Sponsor

Novartis

Generic Drug Name

Aliskiren

Therapeutic Area of Trial

Hypertension

Approved Indication

Investigational

Study Number

CSPP100A2324

Title

An 8-week, randomized, double-blind, parallel-group, multicenter study assessing the efficacy and safety of aliskiren 75 mg, 150 mg, and 300 mg in patients >= 65 years of age with essential hypertension, using 24-hour ABPM with lisinopril 10 mg as a reference

Phase of Development

III

Study Start/End Dates

26-Apr-2005 to 21-Feb-2006

Study Design/Methodology

This was an 8-week, randomized, double-blind, parallel multicenter study with lisinopril 10 mg as a reference and 3 doses of aliskiren 75 mg, 150 mg and 300 mg in patients >= 65 years of age with essential hypertension. The study had three periods: (1) screening/washout period, (2) a single-blind placebo run-in period, and (3) a double-blind treatment period.

Centres

62 Centers in 7 countries: Argentina (6), Austria (2), France (18), Italy (9), Japan (6), Spain (14), and Sweden (7)

Objectives

Primary objective(s)

- To evaluate the blood pressure lowering effect for the change from baseline to study endpoint in mean 24-hour systolic ambulatory blood pressure (ABPM) in patients >= 65 years of age with essential hypertension, by comparing aliskiren 300 mg to 75 mg.

Secondary objective(s)

- To evaluate the blood pressure lowering effect for the change from baseline to study endpoint in mean 24-hour ambulatory diastolic blood pressure (MADBP) in patients >= 65 years of age with essential hypertension, by comparing aliskiren 300 mg to 75 mg.
- To compare the mean 24 hour systolic and diastolic ambulatory blood pressures in aliskiren 300 mg to 150 mg and aliskiren 150 mg to 75 mg.
- To evaluate the blood pressure lowering effects of aliskiren in patients >= 65 years of age with essential hypertension for the change from baseline to study endpoint in mean sitting systolic (msSBP) and mean sitting diastolic office blood pressure (msDBP).
- To evaluate the blood pressure lowering effects of aliskiren in patients >= 65 years of age with essential hypertension for the change from baseline to study endpoint in mean daytime systolic and diastolic ambulatory blood pressure (where daytime is from 6 a.m. to 10 p.m.)
- To evaluate the blood pressure lowering effects of aliskiren in patients >= 65 years of age with essential hypertension for the change from baseline to study endpoint in mean nighttime systolic and diastolic ambulatory blood pressure (where nighttime is from 10 p.m. to 6 a.m.)
- To evaluate the trough-to-peak antihypertensive effect of aliskiren utilizing 24 hour ambulatory blood pressure monitoring (ABPM).
- To evaluate the proportion of patients achieving a target mean sitting office blood pressure of <140/90 mm Hg.
- To compare the blood pressure lowering effects of aliskiren and lisinopril.
- To evaluate the safety and tolerability of aliskiren.

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

Aliskiren 75 mg tablet o.d., p.o. (once daily) (per os / administered orally)

Aliskiren 150 mg tablet o.d., p.o. (once daily) (per os / administered orally)

Aliskiren 300 mg tablet o.d., p.o. (once daily) (per os / administered orally)

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

Lisinopril 10 mg capsule o.d., p.o. (once daily) (per os / administered orally)

Criteria for Evaluation

Primary variables

24-hour ambulatory blood pressure monitoring (ABPM) at Visit 3 (after patient is deemed eligible for randomization) and at Visit 7 or early discontinuation visit.

Secondary variables

Sitting and standing blood pressure at every visit, heart rate at every visit, 24-hour ambulatory blood pressure monitoring (ABPM) at Visit 3 (after patient is deemed eligible for randomization) and at Visit 7 or early discontinuation visit.

Safety and tolerability

Monitoring and recording all adverse events, the regular monitoring of hematology, blood chemistry, and urine values, regular measurements of vital signs, and the performance of physical examinations and electrocardiograms (ECGs).

Pharmacology

N/A

Other

N/A

Statistical Methods

Statistical analyses were performed by Novartis. Demographic and disease characteristics, study medication exposure, and prior and concomitant medication use were summarized for the randomized population.

