Sponsor

Novartis

Generic Drug Name

Aliskiren

Therapeutic Area of Trial

Essential Hypertension

Approved Indication

Hypertension

Study Number

CSPP100A2332

Title

An eight-week, randomized, double-blind, parallel-group, multicenter study to evaluate the efficacy and safety of the combination of aliskiren/HCTZ (300/12.5 mg and 300/25 mg) in comparison with aliskiren 300 mg in patients with essential hypertension not adequately responsive to aliskiren 300 mg monotherapy

Phase of Development

Phase III

Study Start/End Dates

18-Sep-2006 to 03-Jul-2007

Study Design/Methodology

This was an eight-week, randomized, double-blind, parallel group, multi-center study comparing the efficacy and safety of the fixed-dose combination of aliskiren and hydrochlorothiazide (HCTZ) (300/25 mg and 300/12.5 mg) to aliskiren 300 mg alone in patients with essential hypertension who did not adequately respond to aliskiren monotherapy (msDBP >= 90 mmHg and < 110 mmHg after a 4-week treatment with aliskiren 300 mg). The study was comprised of 3 periods and 8 visits.

At Visit 1 (Day -32), patients were screened. If eligible, they discontinued their current antihypertensive medication(s). Patients who were newly diagnosed with uncomplicated essential hypertension or patients who have not received antihypertensive medication for at least 4 weeks prior to Visit 1 were enrolled directly into the four-week single-blind run-in period once deemed eligible. At Visit 2, patients entered a four-week, single-blind, run-in period. Patients received aliskiren 300 mg throughout the four weeks of the single-blind run-in period. At Visit 4 (Day 1),

patients not adequately responsive to aliskiren 300 mg and who fulfilled the inclusion/exclusion criteria were equally randomized to receive one of three treatments: aliskiren/HCTZ (300/25 mg); aliskiren/HCTZ (300/12.5 mg), or aliskiren 300 mg monotherapy for eight weeks. The study duration for each patient, inclusive of all phases, was approximately 12 – 13 weeks.

Centers

114 centers in 8 countries: Argentina (10), France (17), Germany (14), India (4), Italy (25), Peru (10), Russia (10), Spain (24)

Objectives

Primary objective(s)

The primary objective of the study was to assess the efficacy of the fixed-dose combination therapy of aliskiren 300 mg and HCTZ (12.5 mg and 25 mg) on reduction in mean sitting diastolic blood pressure (msDBP) from baseline to end of study when compared to aliskiren 300 mg monotherapy in hypertensive patients who do not show sufficient blood pressure response to a 4-week treatment of aliskiren 300 mg.

Secondary objective(s)

1. To evaluate the efficacy of the fixed-dose combination of aliskiren 300 mg and HCTZ (12.5 mg and 25 mg) on reduction in mean sitting systolic blood pressure (msSBP) from baseline to end of study when compared to aliskiren 300 mg monotherapy in hypertensive patients who do not show sufficient blood pressure response to a 4-week treatment of aliskiren 300 mg
2. To evaluate the safety and tolerability of the fixed-dose combination of aliskiren 300 mg and HCTZ (12.5 mg and 25 mg) compared with aliskiren 300 mg monotherapy in hypertensive patients who do not show sufficient blood pressure response to a 4-week treatment of aliskiren 300 mg.
3. To evaluate the proportion of patients achieving a blood pressure control target of < 140/90 mmHg at the end of study for all treatment arms.

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

Aliskiren 300 mg, aliskiren/HCTZ 300/25 mg, and aliskiren/HCTZ 300/12.5 mg film-coated tablets were administered orally, once daily.

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

Placebo film-coated tablets matched to each of the double-blind medications were administered orally.

Criteria for Evaluation

Primary variables

The primary efficacy variable was change from baseline (Visit 4) in mean sitting diastolic blood pressure (msDBP) at endpoint. For each patient, the last post-baseline measurement during the double-blind period was carried forward to Week 8 as the endpoint measurement for the variable to be analyzed. The primary analysis time point was the endpoint.

Secondary Efficacy variables

Secondary efficacy variables were change from baseline in mean sitting systolic blood pressure (msSBP) at endpoint, and blood pressure control at endpoint.

