Sponsor

Novartis

Generic Drug Name

Aliskiren

Therapeutic Area of Trial

Hypertension

Approved Indication

Investigational

Study Number

CSPP100A2323 and CSPP100A2323E1

Title

A twenty six-week, randomized, double-blind, parallel group, multicenter, active-controlled, dose titration study to evaluate the efficacy and safety of aliskiren compared to HCTZ with the optional addition of amlodipine, followed by a second twenty six weeks of blinded treatment, in patients with essential hypertension

Phase of Development

Phase III

Study Start/End Dates

30-Mar-2005 to 27-Jul-2006

Study Design/Methodology

This was a randomized, double-blind, parallel group, multicenter, active-controlled, dose-titration study in patients with uncomplicated essential hypertension (msDBP >= 95 mm Hg and < 110 mm Hg).

The study comprised of 4 periods:

- Period 1 – A 2 week washout for the supervision of the discontinuation / tapering of prior antihypertensive medications for >= 1 week prior to Period 2, and determination of patient eligibility. Newly diagnosed or untreated patients were directly entered into Period 2.
- Period 2 – A 2 to 4 week single-blind, placebo run-in to determine eligibility for randomization and establish baseline blood pressure (BP). Optional Visit 201 allowed two additional weeks to meet BP criteria. After four weeks, patients who did not meet the eligibility criteria were discontinued.

Period 3 – Randomized study drug treatment period consisting of:

- A 6 week double-blind placebo-controlled period
  - Visit 3 (Randomization) – eligible patients were randomized to receive either aliskiren 150 mg, Hydrochlorothiazide (HCTZ) 12.5 mg, or placebo in a 2:2:1 ratio.
  - Visit 4 – forced titration from aliskiren 150 mg to 300 mg; or HCTZ 12.5 mg to 25 mg.

- A 20 week double-blind active controlled with optional open-label amlodipine:
  - Visit 5 – patients in the placebo group were provided with either aliskiren 300 mg or HCTZ 25 mg in a 1:1 ratio according to their treatment assignment.
  - Visits 7 and 9 – patients receiving monotherapy and not achieving the target BP (<140/90 mm Hg) were provided with low dose amlodipine (5 mg). Visit 9, the amlodipine dose could be increased to 10 mg if the target BP was not achieved.

Period 4 – 26-week blinded maintenance period (Weeks 26 – 52; Visits 11, 12, 13 and 14).

During the last 6 months of the treatment period, most patients were expected to remain on a stable dosage regimen. Patients achieving the target BP during Period 3 continued the treatment regimen on which the target BP was achieved for the remainder of the study. However, if after achieving the target BP, the patient's BP remained above 140/90 mm Hg at two consecutive visits, patients had their open-label study treatment increased to the next titration step. Down titration or discontinuation of open-label amlodipine was permitted, however down titration of aliskiren or HCTZ was not allowed.

Centres

132 centers in 6 countries: Belgium (11), Finland (6), Germany (34), Italy (43), Netherlands (20), Spain (18)

Objectives

Primary objective(s)

The primary objective of this study was to:

- Compare the long term efficacy of an aliskiren-based treatment regimen (aliskiren 150 mg, 300 mg with optional add-on of amlodipine 5 mg/10 mg) to a HCTZ-based treatment regimen (HCTZ 12.5 mg, 25 mg with optional add-on of amlodipine 5 mg/10 mg), in patients with essential hypertension by (i) testing the hypothesis of non-inferiority of the aliskiren-based treatment regimen versus the HCTZ-based treatment regimen on reduction of mean sitting diastolic blood pressure (msDBP) from baseline at 26 weeks, and (ii) the hypothesis of superiority for the aliskiren-based treatment regimen versus the HCTZ-based treatment regimen on reduction in msDBP from baseline, if the hypothesis of non-inferiority was achieved.

