliskiren 300 mg vs aliskiren 150 mg, aliskiren 600 mg vs aliskiren 150 mg,
aliskiren 600 mg vs aliskiren 300 mg

For the log-transformed (base e) variables, the results were backtransformed to report point estimates (ratios), corresponding 95% confidence intervals (CI), and p-values.
For the untransformed variables, point estimates (differences), corresponding 95% CI, and p-values were reported.
The principal statistical comparisons were between aliskiren and placebo.
Scatter plots with Spearman correlation r-values and p-values (all aliskiren groups combined)

were used to explore associations between variables (e.g., between change in UACR and change in special blood assessment parameters, between change in UACR and change in BP, and between change in BP and change in special blood assessment parameters), where 'change in' was defined as the difference between the value on Day 56 of the aliskiren treatment period and the value on Day 56 of the placebo treatment period.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

1. Male or female patients aged 30 to 80 years with hypertension, type 2 diabetes, and incipient or overt nephropathy (urinary albumin excretion ≥100 mg/day but ≤2000 mg/day)
2. GFR ≥40 mL/min/1.73 m^2
3. Ear body temperature within the range of 35.0 °C to 37.5 °C
4. Receiving stable hypoglycemic medications for at least 8 weeks prior to screening
5. Postmenopausal or surgically sterilized (females only)
6. Willing and medically able to discontinue antihypertensive treatment or any other medication prohibited in the study protocol
7. For randomization, patients were required to fulfill the following criteria:
   a) Patients on ongoing hypertensive therapy had to be on stable antihypertensive medications for at least 8 weeks prior to the run-in period **AND** have BP ≥135/85 mm Hg but <170/105 mm Hg following the run-in period (Visit 3 [Day -1, Period 1])
   b) Newly-diagnosed hypertensive patients had to have BP ≥135/85 mm Hg but <170/105 mm Hg following the run-in period (Visit 3 [Day -1, Period 1])

Exclusion criteria

1. Severe hypertension (mean seated diastolic BP [MSDBP] ≥110 mm Hg and/or mean seated systolic BP [MSSBP] ≥180 mm Hg)
2. Type 1 diabetes mellitus or uncontrolled type II diabetes mellitus (glycosylated hemoglobin [HbA1C] >11%)
3. Current diagnosis of heart failure (New York heart Association [NYHA] Class II-IV)
4. History of a major cardiovascular event or procedure, second or third degree heart block without a pacemaker, potentially life-threatening arrhythmia or symptomatic arrhythmia, or clinically significant valvular heart disease
5. Use of any prescription drug or over-the-counter (OTC) medications prohibited by the protocol, acetylsalicylic acid treatment >1 g/day, or regular use of nonsteroidal anti-inflammatory drugs (NSAIDs)
6. Kidney disease not caused by diabetes or hypertension
7. Serum potassium <3.5 mEq/L or >5.1 mEq/L, Serum albumin <2.0 mg/dL
8. GFR <40 mL/min/1.73 m^2 as measured by the Modification of Diet in Renal Disease (MDRD) formula
9. History of hypertensive encephalopathy at any time prior to screening or history of cerebrovascular accident within 12 months prior to screening
10. Transient ischemic cerebral attack during the 6 months prior to screening
11. History of malignancy including leukemia and lymphoma (but not basal cell skin carcinoma) within the past 5 years
12. Pregnant or nursing (females)
13. Known or suspected contraindications to the study medications, including history of allergy to ACE inhibitors and/or to thiazide diuretics or other sulfonamide-derived drug

14. Any surgical or medical condition, which in the opinion of the investigator, could place the patient at higher risk from his/her participation in the study, or prevent the patient from complying with the requirements of the study or completing the study

Other protocol-defined inclusion/exclusion criteria may apply

Number of Subjects

	Aliskiren 150 mg n=25	Aliskiren 300 mg n=24	Aliskiren 600 mg n=22	Placebo n=23	All periods combined n=26
Planned N			24		
Randomised n			26		
Completed n			19		
Reason for discontinuation (n)					
Adverse events	1	0	0	0	1
Abnormal laboratory value	1	1	0	0	2
Abnormal test procedure result	0	0	0	1	1
Protocol violation	0	0	0	1	1
Withdrawal of consent	0	2	0	0	2
Total	**2**	**3**	**0**	**2**	**7**