Safety

Safety assessments consisted of monitoring and recording all AEs and SAEs,

Other

None

Statistical Methods

A hierarchical model was used to assess the effects of HCTZ combinations with aliskiren 300 mg versus aliskiren 300 mg. First aliskiren 300 mg/HCTZ 25 mg was compared to aliskiren 300 mg. If aliskiren 300 mg/HCTZ 25 mg was statistically superior to aliskiren 300 mg (i.e. statistically significant in favor of aliskiren 300 mg/HCTZ 25 mg), then the effectiveness of aliskiren 300 mg/HCTZ 25 mg was established and further assessment for efficacy of aliskiren 300 mg/HCTZ 12.5 mg compared to aliskiren 300 mg was then made. Since this is a closed procedure, no multiple comparison adjustment needed to be made and significance level for the latter test was also 0.05. No inference was made between aliskiren 300 mg/HCTZ 12.5 mg and aliskiren 300 mg if the first test on aliskiren 300 mg/HCTZ 25 mg was not statistically significant.

The primary variable at endpoint was analyzed using a two-way analysis of covariance model with treatment and region as two factors, and the baseline as covariate. This model was considered the primary model. Data from centers was combined by region so that an adequate number of patients were available for analysis.

To assess whether the combination of aliskiren 300 mg/HCTZ 25 mg was superior to aliskiren 300 mg alone, the primary variable at endpoint for the ITT population was analyzed using the primary model. The null hypothesis to be tested was that there was no treatment difference between combination of aliskiren 300 mg/HCTZ 25 mg and aliskiren 300 mg alone versus the alternative hypothesis of a treatment difference. The pair-wise comparison was made based on the primary model at the two-sided significance level of 0.05. The same assessment for the comparison between aliskiren 300 mg/HCTZ 12.5 mg and aliskiren 300 mg alone was made.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria

1. Outpatients 18 years of age and older.
2. Male or female patients were eligible.
3. Patients with a diagnosis of hypertension:
   - Newly diagnosed patients or patients who have not been treated for hypertension within the 4 weeks prior to Visit 1 must have had an msDBP >= 95 mmHg and < 110 mmHg at Visit 1.
   - All patients who have been treated for hypertension within the 4 weeks prior to Visit 1 must have had an msDBP >= 85 mmHg and < 110 mmHg at Visit 2.
   - All patients must have had an msDBP >= 90 mmHg and < 110 mmHg at Visit 4.
4. 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 has been clearly explained to them (written informed consent).

Exclusion criteria

Patients with any of the following at Visit 1, Visit 2, Visit 3, or Visit 4 (unless otherwise stated) were excluded from participation in the study:

1. Pregnant or nursing (lactating) women, where pregnancy was defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test (>= 5 mIU/mL).
2. Women of child-bearing potential (WOCBP), defined as all women physiologically capable of becoming pregnant, including women whose career, lifestyle or sexual orientation precluded intercourse with a male partner and women whose partners have been sterilized by vasectomy or other means, UNLESS they met the following definition of post-menopausal: 12 months of natural (spontaneous) amenorrhea or 6 months of spontaneous amenorrhea with serum follicle stimulating hormone (FSH) levels > 40 mIU/mL or 6 weeks post surgical bilateral oophorectomy with or without hysterectomy OR were using one or more of the following acceptable methods of contraception such as surgical sterilization (e.g. bilateral tubal ligation) and hormonal contraception (implantable, patch, oral). Reliable contraception was to be maintained throughout the study and for 7 days after medication discontinuation.
3. Severe hypertension (msDBP >= 110 mmHg and/or msSBP >= 180 mmHg).
4. History or evidence of a secondary form of hypertension.
5. Known Keith-Wagener grade III or IV hypertensive retinopathy.
6. Previous or current diagnosis of heart failure.
7. History of hypertensive encephalopathy or cerebrovascular accident, transient ischemic cerebral attack (TIA), myocardial infarction, coronary bypass surgery, or any percutaneous coronary intervention (PCI).
8. Serum potassium < 3.5 mEq/L (mmol/L) or >= 5.3 mEq/L (mmol/L), serum sodium less than the lower limit of normal or dehydration.
9. Patients with Type 1 or Type 2 diabetes mellitus who were not well controlled based on the

investigator's clinical judgment. Patients with diabetes mellitus enrolled in this study were to be well controlled. It was recommended that patients currently being treated for diabetes mellitus be on a stable dose of oral antidiabetic medication for at least 4 weeks prior to Visit 1.