Secondary objective(s)

The secondary objectives of this trial were to:

- Compare the long term efficacy of an aliskiren based treatment regimen (aliskiren 150 mg, 300 mg with optional addition of amlodipine 5 mg/10 mg) to a HCTZ based treatment regimen (HCTZ 12.5 mg, 25 mg with optional addition of amlodipine 5 mg/10 mg) in patients with essential hypertension by (i) testing the hypothesis of non-inferiority of the aliskiren regimen versus the HCTZ regimen on reduction of msDBP and msSBP at 52 weeks from baseline and (ii) the hypothesis of superiority for the aliskiren regimen versus the HCTZ regimen on reduction in msDBP and msSBP from baseline, if the hypothesis of non-inferiority was achieved.
- Compare the proportions of patients who respond to treatment (DBP < 90 mm Hg or a decrease from baseline >= 10 mm Hg) or who are controlled (BP < 140/90 mm Hg) with an aliskiren-based treatment regimen (aliskiren 150 mg, 300 mg with optional addition of amlodipine 5 mg/10 mg) and a HCTZ-based treatment regimen (HCTZ 12.5 mg, 25 mg with optional addition of amlodipine 5 mg/10 mg), after 26 and 52 weeks.
- Evaluate the proportion of patients controlled to a target BP of < 140/90 mm Hg on the aliskiren monotherapy regimen when compared to the HCTZ monotherapy regimen, after 26 weeks and 52 weeks.
- Compare the long term safety and tolerability of an aliskiren-based treatment regimen (aliskiren 150 mg, 300 mg with optional addition of amlodipine 5 mg/10 mg) to a HCTZ-based treatment regimen (HCTZ 12.5 mg, 25 mg with amlodipine 5 mg/10 mg) in this patient population after 26 weeks and 52 weeks of treatment.
- Compare the long term effect of treatment with an aliskiren-based treatment regimen (aliskiren 150 mg, 300 mg with optional addition of amlodipine 5 mg/10 mg) to a HCTZ-based treatment regimen (HCTZ 12.5 mg, 25 mg with amlodipine 5 mg/10 mg) on laboratory and metabolic parameters (triglycerides, total cholesterol, LDL, HDL, potassium, uric acid, fasting plasma glucose, homeostasis model assessment of insulin resistance (HOMA-IR), and fasting insulin).
- Compare the long term effect of treatment with an aliskiren-based treatment regimen (aliskiren 150 mg, 300 mg with optional addition of amlodipine 5 mg/10 mg) to a HCTZ-

based treatment regimen (HCTZ 12.5 mg, 25 mg with amlodipine 5 mg/10 mg) on arterial compliance and oral glucose tolerance in a subset of patients.

- Evaluate the long term effect of an aliskiren-based treatment regimen (aliskiren 150 mg, 300 mg with optional addition of amlodipine 5 or 10 mg) to a HCTZ-based treatment regimen (HCTZ 12.5 and 25 mg with amlodipine 5 or 10 mg) on Quality of Life (QOL).

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

Aliskiren 150 mg film-coated tablet
Aliskiren 300 mg film-coated

Placebo film-coated tablet

Each patient was to take medication orally with water at approximately 8:00 A.M, except on the morning of study visits.

Study drugs were provided as medication packs containing 3 bottles each. Aliskiren 150 and 300 mg were provided as film-coated tablets, each of a different size, shape and color. The placebos to aliskiren 150 and 300 mg tablets were matched in respective size, shape, and color to the active tablets. HCTZ 12.5 and 25 mg, and placebo to HCTZ (12.5 and 25 mg) were provided as identically-appearing capsules. In order to adequately blind the study, patients were required to take a total of 2 tablets and one capsule (one from each bottle) throughout the study .

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

Hydrochlorothiazide (HCTZ) 12.5 mg hard gelatin capsule and HCTZ 25 mg hard gelatin capsule

Placebo hard gelatin capsule

Each patient was to take medication orally with water at approximately 8:00 A.M, except on the morning of study visits, from Visit 2 to the end of study

Criteria for Evaluation

Primary variables

msDBP change from Baseline (Visit 3) at endpoint (Visit 11; Week 26).

Secondary variables

Change from baseline for msSBP at 26 weeks, msDBP and msSBP at Week 52, msDBP and msSBP at Week 12 (monotherapy, with no addition of amlodipine), and msDBP at 6 weeks (monotherapy vs. placebo). Additional secondary efficacy variables were based on the proportion of patients controlled to a target BP of < 140/90 mm Hg, the proportion of responders (trough msDBP < 90 mm Hg and/or at least a 10 mm Hg reduction from baseline in msDBP), and Quality of Life, oral glucose tolerance test and arterial compliance (patient subset).