Demographic and Background Characteristics

		D / A / B / C (N = 6)	A/ C / D / B (N = 7)	B /D / C / A (N = 7)	C / B / D / A (N = 6)
Age (years)	Mean	61.8	60.7	66.1	60.3
	SD	10.72	4.82	5.24	11.13
	Median	61.0	60.0	64.0	57.5
	Range	49–78	55-68	58-73	47-77
Gender -n (%)	Male	5 (83.3)	6 (85.7)	7 (100.0)	5 (83.3)
	Female	1 (16.7)	1 (14.3)	2 (22.2)	1 (16.7)
Race -n (%)	Caucasian	6 (100.0)	7 (100.0)	7 (100.0)	6 (100.0)
Height (cm)	Mean	174.3	178.7	177.0	177.5
	SD	7.17	6.73	6.06	10.60
	Median	177.0	179.0	178.0	180.5
	Range	164-182	179.0-186	168-183	158-187
Weight (kg)	Mean	101.13	107.93	88.71	89.93
	SD	14.539	16.060	10.656	24.644
	Median	96.05	107.50	86.60	84.10
	Range	90.2-129.5	77.5-123.8	74.2-106.7	84.10-135.2
Body Mass Index (kg/m^2)	Mean	33.235	33.891	28.390	28.172
	SD	3.8042	5.7407	3.8340	5.2243
	Median	31.765	35.030	26.390	26.145
	Range	30.14-40.42	25.60-43.86	24.57-33.69	24.72-38.66

A = aliskiren 150 mg; B = aliskiren 300 mg daily; C = aliskiren 600 mg daily; D = placebo.

Primary Objective Result(s)

Between-group comparisons of urine PD variables on day 56.

Parameter	Treatment	N	Least-squares mean on Day 56	Ratio (95% CI) vs Treatment A	Ratio (95% CI) vs Treatment B	Ratio (95% CI) vs Treatment D
UAER, mg/d	A	22	222	NC	NC	0.64 (0.49, 0.83)†
B/line geometric mean, 324.4	B	22	182	0.82 (0.63, 1.06)	NC	0.52 (0.40, 0.67)†
	C	22	167	0.75 (0.57, 0.98)*	0.92 (0.71, 1.19)	0.48 (0.37, 0.62)†
	D	23	350	NC	NC	NC
UACR, mg/g	A	22	142	NC	NC	0.63 (0.48, 0.82)†
B/line geometric mean, 207.5	B	22	115	0.81 (0.62, 1.06)	NC	0.51 (0.39, 0.66)†
	C	22	104	0.73 (0.56, 0.96)*	0.91 (0.70, 1.19)	0.46 (0.36, 0.60)†
	D	23	226	NC	NC	NC
24-h urinary creatinine, µmol/day	A	22	14010	NC	NC	1.02 (0.93, 1.13)
B/line geometric mean 13823	B	22	13976	1.00 (0.90, 1.10)	NC	1.02 (0.93, 1.12)
	C	22	14094	1.01 (0.91, 1.11)	1.01 (0.91, 1.11)	1.03 (0.93, 1.13)
	D	23	13705	NC	NC	NC
24-h urinary sodium, mmol/day	A	22	204	NC	NC	1.18 (1.02, 1.36)*
B/line geometric mean 194.4	B	22	187	0.92 (0.79, 1.06)	NC	1.08 (0.94, 1.25)
	C	22	181	0.89 (0.77, 1.03)	0.97 (0.84, 1.12)	1.05 (0.91, 1.21
	D	23	173	NC	NC	NC
24-h urinary urea, mmol/day	A	22	434	NC	NC	1.06 (0.95, 1.17)
B/line geometric mean 434.9	B	22	414	0.95 (0.86, 1.06)	NC	1.01 (0.91, 1.12)

	C	22	422	0.97 (0.87, 1.08)	1.02 (0.92, 1.13)	1.03 (0.93, 1.14)
	D	23	411	NC	NC	NC

*p≤0.05;.†p≤0.001.

