Sponsor

Novartis

Generic Drug Name

Aliskiren

Trial Indication(s)

Hypertension

Protocol Number

CSPP100A2303

Protocol Title

An eight-week, randomized, double-blind, multi-center, active controlled, parallel group study to evaluate the safety and efficacy of an aliskiren based regimen compared to a lisinopril based regimen in patients with uncomplicated severe hypertension

Clinical Trial Phase

Phase III

Phase of Drug Development

Phase III

Study Start/End Dates

28 February 2005 to 25 November 2005

Study Design/Methodology

This was a multicenter, randomized, double-blind, double-dummy, active-controlled, parallel group study of aliskiren compared to lisinopril with the potential addition of hydrochlorothiazide (HCTZ) in adult patients with uncomplicated severe hypertension (mean sitting diastolic blood pressure [msDBP] = 105 mmHg and < 120 mmHg).

Eligible patients discontinued their current antihypertensive medications and entered a washout period. Patients who met the blood pressure eligibility criteria (msDBP =105 mmHg and <120 mmHg) after the washout period could proceed directly to randomization. Patients who did not meet the blood pressure eligibility criteria entered into a single-blind placebo run- in period of 1 to 3 weeks duration in order to establish a baseline study blood pressure (BP) and eligibility for randomization.

Eligible patients were randomized to receive aliskiren 150 mg or lisinopril 20 mg in a 2:1 ratio. Patients were titrated to goal BP (< 140 mmHg systolic and 90 mmHg diastolic) at 4-week intervals (unless early titration was required) following these three steps:
Step 1: Aliskiren 150 mg or Lisinopril 20 mg.
Step 2: Aliskiren 300 mg or Lisinopril 40 mg.
Step 3: Aliskiren 300 mg + HCTZ 25 mg or Lisinopril 40 mg + HCTZ 25 mg.

Centers

26 centers within 3 countries in Europe:

Germany [12], Spain [9], Hungary [5]

Objectives:

The primary objective of this study was:

- To evaluate the overall safety of a regimen of aliskiren 150 mg potentially titrated to 300 mg O.D. with the potential addition of hydrochlorothiazide (HCTZ) compared to a regimen of lisinopril 20 mg potentially titrated to 40 mg O.D. with the potential addition of HCTZ in patients with uncomplicated severe hypertension (msDBP ≥ 105 mmHg and < 120 mmHg).

The secondary objectives of this study were:

- To evaluate the blood pressure lowering effects of a regimen of aliskiren 150 mg potentially titrated to 300 mg O.D. with the potential addition of HCTZ compared to a regimen of lisinopril 20 mg potentially titrated to 40 mg O.D. with the potential addition of HCTZ in patients with uncomplicated severe hypertension (msDBP ≥ 105 mmHg and < 120 mmHg).
- To evaluate the proportion of patients achieving a successful response (msDBP < 90 mmHg or a reduction of ≥ 10 mmHg from baseline) for all treatment groups.

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

Novartis supplied the investigators with all study medication sufficient for the course of the study. Both doses of lisinopril (20 mg and 40 mg), placebo to match lisinopril, HCTZ and placebo to match HCTZ were provided as capsules. Aliskiren 150 mg and its placebo were provided as a film coated tablets. Batch numbers of study medication used are listed as below.

Study drug batch numbers

Study drug	Batch number(s)
Aliskiren 150 mg tablet	X198FA
Lisinopril 20 mg capsule	X330 1004
Lisinopril 40 mg capsule	X331 1004
HCTZ 25 mg capsule	X081 0304
Placebo to match aliskiren 150 mg tablet	X152DA
Placebo to match lisinopril 20 mg and 40 mg capsules	X313 1004
Placebo to match HCTZ 25 mg capsule	X182 0404

Statistical Methods

The primary objective of this study was to evaluate the overall safety of a regimen of aliskiren 150 mg potentially titrated to 300 mg O.D with potential addition of hydrochlorothiazide (HCTZ) compared to a regimen of lisinopril 20 mg potentially titrated to 40 mg O.D with potential addition of HCTZ in patients with uncomplicated severe hypertension (msDBP ≥ 105 mmHg and < 120 mmHg).