Biomarker

Biomarkers in plasma were obtained at Visit 3 (baseline), Visit 7 (after 12 weeks of treatment), Visit 11 (after 26 weeks of treatment), and Visit 14 (after 52 weeks of treatment) in a subset of about 50% of the patients in selected centers. In participating centers, biomarkers were collected for all patients randomized. The specific biomarkers evaluated included hsCRP, sICAM, MCP-1, LpPLA2, PAI-1, plasma renin activity (PRA), plasma renin concentration (direct renin), and aldosterone.

Safety and tolerability

Safety assessments consisted of monitoring and recording all adverse events (AEs) and serious adverse events (SAEs), the regular monitoring of hematology, blood chemistry and urine values, regular measurements of vital signs, and the performance of physical examination and (electrocardiograms) ECGs.

Statistical Methods

Baseline was defined as Visit 3 and Endpoint as Visit 11 (Week 26) or Visit 14 (Week 52), as specified. Patients initially receiving placebo during the first six weeks of the study were pooled as a total placebo group for results up to 6 weeks, and according to the treatment they subsequently received (aliskiren or HCTZ) for results after 6 weeks.

Primary efficacy analysis: The hypothesis of non-inferiority (the margin for non-inferiority was a reduction of 2 mm Hg in msDBP and 4 mm Hg in msSBP) of the aliskiren regimen versus the HCTZ regimen in msDBP reduction from baseline at Visit 11 (Week 26) was tested, and if non-inferiority was achieved, a hypothesis of superiority of the aliskiren regimen was tested. Mean

sitting DBP was analyzed using a two-way analysis of covariance (ANCOVA) model with treatment and country as two factors, and the baseline as a covariate. This was considered the primary model.

The statistical test for non-inferiority was made at a one-sided significance level of 0.025. If the non-inferiority test was statistically significant, non-inferiority for the aliskiren-based regimen versus the HCTZ-based regimen was concluded and a superiority test was performed. The statistical test for superiority was made at a two-sided significance level of 0.05.

All efficacy variables were analyzed for the primary efficacy population (Intent-to-treat [ITT]), with last observation carried forward (LOCF) for missing measurements (for Week 52, only values after Week 26 were carried forward), and msDBP was analyzed at Week 26 and Week 52 for the respective Per-protocol population (PP-26 and PP-52). Further analyses at Weeks 52, 26, 12 and 6 were carried out on the ITT population with both baseline and the relevant timepoint measurements (no LOCF). Mean time profiles by treatment group were produced for msDBP and msSBP.

Responder rates were analyzed by means of a logistic regression model with treatment and country as factors, and Baseline msDBP as a covariate. Two-sided p-values for pairwise comparisons (aliskiren doses vs. HCTZ) were provided. The null hypothesis tested was no treatment difference versus the alternative hypothesis of a treatment difference at the nominal 5% significance level.

Data were listed and also summarized with respect to background and demographic characteristics, efficacy measurements, and safety observations and measurements. Descriptive statistics (mean, standard deviation (SD), median, minimum and maximum) are provided for continuous variables. Categorical variables were summarized with frequency and percentage.

The results of a Health Authority inspection of Center 47 revealed significant GCP findings; therefore, an ad hoc sensitivity analysis, restricted to inferential statistics for the primary and selected secondary objectives, was performed for the ITT population excluding Center 47.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria:

Patients were eligible for inclusion if they met all of the following criteria:

- Outpatients 18 years of age and older.
- Patients with essential hypertension, having a msDBP >= 90 mm Hg and < 110 mm Hg at the visit immediately prior to Visit 3 (i.e. Visit 2 or optional Visit 201).
- Male or female patients. Female patients must have been either post-menopausal for one year, surgically sterile, or using effective contraceptive methods such as an intrauterine device, oral contraceptives, or barrier method with spermicide.
- Patients who were eligible, able to participate, and consented to do so after the purpose and nature of the study had been explained to them (written informed consent).

- At Visit 3 (Randomization) an msDBP >= 95 mm Hg and < 110 mm Hg, and an absolute difference <= 10 mm Hg in msDBP from Visit 2 (or optional Visit 201) were required.

Exclusion criteria:

Patients with any of the following physiological states or concomitant medical conditions prior to randomization were excluded from participation in the study.

