Sponsor

Novartis

Generic Drug Name

Aliskiren

Therapeutic Area of Trial

Cardiovascular

Approved Indication

Investigational Drug

Study Number

CSPP100A2242

Title

An open-label study to evaluate the magnitude and time course of the antiproteinuric and blood pressure lowering effects of renin inhibition with Aliskiren in patients with type 2 diabetes, history of hypertension and incipient or established nephropathy

Phase of Development

Phase II

Study Start/End Dates

28 Sep 2005 to 13 Nov 2006

Study Design/Methodology

This was a single-center, open-label, 1-period, 1-treatment, 2-washout period study in patients with type 2 diabetes with a history of hypertension and incipient and/or established nephropathy (urinary albumin excretion ≥100 but ≤2000 mg/day). All patients were treated with aliskiren 300 mg once daily for 28 days. Both before and after the treatment period, there was a washout period of 1 month. During both washout periods, patients were instructed to discontinue any antihypertensive drugs. During the entire study, all patients were treated with 40 mg of furosemide to control sodium/fluid retention and blood pressure (BP); the dosage could be titrated at the discretion of the investigator. During the washout periods, patients were instructed to measure their BP at home twice a week and to report their values weekly by phone to the study center.

Centres

There was 1 centre in Denmark

Publication

Persson F, Rossing P et al. Time course of the antiproteinuric and antihypertensive effects of direct renin inhibition in type 2 diabetes. Kidney International. 2008; Mar 12; 73:1419-1425

Objectives

Primary objective(s)

- To investigate the time course of the anti-proteinuric and BP lowering effects of renin inhibition with Aliskiren in patients with Type 2 diabetes with a history of hypertension and incipient or established nephropathy.

Secondary objective(s)

- To measure blood pressure changes over time during the onset and offset of renin inhibition with Aliskiren.
- To investigate whether there is a change on biomarkers of inflammation and cardiovascular risk during renin inhibition with Aliskiren.

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

Oral tablets of Aliskiren 300 mg.

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

NA

Criteria for Evaluation

Primary variables

The primary endpoint was urinary albumin/creatinine ratio (UACR) which was measured from daily morning urine collections. 24-hour urine collections were taken at baseline, throughout the treatment period and during washout period 2 to measure albumin and creatinine concentrations.

Secondary variables/Pharmacodynamic

Office blood pressure measurements and 24-hour ambulatory blood pressure monitoring (ABPM) at baseline, during the treatment period and during washout period 2 were performed.

Blood tests were performed at baseline, during the treatment period and during washout period 2 to measure: (1) plasma renin-angiotensin system (RAS) biomarkers including: plasma renin concentration, plasma renin activity (PRA), angiotensin I (Ang I), angiotensin II (Ang II) and aldosterone and (2) other biomarkers including: high-sensitivity C-reactive protein (hsCRP), von Willebrand Factor (VWF), vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), plasminogen activator inhibitor-1 (PAI-1), N-terminal pro-brain natriuretic peptide (NT-proBNP) and asymmetric dimethylarginine (ADMA).

Safety and tolerability

Safety and tolerability assessments included: monitoring and recording of all adverse events (AEs) and serious AEs (SAEs), recording of all concomitant medications/significant non-drug therapies; physical examinations and vital signs; and routine blood laboratory tests (chemistry, hematologic profile), urine analyses and electrocardiograms (ECG).

Statistical Methods

Descriptive summaries were provided for all pharmacodynamic measurements. The UACR was used as an index of the drug-induced anti-proteinuric effect. The BP lowering effect was assessed by measuring systolic BP (SBP) and diastolic BP (DBP) during 24-hour ABPM.
The log-transformed (base e) values of UACR from Days 1 to 54 were analyzed using a mixed model in which the term "Patient" was fitted as a random effect and the term "Day" was fitted as a fixed effect. Days 2 to 52 were divided into intervals of 3 consecutive days (i.e., Days 2-4, Days 5-7 etc.) and Days 53 and 54 were averaged. Pre-dose Day 1 values for UACR served as baseline for all analyses. Comparisons of each 2- or 3-day interval average with baseline were made using appropriate estimate statements. Point estimates and corresponding 95% confidence intervals (CI) were reported.
The severity of albuminuria prior to study entry was evaluated based on historical UACR values over the previous 2 years and categorized as follows:

- Normal: UACR <30 mg/g
- Microalbuminuria: UACR 30-300 mg/g
- Macroalbuminuria: UACR >300 mg/g.