A = aliskiren 150 mg; B = aliskiren 300 mg; C = aliskiren 600 mg; D = placebo; NC = not calculated. All treatments were administered once daily.

Secondary Objective Result(s)

Between-group comparisons of GFR at the end of the study (Day 56)

Parameter	Treatment	N	Least-squares mean on Day 56	Difference (95% CI) vs Treatment A	Difference (95% CI) vs Treat-ment B	Difference (95% CI) vs Treatment D
GFR, mL/min/1.73 m^2	A	23	82	NC	NC	-2.98 (-6.56, 0.60)
B/line mean, 86.5	B	21	80	-2.16 (-5.81, 1.49)	NC	-5.14 (-8.81, -1.48)*
	C	22	79	-3.50 (-7.07, 0.08)	-1.33 (-5.00, 2.33)	-6.48 (-10.12, -2.84)†
	D	22	85	NC	NC	NC

*p≤0.01;.†p≤0.001.

A = aliskiren 150 mg; B = aliskiren 300 mg; C = aliskiren 600 mg; D = placebo; NC = not calculated.

All treatments were administered once daily.

Safety Results

Serious Adverse events - No patients died during this study.

One patient was diagnosed with colon cancer during treatment with aliskiren 600 mg, following colonoscopy for symptoms of development of abdominal pain, dizziness, stool changes and severe anemia. The investigator assessed the event was not immediately life-threatening, but did require hospitalization and the patient was excluded from the study. The patient underwent resection and received chemotherapy. Subsequent follow-up found that the patient died 4 months after the resection. The investigator did not suspect a relationship between this SAE and the study medication, but attributed the SAE to progression of pre-existing colon cancer.

One patient experienced a total of 2 SAEs of syncope. One during treatment with placebo after experiencing nausea, confusion and dizziness, which resulted in hospitalization for a suspected cerebral insult. There were no neurological findings, no paralyses, and no signs of infarction or intra-cerebral hemorrhage on a cerebral computerized tomography scan. The patient was discharged having completely recovered and resumed study treatment. During treatment with aliskiren 600 mg, the patient was hospitalized again with syncope, but again with no neurological findings. The investigator did not suspect a relationship between both SAE and the study medication.

One patient experienced macrohematuria during treatment with aliskiren 600 mg, presenting with signs of urine retention and hematuria which resulted in hospitalization. The patient was found to have an enlarged prostate and recovered completely. His relevant medical history included enlarged prostate and dyslipidemia. The investigator did not suspect a relationship between this SAE and the study medication.

One patient experienced erysipelas during treatment with aliskiren 150 mg after being admitted to hospital with left lower limb erysipelas; symptoms included fever, pain and edema. Following treatment including intravenous antibiotics, the patient completely recovered. The investigator did not suspect a relationship between this SAE and the study medication.

Adverse events - All study treatments were generally well tolerated. The most common AEs reported during the study were dizziness and fatigue. One patient discontinued from the study due to an AE of atrial flutter during treatment with aliskiren 150 mg. The AE was rated as mild in severity and the investigator did not suspect a relationship with study medication.

There was no evidence of a pattern of AEs with any treatment or evidence of toxicity to any major organ system.

Clinical Laboratory results - Some patients exhibited laboratory values out of normal range during the course of the study, but there were no clinically relevant changes or treatment trends. Two patients discontinued the study due to abnormal laboratory values. Potassium levels <3.5 mmol/L were observed in 5 patients at baseline, and 2, 3, 1, and 6 patients during treatment with aliskiren 150 mg, 300 mg, 600 mg, and placebo, respectively. Serum creatinine elevations >176.8 µmol/L occurred in 1 patient during treatment with aliskiren 300 mg and 2 patients during treatment with aliskiren 600 mg. Blood urea nitrogen (BUN) >14.28 mmol/L were observed in 2, 2, and 3 patients during treatment with aliskiren 150 mg, 300 mg, and 600 mg, respectively.

ECG /Edema assessments – There were no notable, clinically relevant changes in ECG findings or edema assessments during the study.