- Pregnant or nursing women
- Conditions that could increase patient risk, prevent study compliance, or jeopardize the evaluation of efficacy or safety, including known or suspected contraindications to the study medications (aliskiren, thiazide diuretics or amlodipine).
- Participation in any investigational drug trial within one month of Visit 1
- Severe hypertension (msDBP >= 110 mm Hg and/or msSBP >= 180 mm Hg)
- History or evidence of:
    - secondary hypertension, hypertensive encephalopathy, cerebrovascular accident, or myocardial infarction
    - transient ischemic cerebral attack, coronary bypass surgery or any percutaneous coronary intervention (PCI) during the 12 months prior to Visit 1
    - known Keith-Wagener grade III or IV hypertensive retinopathy
    - malignancy, excluding basal cell skin cancer, within the past five years
    - drug or alcohol abuse within the last 12 months
- Current diagnosis of heart failure (NYHA Class II-IV), angina pectoris requiring pharmacological therapy (other than stable doses of oral or topical nitrates), second or third degree heart block without a pacemaker, potentially life threatening or symptomatic arrhythmia, clinically significant valvular heart disease
- Type 1 or 2 diabetes mellitus with fasting glycosylated hemoglobin (HbA1c) > 9% or microalbuminuria at Visit 1.
- Proteinuria or serum sodium less than the lower limit of normal, serum potassium < 3.5 mEq/L (3.5 mmol/L) or >= 5.5 mEq/L (5.5 mmol/L), or dehydration at Visit 1.
- Conditions 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 or pancreatic injury, pancreatitis,

impaired pancreatic function/injury indicated by abnormal lipase or amylase

- Currently / prior active inflammatory bowel disease within 12 months prior to Visit 1
- Currently active gastritis, duodenal or gastric ulcers, or gastrointestinal/rectal bleeding within 3 months prior to Visit 1
- Hepatic disease: AST (SGOT) or ALT (SGPT) values exceeding 3 times the upper limit of normal (ULN) at Visit 1, or history of hepatic encephalopathy, esophageal varices, or portocaval shunt
- Renal impairment: serum creatinine > 1.7 mg/dl (150 µmol/L; women) or > 2.0 mg/dl (177 µmol/L; men) at Visit 1, or history of dialysis or nephrotic syndrome
- Current treatment with cholesterol absorption inhibitors

Number of Subjects

Patient disposition for each treatment groups during the double-blind period (Randomized population)

	Aliskiren n (%)	HCTZ n (%)	Total n (%)
Total number of patients enrolled			**1275**
Patients randomized to double-blind treatment	**567 (100.0)**	**557 (100.0)**	**1124 (100.0)**
Completed Weeks 1-26	509 (89.8)	469 (84.2)	978 (87.0)
Continued into the extension phase	501 (88.4)	464 (83.3)	965 (85.6)
Discontinued during Weeks 1-26 – total	58 (10.2)	88 (15.8)	146 (13.0)
Primary reason for discontinuation:			
Subject withdrew consent	25 (4.4)	31 (5.6)	56 (5.0)
Adverse event(s)	22 (3.9)	29 (5.2)	51 (4.5)
Unsatisfactory therapeutic effect	5 (0.9)	16 (2.9)	21 (1.9)
Lost to follow-up	4 (0.7)	7 (1.3)	11 (1.0)
Abnormal test procedure result(s)	1 (0.2)	2 (0.4)	3 (0.3)
Protocol violation	1 (0.2)	2 (0.4)	3 (0.3)
Subject condition no longer requires study drug	0 (0.0)	1 (0.2)	1 (0.1)
Patients entered in the extension phase	**501 (100.0)**	**464 (100.0)**	**965 (100.0)**
Completed Weeks 1-52	485 (96.8)	433 (93.3)	918 (95.1)
Discontinued during Weeks 26-52 – total	16 (3.2)	31 (6.7)	47 (4.9)
Primary reason for discontinuation:			
Adverse event(s)	8 (1.6)	12 (2.6)	20 (2.1)
Patient withdrew consent	5 (1.0)	8 (1.7)	13 (1.3)
Administrative problems	2 (0.4)	6 (1.3)	8 (0.8)
Subject's condition no longer requires study drug	1 (0.2)	1 (0.2)	2 (0.2)
Protocol violation	0 (0.0)	2 (0.4)	2 (0.2)
Unsatisfactory therapeutic effect	0 (0.0)	2 (0.4)	2 (0.2)
Death	0 (0.0) [a]	0 (0.0)	0 (0.0)

Note: Patients who received placebo are counted towards the treatment they were re-randomized to at Week 6.
[a] One patient died during the follow-up period after discontinuing due to an SAE.