Serial measurements of UACR were analyzed as the change in UACR compared to baseline using the Fisher's exact test.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

- Male and/or female patients from 30-80 years of age with a diagnosis of Type 2 diabetes (WHO criteria).
- Incipient or established diabetic nephropathy (urinary albumin excretion ≥ 100 mg/day but ≤ 2000 mg/day).
- GFR ≥ 40 ml/min in the last 4 months.
- Female patients had to be postmenopausal.
- Patients on anti-hypertensive with blood pressure ≥ 135/85 mm Hg but lower than 170/105 mm Hg at baseline AND patients must have been on stable antihypertensive medications for at least 8 weeks prior to baseline. Newly diagnosed hypertensive patients had to have a blood pressure ≥ 135/85 mm Hg but lower than 170/105 mm Hg at baseline.
- Patients must have been on stable hypoglycemic medications for at least 8 weeks prior.
- Patients had to be willing and medically able to discontinue all ACE inhibitors, angiotensin receptor antagonists, aldosterone receptor antagonist and potassium sparing diuretic medications for the duration of the study.
- Oral body temperature within the range 35.0-37.5 °C

Exclusion criteria

- Severe Hypertension Grade 3 WHO classification (MSDBP ≥ 110 mmHg and/or MSSBP ≥ 180 mmHg)
- Aspirin treatment >1g/day or regular use of NSAIDs
- Kidney disease not caused by diabetes or hypertension, serum potassium < 3.5 or > 5.1 mEq/L, GFR < 40 ml/min/1.73m^{2,}, serum albumin < 2.0mg/dL
- History of hypertensive encephalopathy or stroke.
- Current diagnosis of heart failure (NYHA Class II-IV), history of myocardial infarction, unstable angina pectoris, coronary bypass surgery, or any percutaneous coronary intervention (PCI), Second or third degree heart block without a pacemaker, Concurrent potentially life threatening arrhythmia or symptomatic arrhythmia
- Clinically significant valvular heart disease
- Type 1 diabetes mellitus or uncontrolled Type II diabetes mellitus (HbA1C >11 %)
- History of malignancy including leukemia and lymphoma (but not basal cell skin carcinoma) within the past five years
- Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of study drugs including, but not limited to, any of the following:
    - History of major gastrointestinal tract surgery, currently active or previously active inflammatory bowel disease, currently active gastritis, duodenal or gastric ulcers, or gastrointestinal/rectal bleeding
    - Any history of pancreatic injury, pancreatitis or evidence of impaired pancreatic function/injury as indicated by abnormal lipase or amylase
    - Evidence of hepatic disease as determined by SGOT/AST or SGPT/ALT values Gamma GT, a history of hepatic encephalopathy, esophageal varices, or of portocaval shunt
    - Current treatment with cholestyramine or cholestipol resins

- History of immunocompromise, including a positive HIV (ELISA and Western blot) test result, positive Hepatitis B surface antigen (HBsAg) or Hepatitis C test result.
- History of drug or alcohol abuse
- 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, Use of any prescription drug or over-the-counter (OTC) medication prohibited by protocol.
- Patients who previously participated in any Aliskiren study.
- Pregnant or nursing woman.