The primary efficacy variable was change from baseline (Visit 3) to end of study in mean ambulatory 24 hour systolic blood pressure (intent-to-treat). The primary analysis model for treatment comparisons was a two-way repeated measures analysis of covariance model with treatment, region, age group, and post dosing hour as factors and baseline mean 24-hour mean ambulatory systolic blood pressure as covariate. A closed test procedure was used to account for multiple testing. The first test was the test highest versus lowest dosage. If this hypothesis was rejected at the 5% level, the remaining pair-wise comparison of 300 mg versus 150 mg and 150 mg versus 75 mg were examined at the 5% level.

Frequency distributions of safety parameters were summarized for the safety population. Laboratory data were summarized at baseline and endpoint of the double-blind period for absolute values and changes from baseline. Incident counts of patients with patients with pre-specified notable laboratory abnormalities were also provided.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria

- Outpatients >= 65 years of age and older.

Patients with essential hypertension. Patients with an office cuff msSBP >= 140 mm Hg and < 180 mm Hg at Visit 2 or Visit 201 (days -28 to -14 OR -14 to -1) and an office cuff msSBP >= 145 mm Hg and <180 mm Hg at Visit 3. Patients were required to have had a baseline mean 24 hour systolic ABPM >=135 mm Hg at Visit 3.

- Patients must have had an absolute difference of <= 15 mm Hg in their mean office cuff sitting systolic blood pressure (msSBP) during the last two visits (Visit 2 and 3 or the optional Visit 201 (as described above) and 3) of the single-blind placebo run-in period of the study.
- 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 at either Visit 1, Visit 2, optional visit 201 (as described above) or Visit 3 (unless otherwise stated) were excluded from participation in the study.
- Patients who previously entered an aliskiren study and who qualified to be randomized or enrolled into the active drug treatment period.
- Severe hypertension (Office msDBP >= 110 mm Hg and/or Office msSBP >= 180 mm Hg)
- History or evidence of a secondary form of hypertension
- Known Keith-Wagener grade III or IV hypertensive retinopathy.
- History of hypertensive encephalopathy or cerebrovascular accident
- Transient ischemic cerebral attack during the 12 months prior to Visit 1.
- Current or previous diagnosis of heart failure (NYHA Class II-IV).
- History of myocardial infarction, coronary bypass surgery, or any percutaneous coronary intervention (PCI) during the 12 months prior to Visit 1.
- Current angina pectoris requiring pharmacological therapy
- Second or third degree heart block without a pacemaker.
- Concurrent potentially life threatening arrhythmia or symptomatic arrhythmia.
- Clinically significant valvular heart disease.
- Type 1 or Type 2 diabetes mellitus with fasting glycosylated hemoglobin (HbA1c) > 8% at Visit 1.
- Patients employed as a night shift worker.
- Arm circumference <17 cm OR > 42 cm.

- A diagnosis of atrial fibrillation
- 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.
- Any surgical or medical condition which might have significantly altered 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 (serum glutamic-oxaloacetic transaminase) or SGPT (serum glutamic-pyruvic transaminase) values exceeding 3 x ULN (upper limit of normal) 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 X ULN at Visit 1 [ULN: male = 1.3 mg/dL (115 *u*mol/L), female = 1.2 mg/dL (106 *u*mol/l)], a history of dialysis, or a history of nephrotic syndrome.
- History of malignancy including leukemia and lymphoma (but not basal cell skin cancer) within the past five years.
- History or evidence of drug or alcohol abuse within the last 12 months.
- Known or suspected contraindications to the study medications, including history of allergy to angiotensin converting enzyme (ACE) inhibitor.
- 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 have prevented the patient from complying with the requirements of the study or completing the study.
- History of noncompliance to medical regimens or unwillingness to comply with the study protocol.
- Any condition that in the opinion of the investigator or the Novartis medical monitor would have jeopardized the evaluation of efficacy or safety.

Number of Subjects

	Aliskiren 75 mg		Aliskiren 150 mg		Aliskiren 300 mg		Lisinopril 10 mg		Total	
Disposition	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Enrolled									598	
Randomized	91		84		94		86		355	(59.4%)*
Completed	83	(91.2)	80	(95.2)	88	(93.6)	79	(91.9)	330	(93.0)
Discontinued	8	(8.8)	4	(4.8)	6	(6.4)	7	(8.1)	25	(7.0)
Reason for discontinuation										
Adverse Event(s)	6	(6.6)	2	(2.4)	1	(1.1)	5	(5.8)	14	(3.9)
Unsatisfactory therapeutic effect	1	(1.1)	1	(1.2)	2	(2.1)	0	(0.0)	4	(1.1)
Protocol violation	1	(1.1)	0	(0.0)	1	(1.1)	1	(1.2)	3	(0.8)
Subject withdrew consent	0	(0.0)	1	(1.2)	1	(1.1)	1	(1.2)	3	(0.8)
Lost to follow-up		(0.0)	0	(0.0)	1	(1.1)	0	(0.0)	1	(0.3)