Demographic and Background Characteristics

Patient background characteristics group (Randomized population)

Demographic characteristic	Category/statistic	Aliskiren N=567	HCTZ N=557
Sex n (%)	Female	260 (45.9)	245 (44.0)
	Male	307 (54.1)	312 (56.0)
Race n (%)	Asian	5 (0.9)	4 (0.7)
	Black	1 (0.2)	0 (0.0)
	Caucasian	561 (98.9)	552 (99.1)
	Other	0 (0.0)	1 (0.2)
Ethnicity n (%)	Hispanic/Latino	262 (46.2)	253 (45.4)
	Indian (Indian subcont.)	2 (0.4)	3 (0.5)
	Other	303 (53.4)	300 (53.9)
Age (yrs)	Mean (SD)	56.1 (10.90)	55.7 (10.88)
	Median	57.0	56.0
Age group n (%)	< 65 yr	438 (77.2)	430 (77.2)
	>= 65 yr	129 (22.8)	127 (22.8)

	<75	548 (96.6)	538 (96.6)
	>= 75 yr	19 (3.4)	19 (3.4)
Duration of hypertension (yrs)	n	548	544
	Mean (SD)	7.2 (6.62)	7.0 (6.76)
	Median	5.5	5.0
	Naive patients –n (%) [3]	19 (3.4)	13 (2.3)
BMI (kg/m^2)	n	562	555
	Mean (SD)	28.9 (4.60)	29.1 (4.84)
	Median	28.6	28.5
Obesity	BMI ≥ 30 kg/m^2	208 (36.7)	188 (33.8)
	BMI < 30/kg/m^2	354 (62.4)	367 (65.9)
Diabetes n (%) [1]	Yes	62 (10.9)	60 (10.8)
	No	505 (89.1)	497 (89.2)
Metabolic syndrome n (%) [2]	Yes	231 (40.7)	247 (44.3)
	No	335 (59.1)	309 (55.5)
	Not available	1 (0.2)	1 (0.2)
Rigorously defined new onset diabetes at Week 52 [4]	n/ N (%)	19/451 (4.2)	30/435 (6.9)

SD = standard deviation.

[1] Patients were classified as diabetic at entry according to their medical history.

[2] Clinical identification of the metabolic syndrome, any three of the following:
(1) Abdominal obesity – waist circumference >102 cm (i.e., >40 in) in males or >88 cm (i.e., >35 in) in females; (2) Triglycerides >= 150 mg/dL (or >= 1.695 mmol/L); (3) HDL cholesterol < 40 mg/dL (or < 1.04 mmol/L) in males or < 50 mg/dL (or < 1.29 mmol/L) in females; (4) Blood pressure: msSBP >= 130 or msDBP >= 85 mm Hg; (5) Fasting glucose >= 110 mg/dL (or >= 6.1 mmol/L)

[3] Patients who did not take prior antihypertensive medication within 3 months of study start

[4] In patients with no medical history of diabetes, no prior or prior/concomitant use of oral anti-diabetics or insulin, and a fasting plasma glucose of < 7 mmol/L at Visit 1 and Visit 3, one or more of the following criteria resulted in the diagnosis of new onset of diabetes:

- Patients who had the addition of an oral anti-diabetic agent or insulin at any visit during the double-blind treatment (any visits following Visit 3) or who had an AE of diabetes at any visit during double-blind treatment.
- Two separate visits (any visit after start of double-blind medication; including unscheduled visits) with plasma glucose >= 7 mmol/L from samples documented as fasting or >= 11.1 mmol/L from samples documented as non-fasting. If fasting plasma glucose >= 7 mmol/L at one visit, and non-fasting plasma glucose >= 11.1 mmol/L at another visit, then this also meets the criteria.
- End of study visit (Visit 14 or termination visit) with plasma glucose >= 7 mmol/L from samples documented as fasting or >= 11.1 mmol/L from samples documented as nonfasting.

Primary Objective Result(s)

Between treatment analysis for change from baseline in msDBP at Week 26 endpoint (ITT population)

Treatment Group	N	LSM change from baseline (SE)
Aliskiren	560	-14.18 (0.36)
HCTZ	547	-12.97 (0.37)

Pairwise Comparison	LSM difference in change from baseline (SE)	95% CI for LSM difference	P-Value[1]	
			Non-inferiority[+]	Superiority
Aliskiren vs. HCTZ	-1.22 (0.44)	(-2.07,-0.36)	<0.0001	0.0053

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

[+] Non-inferiority margin used in the non-inferiority test was 2 mm Hg. One-sided significance level of 0.025 was only used for the non-inferiority test.