Number of Subjects

	Aliskiren
Planned N	18
Randomised n	15
Completed n (%)	13 (86.45)
Withdrawn n (%)	2 (13.3)
Withdrawn due to adverse events n (%)	2 (13.3)
Withdrawn due to lack of efficacy n (%)	0 (0)
Withdrawn for other reasons n (%)	0 (0)

Demographic and Background Characteristics

	Aliskiren
N (%)	15 (100)
Females : males	2 (13.3) :13 (86.7)
Mean age, years (SD)	63.5 (10.32)
Mean height, cm (SD)	174.3 (5.14)
Mean weight, kg (SD)	99.98 (16.11)
Mean body mass index, kg/m2, (SD)	32.88 (4.88)
Race Caucasian n (%)	15 (100)
Historical albuminuria classification: (based on patients data over a 2 year period) Microalbuminuria Macroalbuminuria	 10 (66.7) 5 (33.3)

Primary Objective Result(s)

Ratio of geometric means relative to baseline for urinary albumin/creatinine ratio

Timepoint	**Ratio of geometric means (relative to baseline [Day 1])**	**95% CI for ratio**	**P-value**
Treatment period			
Days 2 to 4	0.83	(0.69, 0.99)	0.040
Days 5 to 7	0.71	(0.60, 0.85)	<0.001
Days 8 to 10	0.69	(0.58, 0.82)	<0.001
Days 11 to 13	0.62	(0.52, 0.74)	<0.001

Days 14 to 16	0.64	(0.53, 0.76)	<0.001
Days 17 to 19	0.63	(0.53, 0.75)	<0.001
Days 20 to 22	0.60	(0.51, 0.72)	<0.001
Days 23 to 25	0.60	(0.51, 0.72)	<0.001
Days 26 to 28	0.56	(0.47, 0.67)	<0.001
Washout period 2			
Days 29 to 31	0.62	(0.52, 0.75)	<0.001
Days 32 to 34	0.69	(0.57, 0.82)	<0.001
Days 35 to 37	0.74	(0.62, 0.89)	0.001
Days 38 to 40	0.81	(0.67, 0.97)	0.024
Days 41 to 43	0.87	(0.73, 1.04)	0.136
Days 44 to 46	0.91	(0.76, 1.10)	0.325
Days 47 to 49	0.88	(0.73, 1.05)	0.159
Days 50 to 52	0.87	(0.72, 1.05)	0.138
Days 53 to 54	0.82	(0.67, 1.01)	0.058

At baseline, mean (SD) UACR was 326 (457.4) mg/g and ranged from 39 to 1725 mg/g.

Values for UACR were significantly lower than baseline values throughout the entire treatment period. UACR values decreased progressively during treatment compared to baseline with a 17% reduction on Days 2 to 4, a 31% reduction on Days 8 to 10 and a maximum reduction of 44% at the end of the treatment period (Days 26 to 28).

During washout period 2, values for UACR remained below baseline for up to 12 days (Day 29 to 40). Although UACR tended to remain below baseline for the remainder of the washout period, the differences were not statistically significant.

Two patients had macroalbuminuria at baseline. The maximum reduction in UACR during treatment was 68% and 77%.

The results from the 13 patients with microalbuminuria at baseline (excluding the 2 patients with macroalbuminuria) were similar to the results from the all patient analysis.

The correlation between the reduction from baseline in UACR on Days 26 to 28 and the baseline UACR was 0.992 with a corresponding p-value of <0.001, suggesting that treatment had a greater beneficial effect on UACR in patients with more severe albuminuria at baseline.

Secondary Objective Result(s)