10. Current angina pectoris requiring pharmacological therapy.
11. Second or third degree heart block without a pacemaker.
12. Atrial fibrillation or atrial flutter at Visit 1, or potentially life threatening or any symptomatic arrhythmia during the 12 months prior to Visit 1.
13. Clinically significant valvular heart disease.
14. Any medication, surgical or medical condition, which might have significantly altered the absorption, distribution, metabolism, or excretion of medications including, but not limited to, any of the following:
    - History of major gastrointestinal tract surgery such as gastrectomy, gastroenterostomy, or bowel resection.
    - History of active inflammatory bowel disease during the 12 months prior to Visit 1.
    - Currently active gastritis, duodenal or gastric ulcers, or history of gastrointestinal bleeding during the 3 months prior to Visit 1.
    - Evidence of hepatic disease as determined by any one of the following: alanine aminotransferase (ALT) or aspartate aminotransferase (AST) values exceeding 3x upper limit of normal (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 x ULN at Visit 1, a history of dialysis, or a history of nephrotic syndrome.
    - Current treatment with cholestyramine or colestipol resins.
15. History of hypersensitivity to any of the medications or to drugs belonging to the similar therapeutic class (ARB's, ACE-I's, thiazide diuretics, or other sulfonamide derived drugs) as the medications.
16. History of angioedema due to usage of an ACE-I or ARB.
17. History of malignancy of any organ system, treated or untreated, within the past 5 years whether or not there was evidence of local recurrence or metastases, with the exception of localized basal cell carcinoma of the skin.
18. History of gouty arthritis.
19. History or evidence of drug or alcohol abuse within the last 12 months.
20. 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.
21. Patients who previously enrolled in the active drug treatment period of a clinical trial that contained the treatment combination of aliskiren/HCTZ.
22. Use of other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives of enrollment, whichever is longer.
23. History of noncompliance to medical regimens or unwillingness to comply with the study protocol.

24. Any condition that in the opinion of the investigator or the Novartis Medical Monitor would have confounded the evaluation and interpretation of efficacy and/or safety data.

25. Persons directly involved in the execution of this protocol.

Number of Subjects

	Aliskiren 300mg/ HCTZ 25 mg	Aliskiren 300 mg/ HCTZ 12.5 mg	Aliskiren 300 mg	Total
Planned N	242	242	242	726
Randomized n	289[1]	293	298	880
Intent-to-treat population (ITT) n (%)	284 (98.3)	292 (99.7)	296 (99.3)	872 (99.1)
Completed n (%)	266 (92.0)	278 (94.9)	277 (93.0)	821 (93.3)
Withdrawn n (%)	22[1] (7.6)	15 (5.1)	21 (7.0)	58 (6.6)
Withdrawn due to adverse events n (%)	7 (2.4)	6 (2.0)	6 (2.0)	19 (2.2)
Withdrawn due to lack of efficacy n (%)	5 (1.7)	4 (1.4)	7 (2.3)	16 (1.8)
Withdrawn for other reasons n (%)	10 (3.5)	5 (1.7)	8 (2.7)	23 (2.6)

Percentage (%) was calculated using the randomized population as the denominator.
[1] One patient was randomized to treatment group aliskiren 300 mg/HCTZ 25 mg in error (assigned a randomization number while not satisfying randomization criteria). The patient was discontinued in the single-blind period without receiving double-blind medication. This patient was not counted as discontinued in the double-blind period.

Demographic and Background Characteristics

Demographic characteristic category/statistic	Aliskiren 300 mg/HCTZ 25 mg N = 289	Aliskiren 300 mg/HCTZ 12.5 mg N = 293	Aliskiren 300 mg N = 298	Total N = 880
Sex n (%)				
Female	117 (40.5%)	138 (47.1%)	139 (46.6%)	394 (44.8%)
Male	172 (59.5%)	155 (52.9%)	159 (53.4%)	486 (55.2%)
Race n (%)				
Caucasian	239 (82.7%)	241 (82.3%)	245 (82.2%)	725 (82.4%)
Black	6 (2.1%)	5 (1.7%)	3 (1.0%)	14 (1.6%)
Asian	22 (7.6%)	23 (7.8%)	28 (9.4%)	73 (8.3%)
Native American	1 (0.3%)	2 (0.7%)	0 (0.0%)	3 (0.3%)
Other	21 (7.3%)	22 (7.5%)	22 (7.4%)	65 (7.4%)
Age (yrs)				
N	289	293	298	880
Mean	54.4	54.9	55.5	54.9
SD	10.25	10.49	10.60	10.45
Age group n (%)				
< 65	239 (82.7%)	232 (79.2%)	240 (80.5%)	711 (80.8%)
>= 65	50 (17.3%)	61 (20.8%)	58 (19.5%)	169 (19.2%)
< 75	282 (97.6%)	290 (99.0%)	287 (96.3%)	859 (97.6%)
>= 75	7 (2.4%)	3 (1.0%)	11 (3.7%)	21 (2.4%)
Duration of hypertension (yrs)				
N	278	282	291	851
Mean	7.8	7.6	7.9	7.8
SD	6.17	7.18	6.76	6.71
n (naive patients)	11 (3.8%)	11 (3.8%)	7 (2.3%)	29 (3.3%)
Weight (kg)				
N	289	290	296	875
Mean	81.6	81.2	81.1	81.3
SD	16.14	15.86	14.54	15.51
Body Mass Index (kg/m^2)				
N	289	289	294	872
Mean	28.9	29.2	29.2	29.1
SD	4.55	4.92	4.53	4.67
Obesity n (%)				
BMI < 30 (kg/m**2)	181 (62.6%)	179 (61.1%)	181 (60.7%)	541 (61.5%)
BMI >= 30 (kg/m**2)	108 (37.4%)	110 (37.5%)	113 (37.9%)	331 (37.6%)