[1] P-Values and treatment comparisons were evaluated at the average baseline level.

Secondary Objective Result(s)

Between treatment analysis for change from baseline in msSBP at Week 26 endpoint (ITT population)

Treatment Group	N	LSM change from baseline (SE)
Aliskiren	560	-20.27(0.56)
HCTZ	547	-18.58(0.58)

Pairwise Comparison	LSM difference in change from baseline (SE)	95% CI for LSM difference	P-Value[1]	
			Non-inferiority[+]	Superiority
Aliskiren vs. HCTZ	-1.70(0.68)	(-3.04,-0.35)	<0.0001	0.0133

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

[+] Non-inferiority margin used in the non-inferiority test was 4 mm Hg. One-sided significance level of 0.025 was only used for the non-inferiority test.

[1] P-Values and treatment comparisons were evaluated at the average baseline level.

Between treatment analysis for change from baseline in msDBP at Week 52 endpoint (ITT population)

Treatment Group	N	LSM change from baseline (SE)
Aliskiren	499	-15.98 (0.35)
HCTZ	463	-15.03 (0.37)

Pairwise Comparison	LSM difference in change from baseline (SE)	95% CI for LSM difference	P-Value[1]	
			Non-inferiority[+]	Superiority
Aliskiren vs. HCTZ	-0.95 (0.44)	(-1.81, -0.09)	<0.0001	0.0296

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

[+] Non-inferiority margin used in the non-inferiority test was 2 mm Hg. One-sided significance level of 0.025 was only used for the non-inferiority test.

[1] P-Values and treatment comparisons were evaluated at the average baseline level.

Between treatment analysis for change from baseline in msSBP at Week 52 endpoint (ITT population)

Treatment Group	N	LSM change from baseline (SE)
Aliskiren	499	-22.11(0.58)
HCTZ	463	-21.23(0.61)

Pairwise Comparison	LSM difference in change from baseline (SE)	95% CI for LSM difference	P-Value[1]	
			Non-inferiority[+]	Superiority

Aliskiren vs. HCTZ	-0.88(0.72)	(-2.30,0.54)	<0.0001	0.2256

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

[+] Non-inferiority margin used in the non-inferiority test was 4 mmHg. One-sided significance level of 0.025 was only used for the non-inferiority test.

[1] P-Values and treatment comparisons were evaluated at the average baseline level.

Other Secondary Efficacy Result(s)

Between treatment analysis for change from baseline in msDBP at Week 12 endpoint (ITT population)

Treatment Group	N	LSM change from baseline (SE)
Aliskiren	560	-12.20 (0.371)
HCTZ	547	-10.33 (0.381)

Pairwise Comparison	LSM difference in change from baseline (SE)	95% CI for LSM difference	P-Value[1]	
			Non-inferiority[+]	Superiority
Aliskiren vs. HCTZ	-1.87 (0.452)	(-2.76, -0.99)	<0.0001	<0.0001

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

[+] Non-inferiority margin used in the non-inferiority test was 2 mm Hg. One-sided significance level of 0.025 was only used for the non-inferiority test.

[1] p-Values and treatment comparisons were evaluated at the average baseline level.

Between treatment analysis for change from baseline in msSBP at Week 12 endpoint (ITT population)

Treatment Group	N	LSM change from baseline (SE)
Aliskiren	560	-12.20 (0.371)
HCTZ	547	-10.33 (0.381)

Pairwise Comparison	LSM difference in change from baseline (SE)	95% CI for LSM difference	P-Value[1]	
			Non-inferiority[+]	Superiority
Aliskiren vs. HCTZ	-1.87 (0.452)	(-2.76, -0.99)	<0.0001	<0.0001

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

[+] Non-inferiority margin used in the non-inferiority test was 2 mm Hg. One-sided significance level of 0.025 was only used for the non-inferiority test.

[1] p-Values and treatment comparisons were evaluated at the average baseline level.