Descriptive statistics for the blood pressure analyses (n, mean, standard deviation, minimum, median, and maximum) were summarized by randomized treatment group, visit and at endpoint.
The percent of responders (trough msDBP < 90 mmHg and/or at least 10 mmHg reduction from baseline in msDBP) during the double-blind period were provided by randomized treatment group, visit and at endpoint.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria
Patients were eligible for inclusion if they met all of the following criteria:
• Outpatients 18 years of age and older.
• Male or female patients were eligible. Female patients must have been either postmenopausal for at least one year, surgically sterile, or using effective contraceptive methods such as oral contraceptives, barrier method with spermicide or an intrauterine device.
• Patients with uncomplicated severe hypertension. Patients must have had a msDBP ≥ 85mmHg and < 120 mmHg at Visit 2 and a msDBP ≥ 105 mmHg and < 120 mmHg at Visit 3 (day 1 Randomization).
• Patients who were eligible and able to participate in the study, and who consented to do so after the purpose and nature of the investigation had been clearly explained to them (written informed consent).

Exclusion criteria
Patients with any of the following physiological states or concomitant medical conditions were excluded from participation in the study.
• Patients who previously entered an aliskiren study and who qualified to be randomized or enrolled into active drug treatment period.
• History or evidence of a secondary form of hypertension, including but not limited to any of the following: coarctation of the aorta, hyperaldosteronism, unilateral or bilateral renal artery sternosis, Cushing's disease, pheochromocytoma, polycystic kidney disease.
• Patients on combination antihypertensive therapy that included more than 3 classes of antihypertensive medication.
• Diabetic patients requiring insulin treatment.
• Type 2 diabetics defined by fasting glycosylated hemoglobin (HbA1c) > 8% at Visit 1

• Known Keith-Wagener grade III or IV hypertensive retinopathy.
• History of hypertensive encephalopathy or cerebrovascular event to include stroke or transient ischemic cerebral attack (TIA).
• Previous or current diagnosis of heart failure of any class.
• History of myocardial infarction, coronary bypass surgery, or any percutaneous coronary intervention (PCI) at any time prior to Visit 1.
• Any type of angina pectoris (treated or untreated).
• Second or third degree heart block without a pacemaker.
• Concurrent potentially life threatening arrhythmia or symptomatic arrhythmia.
• Clinically significant valvular heart disease.
• Serum sodium less than the lower limit of normal, serum potassium < 3.5 mEq/L or ≥ 5.5 mEq/L or dehydration, at Visit 1.

Participant Flow Table

Patient disposition for each randomized treatment group during double-blind period (Enrolled population)

	Aliskiren n(%)	Lisinopril n (%)	Total n(%)
Number (%) of patients			
Enrolled			194
Randomized	125	58	183
Completed	111 (88.8)	54 (93.1)	165 (90.2)
Discontinued	14 (11.2)	4 (6.9)	18 (9.8)
Main reason for discontinuation			
Administrative problems	3 (2.4)	0 (0.0)	3 (1.6)
Adverse event(s)	4 (3.2)	2 (3.4)	6 (3.3)
Protocol violation	1 (0.8)	0 (0.0)	1 (0.5)
Subject withdrew consent	4 (3.2)	1 (1.7)	5 (2.7)
Unsatisfactory therapeutic effect	2 (1.6)	1 (1.7)	3 (1.6)

Baseline Characteristics

Demographic and baseline characteristics (Randomized population)

Demographic characteristic	Aliskiren N=125	Lisinopril N=58	Total N=183
Sex – n (%)			
Female	55 (44.0)	24 (41.4)	79 (43.2)
Male	70 (56.0)	34 (58.6)	104 (56.8)
Race – n (%)			
Caucasian	124 (99.2)	58 (100)	182 (99.5)
Other	1 (0.8)	0 (0.0)	1 (0.5)
Ethnicity – n (%)			
Hispanic or Latino	29 (23.2)	12 (20.7)	41 (22.4)
Other	96 (76.8)	46 (79.3)	142 (77.6)
Age groups – n (%)			
< 65 years	97 (77.6)	46 (79.3)	143 (78.1)
≥ 65 years	28 (22.4)	12 (20.7)	40 (21.9)
Age groups – n (%)			
< 75 years	116 (92.8)	55 (94.8)	171 (93.4)
≥ 75 years	9 (7.2)	3 (5.2)	12 (6.6)
Age (years)			
n	125	58	183
Mean (SD)	55 (12.3)	56 (11.1)	55 (11.9)
Height (cm)			
n	124	58	182
Mean (SD)	168 (9.6)	167 (8.9)	168 (9.4)