Demographic and Background Characteristics

Demographic variable	Aliskiren 75 mg N=91	Aliskiren 150 mg N=84	Aliskiren 300 mg N=94	Lisinopril 10 mg N=86	Total N=355
Age group (years) - n (%)					
>= 65 - < 75	45(49.5%)	46(54.8%)	50(53.2%)	41(47.7%)	182(51.3%)
>= 75	46(50.5%)	38(45.2%)	44(46.8%)	45(52.3%)	173(48.7%)
Sex - n (%)					
Male	43(47.3%)	36(42.9%)	35(37.2%)	29(33.7%)	143(40.3%)
Female	48(52.7%)	48(57.1%)	59(62.8%)	57(66.3%)	212(59.7%)
Race - n (%)					
Caucasian	79(86.8%)	72(85.7%)	81(86.2%)	76(88.4%)	308(86.8%)
Black	0(0.0%)	0(0.0%)	0(0.0%)	1(1.2%)	1(0.3%)
Asian	12(13.2%)	12(14.3%)	13(13.8%)	9(10.5%)	46(13.0%)
Ethnicity - n (%)					
Hispanic or Latino	46(50.5%)	42(50.0%)	48(51.1%)	43(50.0%)	179(50.4%)
Chinese	0(0.0%)	0(0.0%)	0(0.0%)	1(1.2%)	1(0.3%)
Japanese	12(13.2%)	11(13.1%)	13(13.8%)	8(9.3%)	44(12.4%)
Other	33(36.3%)	31(36.9%)	33(35.1%)	34(39.5%)	131(36.9%)
Age (years)					
n	91	84	94	86	355
Mean (± SD)_	73.6 (5.86)	73.2 (5.61)	73.0 (5.61)	74.2 (6.07)	73.5 (5.78)
Median	75.0	73.5	73.0	75.0	74.0
Range	65.0 – 85.0	65.0 – 86.0	65.0 – 90.0	65.0 – 90.0	65.0 – 90.0

Duration of hyper-tension (years)					
n	89	82	89	85	345
Mean (± SD)	9.5 (7.59)	12.6 (9.86)	10.8 (8.57)	10.4 (8.05)	10.8 (8.57)
Median	8.0	10.5	11.0	9.0	9.0
Range	1.0 – 43.0	1.0 – 41.0	1.0 – 47.0	1.0 – 45.0	1.0 – 47.0
n (naive patients)	2(2.2%)	2(2.4%)	5(5.3%)	1(1.2%)	10(2.8%)
Height (cm)					
n	90	84	94	86	354
Mean (± SD)_	161.8 (9.34)	161.8 (9.77)	160.5 (10.84)	160.3 (9.37)	161.1 (9.85)
Median	160.0	162.0	160.0	159.5	160.0

Primary Objective Result(s)

Change from Baseline (Visit 3) to end-of-study 24-hour MASBP: intent-to-treat population

Treatment Group	**N**	**LSM change from baseline (SE)**		
Aliskiren 75 mg	74	-8.35 (0.83)		
Aliskiren 150 mg	73	-7.06 (0.84)		
Aliskiren 300 mg	80	-8.67 (0.80)		
Lisinopril 10 mg	73	-10.19 (0.86)		
Pairwise Comparison	**LSM difference in change from baseline (SE)**		**95% CI for LSM differ-ence**	**P-Value**
Aliskiren 75mg vs. Aliskiren 300mg	0.32 (1.12)		(-1.88, 2.52)	0.7763
SE = Standard Error;	LSM = Least Squares Means; CI = Confidence Interval			

Secondary Objective Result(s)

Change from Baseline (Visit 3) to end-of-study 24-hour MADBP: intent-to-treat population

Treatment Group	N	LSM change from baseline (SE)
Aliskiren 75 mg	74	-4.51 (0.52)
Aliskiren 150 mg	73	-3.63 (0.52)
Aliskiren 300 mg	80	-3.92 (0.50)
Lisinopril 10 mg	73	-6.32 (0.53)

