Sponsor

Novartis

Generic Drug Name

Aliskiren

Therapeutic Area of Trial

Hypertension

Approved Indication

Indicated for the treatment of hypertension. It may be used alone or in combination with other hypertensive agents

Study Number

CSPP100A2304

Title

A twelve-week, randomized, double-blind, parallel-group, multicenter, dose escalation study to evaluate the efficacy and safety of aliskiren administered alone and in combination with atenolol in patients with essential hypertension

Phase of Development

Phase III

Study Start/End Dates

23-Nov-2005 to 14-Aug-2006

Study Design/Methodology

This was a multicenter, double-blind, parallel group study, in patients with essential hypertension (msDBP >= 95 mmHg and < 110 mmHg). The study had five periods: a 2 week washout period, a 2 to 4 week single-blind run-in period, a 6 week double-blind titration period, a 6 week double-blind maintenance period and a one week double-blind tapering period. Double-blind treatment was initiated with one of the following three treatment arms in a ratio of 1:1:1: aliskiren 150 mg o.d., atenolol 50 mg o.d., or aliskiren 150 mg plus atenolol 50 mg o.d. At Visit 6, patients were force-titrated to elevated doses of their respective treatment groups: aliskiren 300 mg o.d., atenolol 100 mg o.d., or aliskiren 300 mg plus atenolol 100 mg o.d. for an additional six weeks. All patients entered a 7 day treatment tapering off period following 12 weeks of double-blind treatment (or upon early termination from period 3 or 4). Patients who had been receiving atenolol

100 mg (either alone or in combination with aliskiren) received atenolol 50 mg for 7 days. Patients who had been receiving aliskiren 300 mg received placebo for 7 days.

Centres

94 centers in 6 countries: Germany (61), China (1), India (7), South Africa (5), Spain (13), Turkey (7)

Objectives

Primary objective(s)

- Change in mean sitting diastolic blood pressure (msDBP) : baseline to week 12

Secondary objective(s)

- Change in mean sitting systolic blood pressure (msSBP) : baseline to week 12
- Proportion of subjects achieving msDBP and msSBP control (msSBP <140mmHg, msDBP <90mmHg)
- Proportion of subjects achieving msDBP response (msDBP < 90 mm Hg or a reduction of = 10 mm Hg from baseline)
- Evaluate and compare the safety and tolerability

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

Oral tablets of aliskiren 300mg and atenolol 100mg or aliskiren 300mg once each morning.

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

Oral tablets aliskiren 300mg and atenolol 100mg or atenolol 100mg once each morning.

Criteria for Evaluation

Primary variables

- Blood pressure (BP) readings while patients are sitting to determine change in mean sitting diastolic BP

Secondary variables

- BP readings while patients are sitting to determine change in mean sitting systolic BP
- Proportion of subjects achieving msDBP and msSBP control (msSBP <140mmHg, msDBP <90mmHg)
- Proportion of subjects achieving msDBP response (msDBP < 90 mm Hg or a reduction of = 10 mm Hg from baseline)

Safety and tolerability

- Frequency of adverse events, incidence of clinically notable laboratory abnormalities, particularly involving vital signs and electriocardiogram (ECG) data.

Pharmacology

Not applicable

Other

Not applicable

Statistical Methods

The primary efficacy analysis was a treatment comparison from baseline to week 12 endpoint in msDBP of patients who received aliskiren 300 mg and atenolol 100mg combination treatment compared to patients receiving aliskiren 300mg or atenolol 100mg. The proportion of patients in each treatment achieving a response in msDBP during the double-blind period was compared using a logistic regression model with treatment and region as the factors and baseline msDBP value as a covariate at week 6 and week 12 endpoints, for the primary efficacy population. Pairwise treatment comparisons were made at a two-sided significance level of 0.05. The response is defined as a mean sitting diastolic blood pressure < 90 mmHg or a = 10 mmHg decrease compared to baseline (pre-dose measurement at the randomization Visit 3). In addition, the same analysis of the response variable was performed for the proportion of patients in each treatment achieving a blood pressure control (msDBP/msSBP < 140/90 mmHg) during the double-blind period.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

- Male or female outpatients 18 years of age and older. Female patients were either postmenopausal for one year, surgically sterile, or using effective contraceptive methods such as oral contraceptives, barrier method with spermicide or an intrauterine device.
- Patients with essential hypertension.
- 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).
- To be eligible for randomization into the double-blind treatment period at Visit 3, patients must have also fulfilled the following criteria:
  - Patients must have had a msDBP = 90 mmHg and < 110 mmHg at Visit 2 or optional Visit 201, and a msDBP = 95 mmHg and < 110 mmHg at Visit 3 (Day 1).
  - Patients must have had an absolute difference in their msDBP = 10 mmHg during the last two visits (Visit 2 and 3 or the optional Visit 201 and 3) of the single-blind run-in period.