Vital signs- There were no clinically relevant changes in vital signs.

Concomitant medication - All usual antihypertensive medications were discontinued during screening. During the 4-week run-in period, the 32-week treatment period, and the 8-week wash-out period, all patients were treated with furosemide to control fluid retention and BP. Furosemide was initiated at a dosage of 40 mg daily and titrated on a case-by-case basis at the discretion of the investigator. Patients received a number of oral antidiabetic drugs or insulin for type 2 diabetes and drugs for dyslipidemia before and during the study. Several patients received other medication but none of the concomitant therapies used during the study were expected to adversely affect patient safety or interpretation of the data.

No safety or tolerability issues were evident based on patient discontinuations, ECGs, clinical laboratory values, or physical examination findings.

Adverse Events by System Organ Class

	Aliskiren 150 mg n=25	Aliskiren 300 mg n=24	Aliskiren 600 mg n=22	Placebo n=23
Total AEs	**6 (24.0)**	**11 (45.8)**	**9 (40.9)**	**9 (39.1)**
Blood and lymphatic system disorders	0 (0.0)	0 (0.0)	1 (4.5)	0 (0.0)
Cardiac disorders	1 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	1 (4.0)	2 (8.3)	0 (0.0)	2 (8.7)
Site conditions/general disorders/administration	0 (0.0)	1 (4.2)	2 (9.1)	0 (0.0)
Infections and infestations	1 (4.0)	2 (8.3)	2 (9.1)	1 (4.3)
Injury, poisoning and procedural complications	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.3)
Metabolism and nutrition disorders	0 (0.0)	0 (0.0)	1 (4.5)	0 (0.0)
Musculoskeletal and connective tissue disorders	1 (4.0)	2 (8.3)	0 (0.0)	2 (8.7)
Unspecified	0 (0.0)	0 (0.0)	1 (4.5)	0 (0.0)
Nervous system disorders	1 (4.0)	2 (8.3)	3 (13.6)	2 (8.7)
Psychiatric disorders	1 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)
Renal and urinary disorders	0 (0.0)	1 (4.2)	2 (9.1)	0 (0.0)
Reproductive system and breast disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.3)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	0 (0.0)	1 (4.5)	0 (0.0)
Skin and subcutaneous tissue disorders	0 (0.0)	2 (8.3)	2 (9.1)	1 (4.3)
Surgical and medical procedures	1 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vascular disorders	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)

Number (%) of patients with AEs occurring in at least 5% of patients

	Aliskiren 150 mg n=25	Aliskiren 300 mg n=24	Aliskiren 600 mg N=22	Placebo N=23	Overall n=26
Total AEs	**6 (24.0)**	**11 (45.8)**	**9 (40.9)**	**9 (39.1)**	**18 (69.2)**
Dizziness	1 (4.0)	1 (4.2)	1 (4.5)	1 (4.3)	4 (15.4)
Fatigue	0 (0.0)	1 (4.2)	2 (9.1)	0 (0.0)	2 (7.7)

Serious Adverse Events and Deaths

	Aliskiren 150 mg	Aliskiren 300 mg	Aliskiren 600 mg	Placebo
No. (%) of subjects studied	25	24	22	23
No. (%) of subjects with AE(s)	6 (24.0)	11 (45.8)	9 (40.9)	9 (39.1)
Number (%) of subjects with serious or other significant events	n (%)			n (%)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
SAE(s)	1 (4.0)	0 (0.0)	3 (13.6)	1 (4.3)
Discontinued due to SAE(s)	0 (0.0)	0 (0.0)	1 (4.5)	0 (0.0)

Four patients experienced a total of 5 SAEs but no patients during the study. One patient received 600 mg Aliskiren and experienced colon cancer and was discontinued from the study. Two patients also received 600 mg and experienced syncope and macrohematuria. One patient having received 150 mg Aliskiren experienced erysipelas. One patiend having received placebo experienced syncope. No cases were judged to be related to study treatment.

Other Relevant Findings

N/A

Date of Clinical Trial Report

14-Jul-09

Date Inclusion on Novartis Clinical Trial Results Database

01-Feb-2010

Date of Latest Update

N/A