Primary Objective Result(s)

Statistical analysis of change from baseline in mean sitting diastolic blood pressure at endpoint (intent-to-treat population)

Treatment group	N	LSM change from baseline (SE)	
Aliskiren 300 mg/HCTZ 25 mg	284	- 11.00	(0.551)
Aliskiren 300 mg/HCTZ 12.5 mg	292	- 10.54	(0.539)
Aliskiren 300 mg	296	- 7.42	(0.539)
Pairwise comparison	LSM difference in change from baseline	95% CI for LSM difference	P-value
Ali 300 mg/HCTZ 25mg vs. Ali 300 mg	- 3.58	(- 5.01, - 2.15)	< 0.001*
Ali 300 mg/HCTZ 12.5 mg vs. Ali 300 mg	- 3.12	(- 4.54, - 1.70)	< 0.001*

SE = standard error, LSM = least squares mean, CI = confidence interval
Least squares means, confidence intervals, and p-values were from an ANCOVA model containing treatment, region and baseline.
P-values and treatment comparisons were evaluated at the average baseline level.
* indicates statistical significance at 0.05 level.

Secondary Objective Result(s)

Statistical analysis of change from baseline in mean sitting systolic blood pressure at endpoint (intent-to-treat population)

Treatment group	N	LSM change from baselilne (SE)	
Aliskiren 300 mg/HCTZ 25 mg	284	- 15.85	(0.886)
Aliskiren 300 mg/HCTZ 12.5 mg	292	- 13.49	(0.867)
Aliskiren 300 mg	296	- 7.96	(0.866)
Pairwise comparison	LSM difference in change from baseline	95% CI for LSM difference	P-value
Ali 300 mg/HCTZ 25mg vs. Ali 300 mg	- 7.90	(- 10.20, - 5.59)	< 0.001*
Ali 300 mg/HCTZ 12.5 mg vs. Ali 300 mg	- 5.53	(- 7.82, - 3.25)	< 0.001*

SE = standard error, LSM = least squares mean, CI = confidence interval
Least squares means, confidence intervals, and p-values were from an ANCOVA model containing treatment, region and baseline.
P-values and treatment comparisons were evaluated at the average baseline level.
* indicates statistical significance at 0.05 level.

Between treatment comparison for blood pressure control at endpoint by treatment group (intent-to-treat population)

	Treatment A		Treatment B		p-value
Treatment comparison A vs. B	n / N	(%)	n / N	(%)	
Ali 300 mg/HCTZ 25 mg vs. Ali 300 mg	171/284	60.21	121/296	40.88	< 0.001*
Ali 300 mg/HCTZ 12.5 mg vs. Ali 300 mg	169/292	57.88	121/296	40.88	< 0.001*

A patient with control in BP is defined as having a mean sitting diastolic blood pressure < 90 mmHg and a mean sitting systolic blood pressure < 140 mmHg.
The control rate was analyzed by using a logistic regression model with treatment and region as factors and baseline msDBP as a covariate.
Baseline is the Week 0 value.
* indicates statistical significance at 0.05 level.