1. Summary of change from baseline in systolic blood pressure

Parameter	Timepoint	Difference between arithmetic means (relative to baseline [Day -1])	95% CI for difference	P-value
24-hour SBP (mm Hg)	Treatment period			
	Day 3	-2.71	(-8.82, 3.40)	0.381
	Day 7	-6.10	(-11.84, -0.37)	0.037
	Day 14	-8.33	(-14.18, -2.49)	0.006
	Day 28	-6.43	(-12.41, -0.45)	0.035
	Washout period 2			
	Day 31	-7.58	(-13.70, -1.45)	0.016
	Day 35	-3.98	(-10.11, 2.15)	0.200
	Day 42	-2.44	(-8.42, 3.55)	0.421
	Day 54	-2.94	(-9.07, 3.18)	0.343
Daytime SBP (mm Hg)	Treatment period			
	Day 3	-3.06	(-9.67, 3.55)	0.360
	Day 7	-7.30	(-13.50, -1.10)	0.022
	Day 14	-9.66	(-15.98, -3.34)	0.003
	Day 28	-6.99	(-13.46, -0.52)	0.034
	Washout period 2			
	Day 31	-9.07	(-15.69, -2.45)	0.008
	Day 35	-4.66	(-11.28, 1.97)	0.166
	Day 42	-2.35	(-8.82, 4.12)	0.472
	Day 54	-1.76	(-8.39, 4.87)	0.599
Nighttime SBP (mm Hg)	Treatment period			
	Day 3	0.36	(-7.95, 8.67)	0.932
	Day 7	0.69	(-7.12, 8.49)	0.862
	Day 14	-0.36	(-8.32, 7.59)	0.928
	Day 28	0.81	(-7.33, 8.95)	0.844
	Washout period 2			
	Day 31	-1.15	(-9.43, 7.14)	0.784
	Day 35	2.11	(-6.22, 10.45)	0.616
	Day 42	-1.69	(-10.02, 6.64)	0.688
	Day 54	0.93	(-7.36, 9.22)	0.824

1. Summary of change from baseline in diastolic blood pressure

Parameter	Timepoint	Difference between arithmetic means (relative to baseline [Day -1])	95% CI for difference	P-value
24-hour DBP (mm Hg)	Treatment period			
	Day 3	-2.82	(-7.66, 2.02)	0.250
	Day 7	-3.73	(-8.27, 0.81)	0.106
	Day 14	-3.66	(-8.29, 0.97)	0.120
	Day 28	-2.52	(-7.25, 2.22)	0.294
	Washout period 2			
	Day 31	-4.23	(-9.08, 0.62)	0.087
	Day 35	-0.38	(-5.24, 4.47)	0.875
	Day 42	-2.33	(-7.07, 2.41)	0.332
	Day 54	1.28	(-3.57, 6.14)	0.601
Daytime DBP (mm Hg)	Treatment period			
	Day 3	-3.52	(-10.07, 3.03)	0.289
	Day 7	-3.74	(-9.88, 2.41)	0.230
	Day 14	-3.90	(-10.17, 2.36)	0.219
	Day 28	-2.36	(-8.76, 4.05)	0.467
	Washout period 2			
	Day 31	-4.38	(-10.94, 2.18)	0.188
	Day 35	0.11	(-6.46, 6.67)	0.974
	Day 42	-1.70	(-8.11, 4.71)	0.600
	Day 54	4.37	(-2.20, 10.93)	0.190
Nighttime DBP (mm Hg)	Treatment period			
	Day 3	2.53	(-2.76, 7.81)	0.344
	Day 7	-2.60	(-7.57, 2.36)	0.300
	Day 14	-2.12	(-7.18, 2.93)	0.406
	Day 28	0.04	(-5.14, 5.21)	0.988
	Washout period 2			
	Day 31	-2.35	(-7.62, 2.91)	0.377
	Day 35	0.68	(-4.62, 5.98)	0.800
	Day 42	-2.58	(-7.87, 2.72)	0.337
	Day 54	0.55	(-4.72, 5.82)	0.835

1. Summary of change from baseline in pulse rate

Parameter	Timepoint	Difference between arithmetic means (relative to baseline [Day -1])	95% CI for difference	P-value

24-hour pulse rate (bpm)	Treatment period			
	Day 3	0.39	(-2.57, 3.35)	0.793
	Day 7	-0.29	(-3.06, 2.48)	0.837
	Day 14	1.21	(-1.62, 4.04)	0.398
	Day 28	-0.50	(-3.39, 2.39)	0.732
	Washout period 2			
	Day 31	0.13	(-2.83, 3.10)	0.929
	Day 35	-1.26	(-4.23, 1.71)	0.401
	Day 42	1.37	(-1.53, 4.26)	0.350
	Day 54	-1.44	(-4.41, 1.52)	0.336

At baseline, mean (SD) 24-hour BP was 143/75 (12.8/9.6) mm Hg, daytime BP was 147/77 (12.3/10.0) mm Hg and nighttime BP was 130/68 (14.3/10.0) mm Hg.

