Sponsor

Novartis

Generic Drug Name

Aliskiren

Therapeutic Area of Trial

Essential Hypertension

Approved Indication

Hypertension

Study Number

CSPP100A2333

Title

An eight-week, randomized, double-blind, parallel-group, multicenter study to evaluate the efficacy and safety of the combination of aliskiren / HCTZ (150/25 mg and 300/25 mg) in comparison with HCTZ 25 mg in patients with essential hypertension not adequately responsive to HCTZ 25 mg monotherapy

Phase of Development

Phase III

Study Start/End Dates

09-Oct-2006 to 09-Aug-2007

Study Design/Methodology

This was an 8-week, randomized, double-blind, parallel-group, multicenter study comparing the efficacy and safety of the fixed-dose combination of aliskiren and hydrochlorothiazide (HCTZ) (300/25 mg and 150/25 mg) to HCTZ 25 mg alone in patients with essential hypertension who did not adequately respond to HCTZ monotherapy (msDBP >=90 mmHg and <110 mmHg after a 4-week treatment with HCTZ 25 mg). The study was comprised of 3 periods and 9 visits.

Centers

112 centers in 10 countries: Denmark (12), Finland (7), Germany (45), Hungary (4), Iceland (2), India (4), Netherlands (11), Poland (6), Slovakia (5), and Spain (16)

Publication

Blumenstein M, Romaszko J, Calderón A, Andersen K, Ibram G, Liu Z, Zhang J. (2009) Anti-hypertensive efficacy and tolerability of aliskiren/hydrochlorothiazide (HCT) single-pill combinations in patients who are non-responsive to HCT 25 mg alone.

Curr Med Res Opin. 2009 Apr;25(4):903-10.

PMID: 19245300

Objectives

Primary objective(s)

The primary objective of this study was to assess the efficacy of the fixed-dose combination therapy of aliskiren (150 mg and 300 mg) and HCTZ 25 mg on reduction in mean sitting diastolic blood pressure (msDBP) in hypertensive patients who did not show sufficient blood pressure (BP) response to a 4-week treatment of HCTZ 25 mg.

Secondary objective(s)

1. Evaluate the efficacy of the fixed-dose combination therapy of aliskiren (150 mg and 300 mg) and HCTZ 25 mg on reduction in mean sitting systolic BP (msSBP) in hypertensive patients who do not show sufficient BP response to a 4-week treatment of HCTZ 25 mg
2. Evaluate the safety and tolerability of the fixed-dose combination of aliskiren (150 mg and 300 mg) and HCTZ 25 mg compared with HCTZ 25 mg monotherapy in hypertensive patients who do not show sufficient BP response to a 4-week treatment of HCTZ 25 mg
3. Evaluate the proportion of patients achieving a BP control target of < 140/90 mmHg at the end of study for all treatments arms

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

Each patient took one capsule and two tablets of study medication (study drug or matched placebo) orally with water. Investigational therapy included aliskiren 300 mg/HCTZ 25 mg and aliskiren 150 mg/HCTZ 25 mg tablets

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

HCTZ 25 mg capsules taken orally once daily

Criteria for Evaluation

Primary variables

Efficacy of study drug was determined by BP measurements. Sitting and standing BP was measured at trough (24 hours ± 3 hours post dose) and recorded at all study visits. The primary efficacy variable was change from baseline (visit 5) in 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 variables

Secondary efficacy variables were change from baseline (visit 5) in msSBP at endpoint, and blood pressure control (msSBP/msDBP <140/90 mmHg) at endpoint,

Safety and tolerability

Safety assessments consisted of monitoring and recording all adverse events (AEs) and serious AEs (SAEs)

Pharmacology

None

Other

None

Statistical Methods

A hierarchical method was used to assess the effects of aliskiren combinations with HCTZ versus HCTZ monotherapy. First aliskiren 300 mg/HCTZ 25 mg was compared to HCTZ 25 mg. If aliskiren 300/HCTZ 25 was statistically superior to HCTZ 25 (i.e. statistically significant in favor of aliskiren 300/HCTZ 25), the effectiveness of aliskiren 300/HCTZ25 was established and further assessment for efficacy of aliskiren 150/HCTZ 25 compared to HCTZ 25 was then made. As this was a closed procedure, no multiple comparison adjustment was required, and significance level for the latter test was also 0.05. No inference was to be made between aliskiren 150/HCTZ 25 and HCTZ 25 if the first test on aliskiren 300/HCTZ 25 was not statistically significant.