Between treatment analysis for change from baseline in msDBP at Week 6 endpoint (ITT population)

Treatment Group	N	LSM change from baseline (SE)
Aliskiren	453	-10.72 (0.386)
HCTZ	438	-8.85 (0.397)
Placebo	216	-7.29 (0.530)

Pairwise Comparison	LSM difference in change from baseline (SE)	95% CI for LSM difference	P-Value[1]
Aliskiren 150mg/300mg vs. placebo	-3.43 (0.598)	(-4.60, -2.26)	<0.0001
HCTZ 12.5mg/25mg vs. placebo	-1.56 (0.601)	(-2.74, -0.38)	0.0097

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

[+] Non-inferiority margin to be used in the non-inferiority test is 2 mm Hg. One-sided significance level of 0.025 will be only used for the non-inferiority test.

[1] P-Values and treatment comparisons were evaluated at the average baseline level.

Diastolic responder rate by group (ITT population)

The overall responder rates (proportion of patients with msDBP < 90 mm Hg, and/or a ≥ 10 mm Hg reduction from baseline) at Weeks 12, 26, and 52 were higher in patients receiving aliskiren. At Week 12, prior to the optional addition of amlodipine, a greater proportion of patients treated with aliskiren (73.8%) than with HCTZ (65.6%) had diastolic response, and the between-treatment differences were statistically significant in favor of aliskiren (p = 0.0026). At Week 26, the between-treatment comparisons of responders showed that aliskiren, with an 85.5% responder rate, was statistically superior to HCTZ, with an 80.3% responder rate (p = 0.0170). The Week 52 between-treatment comparisons of responders showed that aliskiren, with an 88.8% responder rate, was statistically superior to HCTZ with an 82.5% responder rate (p = 0.0068)

BP control rates by treatment group (ITT)

Blood pressure control (msSBP < 140 mmHg and msDBP < 90 mm Hg) in the aliskiren-based regimen was greater than in the HCTZ-based regimen at Weeks 12, 26, and 52. At Week 12 (prior to the optional addition of amlodipine), there was a statistically significant difference in the proportion of patients with blood pressure control (60.0% vs. 50.6% in the aliskiren monotherapy and HCTZ monotherapy treatments, respectively, p = 0.0012). Although a numerically greater proportion of patients receiving an aliskiren-based regimen achieved control at Week 26 (67.3% vs. 64.0% in the HCTZ-based regimen), the treatment differences did not reach statistical significance (p = 0.2583). In patients receiving monotherapy at Week 26, the control rates were comparable for both treatments (79.7% vs. 80.5%, aliskiren and HCTZ regimens, respectively; p = 0.9954). The Week 52 between-treatment comparisons of blood pressure control showed that the proportion of patients achieving blood pressure control with aliskiren (69.9%) was numerically superior to HCTZ (63.5%) and only narrowly missed statistical significance (p=0.0567). At Week 52, 249 of 524 eligible patients (reaching Week 12) or 47.5% on aliskiren had received amlodipine to further reduce blood pressure compared to 264 of 503 patients or 52.5% on the HCTZ regimen. In addition, of the patients on aliskiren 105/524 or 20% had required an increase to amlodipine 10 mg/day while 117/503 or 23.3% had required an increase in amlodipine to 10 mg per day for blood pressure control. Thus, despite somewhat less frequent use of amlodipine and use at a lower dose, aliskiren was numerically superior to HCTZ in allowing patients to achieve blood pressure control at the Week 52 endpoint

Analysis of biomarkers at Week 26 (ITT population)

Plasma Renin Activity	**Treatment Group**	**N**	**LSM change from baseline (SE)**	
	Aliskiren	57	0.35(1.11)	
	HCTZ	48	2.30(1.12)	
	Pairwise Comparison	**LSM difference in change from baseline (SE)**	**95% CI for LSM difference**	**P-Value[1]**
	Aliskiren vs. HCTZ	0.15(1.17)	(0.11,0.21)	<0.0001
Renin Concentration	**Treatment Group**	**N**	**LSM change from baseline (SE)**	
	Aliskiren	52	7.56(1.13)	
	HCTZ	40	2.15(1.15)	
	Pairwise Comparison	**LSM difference in change from baseline (SE)**	**95% CI for LSM difference**	**P-Value[1]**
	Aliskiren vs. HCTZ	3.52(1.20)	(2.46,5.05)	<0.0001