Safety Results

Number (%) of patients with overall AEs starting in double-blind period by treatment group and primary system organ class (safety double-blind population)

Primary system organ class	Aliskiren 300 mg/ HCTZ 25mg N = 288 n (%)	Aliskiren 300 mg/ HCTZ 12.5 mg N = 293 n (%)	Aliskiren 300 mg N = 298 n (%)	Total N = 879 n (%)
Any primary system organ class	65 (22.6)	53 (18.1)	71 (23.8)	189 (21.5)
Infections and infestations	21 (7.3)	15 (5.1)	19 (6.4)	55 (6.3)
Metabolism and nutrition disorders	20 (6.9)	6 (2.0)	16 (5.4)	42 (4.8)
Nervous system disorders	12 (4.2)	11 (3.8)	13 (4.4)	36 (4.1)
Gastrointestinal disorders	9 (3.1)	11 (3.8)	10 (3.4)	30 (3.4)
Injury, poisoning and procedural complications	6 (2.1)	2 (0.7)	2 (0.7)	10 (1.1)
Musculoskeletal and connective tissue disorders	6 (2.1)	10 (3.4)	11 (3.7)	27 (3.1)
Investigations	5 (1.7)	3 (1.0)	4 (1.3)	12 (1.4)
Vascular disorders	4 (1.4)	3 (1.0)	1 (0.3)	8 (0.9)
Cardiac disorders	3 (1.0)	0 (0.0)	2 (0.7)	5 (0.6)
Ear and labyrinth disorders	3 (1.0)	2 (0.7)	1 (0.3)	6 (0.7)
General disorders and administration site conditions	3 (1.0)	1 (0.3)	7 (2.3)	11 (1.3)
Renal and urinary disorders	2 (0.7)	1 (0.3)	2 (0.7)	5 (0.6)
Respiratory, thoracic and mediastinal disorders	2 (0.7)	2 (0.7)	3 (1.0)	7 (0.8)
Skin and subcutaneous tissue disorders	2 (0.7)	3 (1.0)	3 (1.0)	8 (0.9)
Blood and lymphatic system disorders	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
Eye disorders	1 (0.3)	2 (0.7)	1 (0.3)	4 (0.5)
Hepatobiliary disorders	1 (0.3)	0 (0.0)	1 (0.3)	2 (0.2)
Psychiatric disorders	1 (0.3)	2 (0.7)	2 (0.7)	5 (0.6)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	0 (0.0)	1 (0.3)	1 (0.3)	2 (0.2)
Reproductive system and breast disorders	0 (0.0)	1 (0.3)	1 (0.3)	2 (0.2)

System organ classes (SOC) are sorted in descending frequency, as reported in the Aliskiren 300 mg/HCTZ 25 mg column.
A patient with multiple AEs within an SOC is counted only once.

Number (%) of patients with AEs (at least 2%) starting in double-blind period by treatment group (safety double-blind population)

Preferred term	Aliskiren 300 mg/ HCTZ 25 mg N = 288 n (%)	Aliskiren 300mg/ HCTZ 12.5 mg N = 293 n (%)	Aliskiren 300 mg N = 298 n (%)	Total N = 879 n (%)
Any AEs -Total	65 (22.6)	53 (18.1)	71 (23.8)	189 (21.5)
Headache	8 (2.8)	6 (2.0)	10 (3.4)	24 (2.7)
Hypercholesterolemia	7 (2.4)	2 (0.7)	3 (1.0)	12 (1.4)
Nasopharyngitis	3 (1.0)	2 (0.7)	6 (2.0)	11 (1.3)

Serious Adverse Events and Deaths

Number (%) of patients with deaths, serious adverse events, and discontinuations due to adverse events, and abnormal laboratory values during double-blind period (safety double-blind population)

	Aliskiren 300 mg /HCTZ 25 mg N = 288 n (%)	Aliskiren 300mg /HCTZ 12.5 mg N = 293 n (%)	Aliskiren 300 mg N = 298 n (%)	Total N = 879 n (%)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
SAEs	3 (1.0)	2 (0.7)	4 (1.3)	9 (1.0)
AE discontinuations	7 (2.4)	5 (1.7)	6 (2.0)	18 (2.1)
- drug-related AE discontinuations	5 (1.7)	3 (1.0)	2 (0.7)	10 (1.1)
- SAE discontinuations	1 (0.4)	1 (0.3)	2 (0.7)	4 (0.5)
Discontinuations for abnormal lab values	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)

SAEs:atrial fibrillation (2) cholecystitis (3), cardiovascular heart disease, syncope (fainting), colorectal cancer, and diverticulitis

Other Relevant Findings

None

Date of Clinical Trial Report 16-Jan-2008
Date Inclusion on Novartis Clinical Trial Results Database 02-July-2008
Date of Latest Update 28-October-2009