Exclusion criteria

Patients with any of the following physiological states or concomitant medical conditions at either Visit 1, Visit 2, optional Visit 201, or Visit 3 (unless otherwise stated) were excluded from participation in the study.

1. Severe hypertension (msDBP = 110 mmHg and/or msSBP = 180 mmHg).
2. History or evidence of a secondary form of hypertension.
3. Known Keith-Wagener grade III or IV hypertensive retinopathy.
4. History of hypertensive encephalopathy or cerebrovascular accident.
5. Transient ischemic cerebral attack during the 12 months prior to Visit 1.
6. Current diagnosis of heart failure (NYHA Class II-IV).
7. History of myocardial infarction, coronary bypass surgery, or any percutaneous coronary intervention (PCI) during the 6 months prior to Visit 1.
8. Current angina pectoris requiring pharmacological therapy (other than patients on a stable dose of oral or topical nitrates).
9. Second or third degree heart block without a pacemaker.
10. Sinus bradycardia (heart rate < 55 bpm).
11. Concurrent potentially life threatening arrhythmia or symptomatic arrhythmia.
12. History of sick sinus syndrome.
13. Clinically significant valvular heart disease.
14. Type 1 or Type 2 diabetes mellitus with glycosylated hemoglobin (HbA1c) > 9% at Visit 1.
15. History of bronchospasm, asthma or chronic obstructive pulmonary disease.
16. Symptomatic peripheral artery disease.
17. 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.

18. 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 such as gastrectomy, gastroenterostomy, or bowel resection.
    - Currently active or previously active inflammatory bowel disease during the 12 months prior to Visit 1.
    - Currently active gastritis, duodenal or gastric ulcers, or gastrointestinal/rectal bleeding during the 3 months prior to Visit 1.
    - 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 any one of the following: SGOT or SGPT values exceeding 3 x ULN at Visit 1, a history of hepatic encephalopathy, a history of esophageal varices, or a history of portocaval shunt.
    - Evidence of renal impairment as determined by any one of the following: serum creatinine > 1.5 times the upper limit of normal at Visit 1, a history of dialysis, or a history of nephrotic syndrome.
    - Current treatment with cholestyramine and colestipol resins.
19. History of malignancy including leukemia and lymphoma (but not basal cell skin cancer) within the past five years.
20. History or evidence of drug or alcohol abuse within the last 12 months.
21. Pregnant or nursing women.
22. Any surgical or medical condition, which in the opinion of the investigator, may have placed the patient at higher risk from his/her participation in the study, or was likely to prevent the patient from complying with the requirements of the study or completing the study
23. Known or suspected contraindications to the study medications including history of allergy to atenolol or other ß-blockers.
24. History of noncompliance to medical regimens or unwillingness to comply with the study protocol.
25. Any condition that in the opinion of the investigator or the Novartis medical monitor would have jeopardized the evaluation of efficacy or safety.
26. Participation in any investigational drug study within one month of Visit 1.
27. Persons directly involved in the execution of this protocol.

Number of Subjects

	Novartis product	Comparator	Combination
Planned N	201	201	201
Randomised n	231	231	232
Intent-to-treat population (ITT) n (%)	230 (99.6)	230 (99.6)	230 (99.1)
Completed n (%)	211 (91.3)	213 (92.2)	205 (88.4)

Withdrawn n (%)	20 (8.7)	18 (7.8)	26 (11.2)
Withdrawn due to adverse events n (%)	5 (2.2)	10 (4.3)	14 (6.0)
Withdrawn due to lack of efficacy n (%)	6 (2.6)	1 (0.4)	3 (1.3)
Withdrawn due to protocol violation	4 (1.7)	3 (1.3)	5 (2.2)
Withdrawn for other reasons n (%)	5 (2.2)	4 (1.7)	4 (1.7)