Pairwise Comparison	LSM difference in change from baseline (SE)	95% CI for LSM difference	P-Value
Aliskiren 75mg vs. Aliskiren 300mg	-0.59 (0.69)	(-1.95, 0.77)	0.3967
Aliskiren 75mg vs. Aliskiren 150mg	-0.87 (0.71)	(-2.27, 0.52)	0.2174
Aliskiren 150mg vs. Aliskiren 300mg	0.29 (0.69)	(-1.08, 1.65)	0.6784

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

Change from baseline (Visit 3) to end-of-study in msSBP: intent-to-treat population

Treatment Group	N	LSM change from baseline (SE)
Aliskiren 75 mg	91	-13.03 (1.48)
Aliskiren 150 mg	84	-13.48 (1.54)
Aliskiren 300 mg	94	-14.54 (1.45)
Lisinopril 10 mg	85	-14.93 (1.55)

Pairwise Comparison	LSM difference in change from baseline (SE)	95% CI for LSM difference	P-Value
Aliskiren 75mg vs. Aliskiren 300mg	1.52 (1.97)	(-2.36, 5.40)	0.4418
Aliskiren 75mg vs. Aliskiren 150mg	0.45 (2.03)	(-3.54, 4.45)	0.8237
Aliskiren 150mg vs. Aliskiren 300mg	1.07 (2.01)	(-2.89, 5.03)	0.5967

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

Change from baseline (Visit 3) to week 8 in msSBP: intent-to-treat population

Treatment Group	N	LSM change from baseline (SE)
Aliskiren 75 mg	84	-13.73 (1.46)
Aliskiren 150 mg	80	-14.58 (1.49)
Aliskiren 300 mg	89	-15.54 (1.41)
Lisinopril 10 mg	79	-15.62 (1.52)

Pairwise Comparison	LSM difference in change from baseline (SE)	95% CI for LSM difference	P-Value
Aliskiren 75mg vs. Aliskiren300mg	1.81 (1.93)	(-1.99, 5.62)	0.3483
Aliskiren 75mg vs. Aliskiren150mg	0.85 (1.98)	(-3.05, 4.75)	0.6684
Aliskiren 150mg vs. Aliskiren 300mg	0.96 (1.96)	(-2.88, 4.81)	0.6222

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

Change from baseline (Visit 3) to end-of-study in msDBP: intent-to-treat population

Treatment Group	N	LSM change from baseline (SE)
Aliskiren 75 mg	91	-5.53 (0.83)
Aliskiren 150 mg	84	-6.21 (0.86)
Aliskiren 300 mg	94	-6.41 (0.81)
Lisinopril 10 mg	85	-5.38 (0.87)

Pairwise Comparison	LSM difference in change from baseline (SE)	95% CI for LSM difference	P-Value
Aliskiren 75mg vs. Aliskiren 300mg	0.88 (1.11)	(-1.31, 3.07)	0.4299
Aliskiren 75mg vs. Aliskiren 150mg	0.69 (1.14)	(-1.56, 2.93)	0.5484
Aliskiren 150mg vs. Aliskiren 300mg	0.19 (1.13)	(-2.03, 2.42)	0.8647

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

Change from baseline (Visit 3) to week 8 in msDBP: intent-to-treat population

Treatment Group	N	LSM change from baseline (SE)
Aliskiren 75 mg	84	-4.90 (0.83)
Aliskiren 150 mg	80	-6.58 (0.84)
Aliskiren 300 mg	89	-6.46 (0.80)
Lisinopril 10 mg	79	-5.75 (0.86)

Pairwise Comparison	LSM difference in change from baseline (SE)	95% CI for LSM difference	P-Value
Aliskiren 75mg vs. Aliskiren 300mg	1.55 (1.10)	(-0.61, 3.72)	0.1592
Aliskiren 75mg vs. Aliskiren 150mg	1.67 (1.13)	(-0.55, 3.89)	0.1388
Aliskiren 150mg vs. Aliskiren 300mg	-0.12 (1.11)	(-2.30, 2.06)	0.9145

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

Safety Results

Number (%) of patients with AEs overall and by body system (= 1% in any group) during the double-blind period (safety population)