The primary variable at endpoint was analyzed using a two-way analysis of covariance (ANCOVA) model with treatment and region as two factors and the baseline as a 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/HCTZ 25 was superior to HCTZ 25 alone, the primary variable at endpoint for the intent-to-treat (ITT) population was analyzed using the primary model. The null hypothesis to be tested was that there was no treatment difference be-

tween the combination of aliskiren 300 mg/HCTZ 25 mg and HCTZ 25 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 was made for the comparison between aliskiren 150 mg/HCTZ 25 mg and HCTZ 25 mg alone.

The analysis described for msDBP was also performed for msSBP. Blood pressure response (msDBP <90 mmHg or a >=10 mmHg decrease compared to baseline) and blood pressure control (msSBP/msDBP <140/90 mmHg) were also evaluated.

Occurrence and frequency of AEs were summarized by treatment group, body system, and preferred term. AEs were also summarized by severity and relationship to study drug. In addition, the incidences of deaths, serious AEs, and AEs leading to discontinuation were summarized separately by treatment group, primary system organ class, and preferred term.

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 had 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 had 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 5.
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 had been clearly explained to them (written informed consent).

Exclusion Criteria

Patients exhibiting any of the following at visit 1, visit 2, visit 3, visit 4, or visit 5 (unless otherwise stated) were excluded from participation in the study:

1. Pregnant or nursing (lactating) women or women of child-bearing potential (WOCBP) UNLESS they met a definition of post-menopausal OR were using 1 or more of the acceptable methods of contraception. Reliable contraception was requested to be maintained throughout the study and for 7 days after medication discontinuation.
2. Severe hypertension (msDBP >= 110 mmHg and/or msSBP >= 180 mmHg), history or evidence of a secondary form of hypertension, or known Keith-Wagener grade III or IV hypertensive retinopathy.
3. Previous or current diagnosis of heart failure. History of hypertensive encephalopathy or cerebrovascular accident, transient ischemic cerebral attack (TIA), myocardial infarction (MI), coronary bypass surgery, any percutaneous coronary intervention (PCI). Current angina pectoris requiring pharmacological therapy; second or third degree heart block without a pacemaker; or clinically significant valvular heart disease.

4. 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.
5. Type 1 or Type 2 diabetes mellitus, which was not well controlled based on the investigator's clinical judgment.
6. Atrial fibrillation or atrial flutter at visit 1, or potentially life threatening or any symptomatic arrhythmia during the 12 months prior to visit 1.
7. Any medication or 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.
   - 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 1 of the following: alanine aminotransferase (ALT) or aspartate aminotransferase (AST) values exceeding 3 x the 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 1 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 and colestipol resins.
8. History of hypersensitivity to any of the study drugs or to drugs belonging to the similar therapeutic class (ARBs, ACEIs, thiazide diuretics, or other sulfonamide derived drugs) as the study drugs.
9. History of angioedema due to usage of an ACEI or ARB.
10. 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.
11. History of gouty arthritis
12. History or evidence of drug or alcohol abuse within the last 12 months.
13. 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.
14. Previous enrollment in the active drug treatment period of a clinical trial that contained the treatment combination of aliskiren/HCTZ.
15. Use of other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives of enrollment, whichever was longer.
16. History of noncompliance to medical regimens or unwillingness to comply with the study protocol.
17. Any condition that in the opinion of the investigator or the Novartis Medical Monitor would confound the evaluation and interpretation of efficacy and/or safety data.
18. Directly involved in the execution of the protocol.

Number of Subjects

	Aliskiren 300 mg/ HCTZ 25 mg N (%)	Aliskiren 150 mg/ HCTZ 25 mg N (%)	HCTZ 25 mg N (%)	Total N (%)
Planned N	242	242	242	726
Randomized n	232	244	246	722
Intent-to-treat population (ITT) n (%)	232 (100.0)	242 (99.2)	244 (99.2)	718 (99.4)
Completed n (%)	225 (97.0)	235 (96.3)	231 (93.9)	691 (95.7)
Withdrawn n (%)	7 (3.0)	8 (3.3)	14 (5.7)	29 (4.0)
Withdrawn due to adverse events n (%)	4 (1.7)	4 (1.6)	5 (2.0)	13 (1.8)
Withdrawn due to lack of efficacy n (%)	2 (0.9)	1 (0.4)	1 (0.4)	4 (0.6)
Withdrawn for other reasons n (%)	1 (0.4)	3 (1.2)	8 (3.3)	12 (1.7)

Percentage (%) is calculated using the randomized population as the denominator.