Demographic and Background Characteristics

	Novartis product	**Comparator**	**Combination**
N (ITT)	230 (99.6)	230 (99.6)	230 (99.1)
Females : males	42:58	51.1: 48.9	48.3: 51.7
Mean age, years (SD)	55.8 (11.92)	54.7 (11.54)	55.2 (10.93)
Body Mass Index (kg/m2)	28.89 (4.522)	29.20 (5.133)	29.48 (4.955)
Race White n (%) Black n (%) Asian n (%) Other n (%)	 191 (82.7) 11 (4.8) 29 (12.6) 0	 196 (84.8) 5 (2.2) 24 (10.4) 6 (2.6)	 194 (83.6) 8 (3.4) 26 (11.2) 4 (1.7)
Mean duration of Hypertension - years (SD)	6.8 (6.65)	6.3 (5.64)	7.0 (6.82)

Primary Objective Result(s)

Change in mean sitting diastolic blood pressure (msDBP) : baseline to week 12

Treatment Group	N	LSM change from baseline (SE)	
Aliskiren (300 mg)	230	-11.26 (0.599)	
Atenolol (100 mg)	230	-13.66 (0.598)	
Aliskiren (300 mg) /Atenolol (100 mg)	230	-14.14 (0.601)	
Pairwise Comparison	LSM difference in change from base-line (SE)	95% CI for LSM difference	P-Value
Aliskiren /Atenolol vs. Aliskiren	-2.88 (0.802)	(-4.46,-1.31)	<0.001*
Aliskiren /Atenolol vs. Atenolol	-0.49 (0.803)	(-2.06, 1.09)	0.5447
Aliskiren vs. Atenolol	2.39 (0.803)	(0.82, 3.97)	0.0030*

SE=Standard Error; LSM=Least Squares Mean; CI=Confidence Interval

P-Values and treatment comparisons were evaluated at the average baseline level. *Indicates statistical significance at 0.05 level.

Secondary Objective Result(s)

Change in mean sitting systolic blood pressure (msSBP) : baseline to week 12

Treatment Group	N	LSM change from baseline (SE)
Aliskiren (300 mg)	230	-14.34 (1.064)
Atenolol (100 mg)	230	-14.26 (1.064)
Aliskiren (300 mg) /Atenolol (100 mg)	230	-17.28 (1.067)

Pairwise Comparison	LSM difference in change from base-line (SE)	95% CI for LSM difference	P-Value
Aliskiren /Atenolol vs. Aliskiren	-2.94 (1.424)	(-5.74, -0.14)	0.0393*
Aliskiren /Atenolol vs. Atenolol	-3.02 (1.427)	(-5.82, -0.22)	0.0344*
Aliskiren vs. Atenolol	-0.08 (1.427)	(-2.89, 2.72)	0.9536

SE=Standard Error; LSM=Least Squares Mean; CI=Confidence Interval
P-Values and treatment comparisons were evaluated at the average baseline level.

*Indicates statistical significance at 0.05 level.

Proportion of subjects achieving msDBP and msSBP control (msSBP <140mmHg, msDBP <90mmHg)

Pairwise Comparison	Treatment A		Treatment B		
A vs. B	n/N	%	n/N	%	p-Value
Aliskiren 300mg /Atenolol 100mg vs. Aliskiren 300mg	118/230	51.3	83/230	36.1	<0.001*
Aliskiren 300mg /Atenolol 100mg vs. Atenolol 100mg	118/230	51.3	97/230	42.2	0.0086*
Aliskiren 300mg vs. Atenolol 100mg	83/230	36.1	97/230	42.2	0.3875

P-Values were from a logistic regression model with treatment and region as factors and baseline as a covariat
Baseline is the Week 0 value.
*Indicates statistical significance at 0.05 level.

Proportion of subjects achieving msDBP response (msDBP < 90 mm Hg or a reduction of = 10 mm Hg from baseline)

Pairwise Comparison	Treatment A		Treatment B		
A vs. B	n/N	%	n/N	%	p-Value
Aliskiren 300mg / Atenolol 100mg vs. Aliskiren 300mg	182/230	79.1	145/230	63.0	<0.001*
Aliskiren 300mg / Atenolol 100mg vs. Atenolol 100mg	182/230	79.1	172/230	74.8	0.2503
Aliskiren 300mg vs. Atenolol 100mg	145/230	63.0	172/230	74.8	0.0078*

P-Values were from a logistic regression model with treatment and region as factors and baseline as a covariate.
N= Number of patients with baseline and endpoint msDBP values.
*Indicates statistical significance at 0.05 level.