Weight (kg)			
n	125	58	183
Mean (SD)	86 (16.6)	85 (20.0)	86 (17.7)
Body Mass Index (kg/m^2)			
n	124	58	182
Mean (SD)	31 (5.2)	30 (6.3)	30 (5.6)
Obesity – n (%)			
BMI < 30 (kg/m^2)	64 (51.2)	33 (56.9)	97 (53.0)
BMI ≥ 30 (kg/m^2)	60 (48.0)	25 (43.1)	85 (46.4)
Waist circumference (cm)			
n	123	56	179
Mean (SD)	103 (14.2)	101 (12.4)	102 (13.7)
Waist circumference (cm), male			
n	68	33	101
Mean (SD)	105 (10.5)	104 (11.4)	105 (10.7)
Waist circumference (cm), female			
N	55	23	78
Mean (SD)	100 (17.5)	95 (12.1)	99 (16.2)
Duration of hypertension history (years)			
n	124	55	179
Mean (SD)	9 (9.3)	10 (7.4)	9 (8.7)
Metabolic syndrome [#] – n (%)			
Yes	66 (52.8)	34 (58.6)	100 (54.6)
No	59 (47.2)	24 (41.4)	83 (45.4)
Diabetes [##] – n (%)			
Yes	15 (12.0)	8 (13.8)	23 (12.6)
No	110 (88.0)	50 (86.2)	160 (87.4)

[#] Metabolic syndrome=Yes, if any 3 of the following are true:
1. Waist circumference (>102 cm (or 40 in) for men or > 88 cm (or 35 in) for women); 2. Triglycerides >= 150 mg/dL (or 1.69 mmol/L); 3. HDL cholesterol (1.04 mmol/L (or <40 mg/dL) for men or 1.29 mmol/L (or <50 mg/dL) for women); 4. Blood pressure SBP>= 130 or DBP>=85 mmHg; 5. Fasting glucose >=6.1 mmol/L (or 110 mg/dL), [##] From medical history. SD = standard deviation

Summary of baseline values for mean sitting diastolic and systolic blood pressure, standing diastolic and systolic blood pressure by randomized treatment group (Randomized population)

	Aliskiren N=125	Lisinopril N=58	Total N=183
msDBP (mmHg)			
n	125	58	183
Mean (SD)	108.4 (3.1)	108.0 (2.5)	108.3 (3.0)
Median	107.3	107.3	107.3
Min	103.3	105.0	103.3
Max	118.0	116.7	118.0
msSBP (mmHg)			
n	125	58	183
Mean (SD)	163.4 (13.5)	161.7 (12.6)	162.8 (13.2)
Median	162.0	160.8	161.7
Min	131.7	131.7	131.7
Max	198.7	195.0	198.7
Standing DBP (mmHg)			
n	125	58	183
Mean (SD)	108.8 (5.3)	108.4 (5.4)	108.6 (5.3)
Median	108.0	109.5	109.0
Min	94.0	98.0	94.0
Max	125.0	120.0	125.0
Standing SBP (mmHg)			
N	125	58	183
Mean (SD)	164.6 (15.4)	162.5 (14.2)	163.9 (15.1)
Median	162.0	160.0	160.0
Min	130.0	140.0	130.0
Max	204.0	199.0	204.0

SD = standard deviation

Summary of Efficacy

Primary Outcome Result(s)

Please refer to safety result section.

Secondary Outcome Result(s)

Changes from baseline in mean sitting diastolic blood pressure (msDBP, mmHg) at double-blind visit by randomized treatment group (ITT population)

		Aliskiren		Lisinopril	
Visit	Day	N*	Mean (SD)	N*	Mean (SD)
3	1	124		58	
4	7	124	-10.1 (8.6)	58	-11.0 (8.6)
5	14	123	-13.3 (8.6)	58	-15.0 (10.2)
6	28	118	-16.1 (9.2)	57	-17.7 (9.8)
7	42	115	-19.4 (8.7)	56	-18.5 (9.2)
8	56	113	-19.1 (8.4)	54	-20.0 (8.0)
Endpoint**		124	-18.5 (8.7)	58	-20.1 (7.9)

(*) N is the number of patients with values at both baseline and post-baseline visit.
(**) Endpoint is Day 56, or last visit carried forward.
Note: A decrease in the mean change indicates improvement

Changes from baseline in mean sitting systolic blood pressure (msSBP, mmHg) at double-blind visit by randomized treatment group (ITT population)