[1] Two patients were randomized in error. They were assigned a randomization number (1 to the aliskiren 150 mg/HCTZ 25 mg group and 1 to the HCTZ 25 mg group) before the assessment of the randomization criteria. The patients were discontinued from the single-blind period (due to not meeting BP criteria for randomization) without taking any double-blind study medication. Therefore, these 2 patients were not counted as discontinued from the double-blind period.

Demographic and Background Characteristics

Demographic Characteristic Category/statistic	Aliskiren 300 mg/ HCTZ 25 mg N=232	Aliskiren 150 mg/ HCTZ 25 mg N=244	HCTZ 25 mg N=246	Total N=722
Sex n (%)				
Female	92 (39.7%)	100 (41.0%)	103 (41.9%)	295 (40.9%)
Male	140 (60.3%)	144 (59.0%)	143 (58.1%)	427 (59.1%)
Race n (%)				
Caucasian	210 (90.5%)	224 (91.8%)	224 (91.1%)	658 (91.1%)
Black	0 (0.0%)	1 (0.4%)	1 (0.4%)	2 (0.3%)
Asian	20 (8.6%)	17 (7.0%)	18 (7.3%)	55 (7.6%)
Other	2 (0.9%)	2 (0.8%)	3 (1.2%)	7 (1.0%)
Ethnicity n (%)				
Hispanic or Latino	35 (15.1%)	34 (13.9%)	35 (14.2%)	104 (14.4%)
Indian (Indian Subcontinent)	19 (8.2%)	16 (6.6%)	18 (7.3%)	53 (7.3%)
Mixed ethnicity	0 (0.0%)	1 (0.4%)	0 (0.0%)	1 (0.1%)
Other	178 (76.7%)	193 (79.1%)	193 (78.5%)	564 (78.1%)
Age (yrs)				
N	232	244	246	722
Mean	54.1	53.6	52.9	53.5
SD	9.45	11.11	11.49	10.74
Age group n (%)				
< 65	200 (86.2%)	206 (84.4%)	211 (85.8%)	617 (85.5%)
≥ 65	32 (13.8%)	38 (15.6%)	35 (14.2%)	105 (14.5%)
< 75	230 (99.1%)	242 (99.2%)	237 (96.3%)	709 (98.2%)
≥ 75	2 (0.9%)	2 (0.8%)	9 (3.7%)	13 (1.8%)
Duration of hypertension (yrs)				
N	217	228	233	678
Mean	7.1	6.5	6.9	6.8
SD	7.19	5.66	6.07	6.32
n (naive patients)	15 (6.5%)	16 (6.6%)	13 (5.3%)	44 (6.1%)
Body Mass Index (kg/m^2)				
N	230	243	243	716
Mean	29.9	28.9	29.7	29.5
SD	5.00	4.71	4.99	4.91
Obesity n (%)				
BMI < 30 (kg/m^2)	119 (51.3%)	153 (62.7%)	140 (56.9%)	412 (57.1%)
BMI ≥ 30 (kg/m^2)	111 (47.8%)	90 (36.9%)	103 (41.9%)	304 (42.1%)

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	232	- 10.73	(0.481)
Aliskiren 150 mg/HCTZ 25 mg	242	- 8.52	(0.471)
HCTZ 25 mg	244	- 4.80	(0.469)

Pairwise comparison	LSM difference in change from baseline	95% CI for LSM difference	P-value
Ali 300 mg/HCTZ 25mg vs. HCTZ 25 mg	- 5.94	(- 7.24, - 4.63)	< 0.001*
Ali 150 mg/HCTZ 25 mg vs. HCTZ 25 mg	- 3.73	(- 5.02, - 2.43)	< 0.001*

SE = standard error, LSM = least squares mean, CI = confidence interval
Ali = aliskiren; HCTZ = hydrochlorothiazide
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)

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. HCTZ 25 mg	135/232	58.19	63/244	25.82	< 0.001*
Ali 150 mg/HCTZ 25 mg vs. HCTZ 25 mg	118/242	48.76	63/244	25.82	< 0.001*

Blood pressure control is defined as having a mean sitting diastolic blood pressure (msDBP) < 90 mmHg and a mean sitting systolic blood pressure (msSBP) < 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.
Ali = aliskiren; HCTZ = hydrochlorothiazide