Safety Results

Adverse Events by System Organ Class

Primary System Organ Class	Aliskiren N=231 n (%)	Atenolol N=231 n (%)	Aliskiren / Atenolol N=231 n (%)	Total N=693 n (%)
Any Adverse Events	98 (42.4)	111 (48.1)	103 (44.6)	312 (45.0)
Blood and lymphatic system disorders	6 (2.6)	0	1 (0.4)	7 (1.0)
Cardiac disorders	4 (1.7)	7 (3.0)	6 (2.6)	17 (2.5)
Ear and labyrinth disorders	2 (0.9)	5 (2.2)	1 (0.4)	8 (1.2)
Eye disorders	0	4 (1.7)	4 (1.7)	8 (1.2)
Gastrointestinal disorders	19 (8.2)	21 (9.1)	25 (10.8)	65 (9.4)
General disorders and administration site conditions	8 (3.5)	12 (5.2)	18 (7.8)	38 (5.5)
Hepatobiliary disorders	2 (0.9)	0	1 (0.4)	3 (0.4)
Immune system disorders	3 (1.3)	3 (1.3)	1 (0.4)	7 (1.0)
Infections and infestations	30 (13.0)	34 (14.7)	31 (13.4)	95 (13.7)
Injury, poisoning and procedural complications	3 (1.3)	10 (4.3)	4 (1.7)	17 (2.5)
Investigations	5 (2.2)	9 (3.9)	7 (3.0)	21 (3.0)
Metabolism and nutrition disorders	1 (0.4)	2 (0.9)	3 (1.3)	6 (0.9)
Musculoskeletal and connective tissue disorders	19 (8.2)	20 (8.7)	18 (7.8)	57 (8.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.4)	0	0	1 (0.1)
Nervous system disorders	19 (8.2)	25 (10.8)	22 (9.5)	66 (9.5)
Psychiatric disorders	2 (0.9)	6 (2.6)	6 (2.6)	14 (2.0)
Renal and urinary disorders	1 (0.4)	4 (1.7)	1 (0.4)	6 (0.9)
Reproductive system and breast disorders	2 (0.9)	3 (1.3)	2 (0.9)	7 (1.0)
Respiratory, thoracic and mediastinal disorders	6 (2.6)	6 (2.6)	5 (2.2)	17 (2.5)
Skin and subcutaneous tissue disorders	9 (3.9)	6 (2.6)	4 (1.7)	19 (2.7)
Vascular disorders	1 (0.4)	6 (2.6)	5 (2.2)	12 (1.7)

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

	Aliskiren N=231 n (%)	Atenolol N=231 n (%)	Aliskiren / Atenolol N=231 n (%)	Total N=693 n (%)
Any Adverse Events	98 (42.4)	111 (48.1)	103 (44.6)	312 (45.0)
Headache	10 (4.3)	14 (6.1)	13 (5.6)	37 (5.3)
Nasopharyngitis	8 (3.5)	15 (6.5)	3 (1.3)	26 (3.8)
Diarrhea	8 (3.5)	6 (2.6)	5 (2.2)	19 (2.7)
Dizziness	6 (2.6)	7 (3.0)	4 (1.7)	17 (2.5)
Fatigue	3 (1.3)	2 (0.9)	10 (4.3)	15 (2.2)
Back pain	6 (2.6)	2 (0.9)	6 (2.6)	14 (2.0)
Influenza	2 (0.9)	5 (2.2)	5 (2.2)	12 (1.7)
Asthenia	1 (0.4)	5 (2.2)	3 (1.3)	9 (1.3)
Blood urea increased	0	5 (2.2)	3 (1.3)	8 (1.2)
Bradycardia	0	5 (2.2)	3 (1.3)	8 (1.2)

Serious Adverse Events and Deaths

	Novartis product	Comparator
No. (%) of subjects studied		
No. (%) of subjects with AE(s)		
Number (%) of subjects with serious or other significant events	n (%)	n (%)
Death		
SAE(s)		
Discontinued due to SAE(s)		

Date of Clinical Trial Report

9 November 2006

Date Inclusion on Novartis Clinical Trial Results Database

17 October 2007

Date of Latest Update

15 December 2008