		Aliskiren		Lisinopril	
Visit	Day	N*	Mean (SD)	N*	Mean (SD)
3	1	124		58	
4	7	124	-8.2 (13.3)	58	-10.9 (13.3)
5	14	123	-12.5 (13.7)	58	-13.4 (15.3)
6	28	118	-15.7 (15.1)	57	-18.7 (15.0)
7	42	115	-20.0 (13.7)	56	-20.2 (14.2)
8	56	113	-21.2 (15.0)	54	-23.0 (14.6)
Endpoint**		124	-20.0 (15.3)	58	-22.3 (14.6)

(*) N is the number of patients with values at both baseline and post-baseline visit.
(**) Endpoint is Day 56, or last visit carried forward.
Note: A decrease in the mean change indicates improvement

Number (%) of responders in mean sitting diastolic blood pressure (msDBP, mmHg) at double-blind endpoint by randomized treatment group (ITT population)

	Aliskiren n/N (%)	Lisinopril n/N (%)	Total n/N (%)
Number (%) of responders at endpoint	101/124 (81.5)	51/ 58 (87.9)	152/182 (83.5)

N is the number of patients with both baseline and endpoint msDBP values.
A responder is defined as a patient with a trough msDBP < 90 mmHg and/or at least 10 mmHg reduction from baseline in msDBP.

Summary of Safety

Safety Results

Number (%) of patients with AEs (at least 2% in total) by primary system organ class during the double-blind period (Safety population)

Primary System Organ Class	Aliskiren N=125 n(%)	Lisinopril N=58 n(%)	Total N=183 n(%)
Total	41 (32.8)	17 (29.3)	58 (31.7)
Gastrointestinal disorders	5 (4.0)	2 (3.4)	7 (3.8)
General disorders and administration site conditions	4 (3.2)	3 (5.2)	7 (3.8)
Infections and infestations	6 (4.8)	3 (5.2)	9 (4.9)
Musculoskeletal and connective tissue disorders	3 (2.4)	4 (6.9)	7 (3.8)
Nervous system disorders	13 (10.4)	6 (10.3)	19 (10.4)
Respiratory, thoracic and mediastinal disorders	4 (3.2)	1 (1.7)	5 (2.7)
Skin and subcutaneous tissue disorders	6 (4.8)	0 (0.0)	6 (3.3)

Number (%) of patients with common AEs (at least 1% in total) by preferred term during the double-blind period (Safety population)

Preferred term	Aliskiren N=125 n(%)	Lisinopril N=58 n(%)	Total N=183 n(%)
Headache	11 (8.8)	5 (8.6)	16 (8.7)
Nasopharyngitis	3 (2.4)	2 (3.4)	5 (2.7)
Dizziness	1 (0.8)	2 (3.4)	3 (1.6)
Fatigue	1 (0.8)	2 (3.4)	3 (1.6)
Edema peripheral	2 (1.6)	0 (0.0)	2 (1.1)
Vertigo	2 (1.6)	0 (0.0)	2 (1.1)
Back pain	1 (0.8)	1 (1.7)	2 (1.1)
Cough	1 (0.8)	1 (1.7)	2 (1.1)
Neck pain	1 (0.8)	1 (1.7)	2 (1.1)

Number (%) of patients who died or had other serious or significant adverse events during the double-blind period (Safety population)

	Aliskiren N=125 n(%)	Lisinopril N=58 n(%)	Total N=183 n(%)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)
SAEs	0 (0.0)	2 (3.4)	2 (1.1)
AE discontinuations	4 (3.2)	2 (3.4)	6 (3.3)
SAE discontinuations	0 (0.0)	2 (3.4)	2 (1.1)
Discontinuations for abnormal lab values	0 (0.0)	0 (0.0)	0 (0.0)

Number (%) of patients with SAEs by preferred term and randomized treatment group during the double-blind period (Safety population)

Preferred term	Aliskiren N=125 n(%)	Lisinopril N=58 n(%)	Total N=183 n(%)
Total no. of patients with SAEs	0 (0.0)	2 (3.4)	2 (1.1)
Angina pectoris	0 (0.0)	1 (1.7)	1 (0.5)
Appendicitis	0 (0.0)	1 (1.7)	1 (0.5)
Myocardial infarction	0 (0.0)	1 (1.7)	1 (0.5)

Angina pectoris and myocardial infarction occurred in the same patient.

Other Relevant Findings

None

Date of Clinical Trial Report

04 APR 2006

Date of Initial Inclusion on Novartis Clinical Trial Results website

07 DEC 2006

Date of Latest Update

8 MAY 2014