Average values for 24-hour SBP decreased from baseline during the treatment period, with statistically significant reductions of between 6.1 mm Hg and 8.3 mm Hg being observed on Days 7, 14 and 28. The average values of the daytime SBP showed similar results to the 24-hour SBP. There were no apparent trends in the changes from baseline in the average values of the nighttime SBP.

During the washout period, SBP tended to remain below baseline values, although the difference was statistically significant only on Day 31.

Average values for 24-hour DBP, daytime DBP and nighttime DBP were not significantly different from baseline during the treatment and washout periods.

There were no statistically significant changes from baseline in the average values of the 24-hour pulse rate. The results from the microalbuminuria group were similar to the results from all patients.

2. Ratio of geometric means relative to baseline for plasma renin concentration, PRA, Ang I and Ang II

Parameter	**Timepoint**	**Ratio of geometric means (relative to baseline [Day -1])**	**95% CI for ratio**	**P-value**
Plasma renin concentration (ng/L)	Treatment period			
	Day 7	5.04	(3.81, 6.66)	<0.001
	Day 14	5.34	(4.02, 7.11)	<0.001
	Day 28	5.61	(4.24, 7.42)	<0.001
	Washout period 2			
	Day 35	3.37	(2.51, 4.51)	<0.001
	Day 54	1.73	(1.30, 2.30)	<0.001
PRA (ng/mL/h)	Treatment period			
	Day 7	0.23	(0.14, 0.37)	<0.001
	Day 14	0.27	(0.17, 0.44)	<0.001
	Day 28	0.33	(0.21, 0.54)	<0.001

	Washout period 2			
	Day 35	0.51	(0.31, 0.85)	0.010
	Day 54	0.82	(0.50, 1.34)	0.420
Ang I (pmol/L)	Treatment period			
	Day 7	0.20	(0.15, 0.28)	<0.001
	Day 14	0.20	(0.15, 0.27)	<0.001
	Day 28	0.19	(0.14, 0.25)	<0.001
	Washout period 2			
	Day 35	0.32	(0.24, 0.44)	<0.001
	Day 54	0.58	(0.43, 0.79)	<0.001
Ang II (pmol/L)	Treatment period			
	Day 7	0.42	(0.31, 0.56)	<0.001
	Day 14	0.50	(0.36, 0.68)	<0.001
	Day 28	0.57	(0.42, 0.77)	<0.001
	Washout period 2			
	Day 35	0.66	(0.48, 0.90)	0.010
	Day 54	0.93	(0.68, 1.27)	0.663

As expected, treatment with aliskiren resulted in statistically significant increases in plasma renin concentration and decreases in PRA, Ang 1 and Ang II. Comparable reductions in Ang I levels were observed on Days 28 (81%) and 7 (80%) (p=0.546). The reduction in Ang II levels on Day 28 (43%) tended to be slightly smaller than the reduction on Day 7 (58%) (p=0.044).

During washout period 2, levels of plasma RAS biomarkers gradually returned towards baseline values. Mean levels of aldosterone were 81.8 ng/L at baseline, 72.5 ng/L at the end of treatment and 85.5 ng/L at the end of the study.

The PRA/plasma renin concentration ratio remained suppressed during the treatment period and began to gradually increase towards baseline during washout period 2. At no timepoint was there a statistically significant correlation between Ang I and the PRA/plasma renin concentration ratio or between the percent change from baseline in the UACR and log-transformed PRA. A significant correlation between log-transformed Ang I and PRA was observed on Days 14 (r=0.543, p=0.0448), 35 (r=0.748, p=0.0033) and 54 (r=0.660, p=0.0102).