Safety Results

Adverse Events by System Organ Class

Primary system organ class	Aliskiren 300 mg/ HCTZ 25 mg N=232 n (%)	Aliskiren 150 mg/ HCTZ 25 mg N=243 n (%)	HCTZ 25 mg N=245 n (%)	Total N=720 n (%)
Any system organ class	86 (37.1)	84 (34.6)	83 (33.9)	253 (35.1)
Infections and infestations	22 (9.5)	24 (9.9)	19 (7.8)	65 (9.0)
Gastrointestinal disorders	13 (5.6)	13 (5.3)	6 (2.4)	32 (4.4)
Musculoskeletal and connective tissue disorders	13 (5.6)	12 (4.9)	14 (5.7)	39 (5.4)
Nervous system disorders	11 (4.7)	10 (4.1)	17 (6.9)	38 (5.3)
General disorders and administration site conditions	8 (3.4)	5 (2.1)	6 (2.4)	19 (2.6)
Ear and labyrinth disorders	7 (3.0)	1 (0.4)	0 (0.0)	8 (1.1)
Metabolism and nutrition disorders	7 (3.0)	12 (4.9)	8 (3.3)	27 (3.8)
Cardiac disorders	6 (2.6)	2 (0.8)	4 (1.6)	12 (1.7)
Injury, poisoning and procedural complications	6 (2.6)	3 (1.2)	6 (2.4)	15 (2.1)
Respiratory, thoracic and mediastinal disorders	6 (2.6)	8 (3.3)	7 (2.9)	21 (2.9)
Investigations	3 (1.3)	3 (1.2)	0 (0.0)	6 (0.8)
Psychiatric disorders	3 (1.3)	2 (0.8)	4 (1.6)	9 (1.3)
Vascular disorders	3 (1.3)	4 (1.6)	3 (1.2)	10 (1.4)
Eye disorders	2 (0.9)	3 (1.2)	1 (0.4)	6 (0.8)
Skin and subcutaneous tissue disorders	2 (0.9)	3 (1.2)	9 (3.7)	14 (1.9)
Blood and lymphatic system disorders	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)
Renal and urinary disorders	1 (0.4)	0 (0.0)	2 (0.8)	3 (0.4)
Hepatobiliary disorders	0 (0.0)	2 (0.8)	0 (0.0)	2 (0.3)
Immune system disorders	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Reproductive system and breast disorders	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)

System organ classes are sorted in descending frequency, as reported in the aliskiren 300 mg/HCTZ 25 mg column.

A patient with multiple adverse events within a primary system organ class is counted only once.

Number (%) of patients with adverse events (>=2.0%) starting in double-blind period by treatment group (safety double-blind population)

Preferred term	Aliskiren 300 mg/ HCTZ 25 mg N=232 n (%)	Aliskiren 150 mg/ HCTZ 25 mg N=243 n (%)	HCTZ 25mg N=245 n (%)	Total N=720 n (%)
Any adverse events (total)	86 (37.1)	84 (34.6)	83 (33.9)	253 (35.1)
Nasopharyngitis	7 (3.0)	8 (3.3)	6 (2.4)	21 (2.9)
Dizziness	6 (2.6)	3 (1.2)	3 (1.2)	12 (1.7)
Back pain	5 (2.2)	1 (0.4)	2 (0.8)	8 (1.1)
Vertigo	5 (2.2)	0 (0.0)	0 (0.0)	5 (0.7)
Headache	2 (0.9)	5 (2.1)	10 (4.1)	17 (2.4)

Preferred terms are sorted in descending frequency, as reported in the aliskiren 300 mg/HCTZ 25 mg column.

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

	Aliskiren 300 mg/ HCTZ 25 mg N=232 n(%)	Aliskiren 150 mg/ HCTZ 25 mg N=243 n(%)	HCTZ 25 mg N=245 n(%)	Total N=720 n(%)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
SAEs	1 (0.4)	1 (0.4)	0 (0.0)	2 (0.3)
AE discontinuations	4 (1.7)	4 (1.6)	5 (2.0)	13 (1.8)
drug-related AE discontinuations	3 (1.3)	2 (0.8)	3 (1.2)	8 (1.1)
SAE discontinuations	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Discontinuations for abnormal lab values	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)

1 gastroenteritis, 1 clavicle fracture.

Other Relevant Findings

None

Date of Clinical Trial Report 29 October 2007
Date Inclusion on Novartis Clinical Trial Results Database 02 July 2008
Date of Latest Update 28 October 2009