Table	Aliskiren 75 mg N=91 n (%)	Aliskiren 150 mg N=84 n (%)	Aliskiren 300 mg N=94 n (%)	Lisinopril 10 mg N=86 n (%)	Total N=355 n (%)
Any Body System	27(29.7)	34(40.5)	23(24.5)	26(30.2)	110(31.0)
Cardiac disorders	2(2.2)	2(2.4)	0(0.0)	0(0.0)	4(1.1)
Ear and labyrinth disorders	2(2.2)	4(4.8)	2(2.1)	1(1.2)	9(2.5)
Endocrine disorders	0(0.0)	0(0.0)	0(0.0)	1(1.2)	1(0.3)
Eye disorders	0(0.0)	1(1.2)	0(0.0)	0(0.0)	1(0.3)
Gastrointestinal disorders	7(7.7)	6(7.1)	7(7.4)	3(3.5)	23(6.5)
General disorders and administration site Conditions	3(3.3)	5(6.0)	2(2.1)	4(4.7)	14(3.9)
Infections and infestations	7(7.7)	9(10.7)	3(3.2)	5(5.8)	24(6.8)
Injury, poisoning and procedural complications	0(0.0)	0(0.0)	1(1.1)	3(3.5)	4(1.1)
Investigations	2(2.2)	1(1.2)	1(1.1)	0(0.0)	4(1.1)
Metabolism and nutrition disorders	1(1.1)	0(0.0)	0(0.0)	1(1.2)	2(0.6)
Musculoskeletal and connective tissue disorders	3(3.3)	4(4.8)	2(2.1)	5(5.8)	14(3.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0(0.0)	0(0.0)	2(2.1)	0(0.0)	2(0.6)
Nervous system disorders	6(6.6)	10(11.9)	0(0.0)	9(10.5)	25(7.0)
Psychiatric disorders	2(2.2)	2(2.4)	1(1.1)	0(0.0)	5(1.4)
Renal and urinary disorders	0(0.0)	0(0.0)	0(0.0)	1(1.2)	1(0.3)
Respiratory, thoracic and mediastinal disorders	2(2.2)	1(1.2)	2(2.1)	3(3.5)	8(2.3)
Skin and subcutaneous tissue disorders	1(1.1)	1(1.2)	0(0.0)	3(3.5)	5(1.4)
Surgical and medical procedures	0(0.0)	0(0.0)	1(1.1)	0(0.0)	1(0.3)
Vascular disorders	2(2.2)	2(2.4)	2(2.1)	2(2.3)	8(2.3)

Primary system organ class are presented alphabetically

Incidence rate of common adverse events (>=2 %) in any treatment group by the order of frequency (safety population)

Preferred term	Aliskiren 75 mg N=91 n (%)	Aliskiren 150 mg N=84 n (%)	Aliskiren 300 mg N=94 n (%)	Lisinopril 10 mg N=86 n (%)	Total N=355 n (%)
Diarrhea	0(0.0)	3(3.6)	4(4.3)	1(1.2)	8(2.3)
Dyspepsia	2(2.2)	1(1.2)	2(2.1)	1(1.2)	6(1.7)
Urinary tract infection	2(2.2)	1(1.2)	2(2.1)	1(1.2)	6(1.7)
Cough	1(1.1)	0(0.0)	1(1.1)	2(2.3)	4(1.1)
Nasopharyngitis	2(2.2)	2(2.4)	1(1.1)	2(2.3)	7(2.0)
Vertigo	1(1.1)	2(2.4)	1(1.1)	1(1.2)	5(1.4)
Abdominal pain	1(1.1)	2(2.4)	0(0.0)	0(0.0)	3(0.8)
Asthenia	2(2.2)	4(4.8)	0(0.0)	2(2.3)	8(2.3)
Dizziness	3(3.3)	5(6.0)	0(0.0)	2(2.3)	10(2.8)
Headache	3(3.3)	2(2.4)	0(0.0)	5(5.8)	10(2.8)

Preferred terms are presented with decreasing frequency within the aliskiren 300 mg group

Incidence rate of deaths, serious adverse events and laboratory abnormalities and adverse events leading to permanent treatment discontinuations (safety population)

	Aliskiren 75 mg N=91		Aliskiren 150 mg N=84		Aliskiren 300 mg N=94		Lisinopril 10 mg N=86		Total N=355	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Death	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
SAEs	0	(0.0)	1	(1.2)	1	(1.1)	0	(0.0)	2	(0.6)
AE discontinuations	5	(5.5)	2	(2.4)	1	(1.1)	5	(5.8)	13	(3.7)
SAE discontinuations	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	1	(0.3)
Discontinuations for abnormal lab values	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

No patient died during the single-blind or double-blind periods of the study. In the washout period and follow-up period, two deaths were reported.

Other Relevant Findings

None

Date of Clinical Trial Report 23 May 2006
Date Inclusion on Novartis Clinical Trial Results Database 11 April 2007
Date of Latest Update 15 December 2008