2. Mean (SD) concentrations of hsCRP, VWF, VCAM-1, ICAM-1, PAI-1, NT-proBNP and ADMA

Study day Variable	**hsCRP (mg/L)**	**VWF (%)**	**VCAM-1 (µg/L)**	**ICAM-1 (µg/L)**	**PAI-1 (µg/L)**	**NT-proBNP (pmol/L)**	**ADMA (µmol/L)**
-1 (Baseline)							
Mean	3.333	151.467	885.667	637.067	97.667	337.667	0.487
SD	3.4723	51.6414	302.9787	293.9328	48.5735	72.8508	0.0516
28 (End of treatment)							
Mean	3.687	144.067	955.867	618.533	134.800	307.867	0.493
SD	3.8669	44.8879	471.0837	262.5963	86.5689	60.1508	0.0594

End of study							
Mean	4.179	144.143	913.143	617.929	130.714	318.286	0.500
SD	5.2908	47.8119	342.0456	253.1085	99.0574	58.6258	0.0555

There were no relevant changes in levels of hsCRP, VWF, VCAM-1, ICAM-1, PAI-1, NT-proBNP or ADMA on-treatment or during washout compared to baseline.

Safety Results

Vital signs- Blood pressure was found to be above the safety limit per the investigator in one patient . One patient was discontinued on Day 35 of washout period 2 following sitting and standing BP measurements of 148/100 and 158/98 mm Hg, respectively.

ECG - There were no changes in results at the end of the study compared to baseline. Three patients entered the study with clinically significant abnormalities: One had a pacemaker, one a history of prior myocardial infarction and one left anterior hemiblock.

Clinical Laboratory results - Most patients exhibited multiple clinical laboratory values outside the normal range, most of which were present at screening and/or baseline as would be expected with this patient population.

Concomitant medication -All patients were required to discontinue any drugs approved for the treatment of hypertension prior to Visit 2, even if prescribed for another indication. Data after Day 28 for one patient were excluded from analysis summaries of pharmacodynamic variables because the patient took losartan during the washout period 2 on Day 29.

Several other patients initiated concomitant therapy post-baseline: One was treated with Novomix 30 for blood glucose control, although this patient did not have a related reported AE; one received Insulatard and Novomix 30 for blood glucose control, which accompanied a reported AE of increased insulin requirement; and one used a non-drug orthopedic device for the treatment of gout, reported as an AE. None of these concomitant therapies was expected to adversely affect the integrity of the study results or patient safety.

Adverse events - There were no deaths or SAEs reported during the treatment period. One patient died during the initial washout period. This patient did not receive aliskiren and the cause of death was unknown.

A total of 4 (26.7%) patients experienced AEs during the study. The most common AE, which occurred in 2 of 15 (13.3%) patients, was symptoms suggestive of hypoglycemia. Both of these events were judged by the investigator to be mild, unrelated to study medication and occurred during washout period 2 (Days 35 and 38). Glucose levels were not available for either patient at the time of these events. One of the patients who experienced hypoglycemia had received Glucophage throughout the study; the other patient had received Insulatard and Novo Mix 30 at various times during the treatment period and Novo Mix 30 at various times during washout period 2.

One patient discontinued the study due to an AE of uncontrolled hypertension on Day 42 (washout period 2) following sitting and standing BP measurements of 170/80 and 177/87 mm Hg, respectively.

Adverse Events by System Organ Class

Summary of patients with adverse events by body system and preferred term

Body system Preferred term	Aliskiren
Any body system	4 (26.7)
Infections and infestations	1 (6.7)
Nasopharyngitis	1 (6.7)

Metabolism and nutrition disorders	3 (20.0)
Gout	1 (6.7)
Hypoglycemia	2 (13.3)
Increased insulin requirement	1 (6.7)
Musculoskeletal and connective tissue disorders	1 (6.7)
Pain in extremity	1 (6.7)
Skin and subcutaneous tissue disorders	1 (6.7)
Rash	1 (6.7)
Vascular disorders	1 (6.7)
Hypertension	1 (6.7)

Serious Adverse Events and Deaths NA
Other Relevant Findings NA
Date of Clinical Trial Report 16 Feb 2007
Date Inclusion on Novartis Clinical Trial Results Database 24 July 2008
Date of Latest Update NA