Aldosterone	**Treatment Group**	**N**	**LSM change from baseline (SE)**	
	Aliskiren	74	0.90(1.07)	
	HCTZ	68	1.44(1.07)	
	Pairwise Comparison	**LSM difference in change from baseline (SE)**	**95% CI for LSM difference**	**P-Value[1]**
	Aliskiren vs. HCTZ	0.62(1.09)	(0.52,0.75)	<0.0001
hsCRP	**Treatment Group**	**N**	**LSM change from baseline (SE)**	
	Aliskiren	83	1.05(1.10)	
	HCTZ	75	1.32(1.11)	
	Pairwise Comparison	**LSM difference in change from baseline (SE)**	**95% CI for LSM difference**	**P-Value[1]**
	Aliskiren vs. HCTZ	0.79(1.15)	(0.60,1.04)	0.0981
sICAM	**Treatment Group**	**N**	**LSM change from baseline (SE)**	
	Aliskiren	82	1.05(1.02)	
	HCTZ	78	1.06(1.02)	
	Pairwise Comparison	**LSM difference in change from baseline (SE)**	**95% CI for LSM difference**	**P-Value[1]**
	Aliskiren vs. HCTZ	0.99(1.03)	(0.94,1.05)	0.7419
MCP-1	**Treatment Group**	**N**	**LSM change from baseline (SE)**	
	Aliskiren	81	1.01(1.05)	
	HCTZ	77	0.96(1.05)	
	Pairwise Comparison	**LSM difference in change from baseline (SE)**	**95% CI for LSM difference**	**P-Value[1]**
	Aliskiren vs. HCTZ	1.05(1.07)	(0.92,1.20)	0.4534
LpPLA2	**Treatment Group**	**N**	**LSM change from baseline (SE)**	
	Aliskiren	79	-30.98(4.95)	
	HCTZ	72	-25.88(5.19)	
	Pairwise Comparison	**LSM difference in change from baseline (SE)**	**95% CI for LSM difference**	**P-Value[1]**
	Aliskiren vs. HCTZ	-5.10(7.13)	(-19.19,8.98)	0.4751
PAI-1	**Treatment Group**	**N**	**LSM change from baseline (SE)**	
	Aliskiren	78	1.12(1.08)	
	HCTZ	70	1.29(1.08)	
	Pairwise Comparison	**LSM difference in change from baseline (SE)**	**95% CI for LSM difference**	**P-Value[1]**
	Aliskiren vs. HCTZ	0.87(1.11)	(0.70,1.08)	0.2002
Fasting Plasma Glucose	**Treatment Group**	**N**	**LSM change from baseline (SE)**	
	Aliskiren	477	1.01(1.01)	
	HCTZ	453	1.03(1.01)	
	Pairwise Comparison	**LSM difference in change from baseline (SE)**	**95% CI for LSM difference**	**P-Value[1]**
	Aliskiren vs. HCTZ	0.98(1.01)	(0.96,1.00)	0.0193
Fasting Plasma Insulin	**Treatment Group**	**N**	**LSM change from baseline (SE)**	
	Aliskiren	373	1.03(1.04)	
	HCTZ	333	1.03(1.04)	
	Pairwise Comparison	**LSM difference in change from baseline (SE)**	**95% CI for LSM difference**	**P-Value[1]**

	Aliskiren vs. HCTZ	1.00(1.05)	(0.91,1.10)	0.9874
HOMA-IR	**Treatment Group**	**N**	**LSM change from baseline (SE)**	
	Aliskiren	369	1.05(1.04)	
	HCTZ	327	1.07(1.04)	
	Pairwise Comparison	**LSM difference in change from baseline (SE)**	**95% CI for LSM difference**	**P-Value[1]**
	Aliskiren vs. HCTZ	0.98(1.05)	(0.88,1.09)	0.7078
QUICKI	**Treatment Group**	**N**	**LSM change from baseline (SE)**	
	Aliskiren	369	0.99(1.01)	
	HCTZ	327	0.98(1.01)	
	Pairwise Comparison	**LSM difference in change from baseline (SE)**	**95% CI for LSM difference**	**P-Value[1]**
	Aliskiren vs. HCTZ	1.00(1.02)	(0.97,1.04)	0.8422

SE = Standard Error, LSM = Least Squares Mean, CI = Confidence Interval
[1] P-Values and treatment comparisons were evaluated at the average baseline level.
Analyses of biomarkers (except LpPLA2) were done on log-transformed data. The output of the ANCOVA (LSM estimates, standard errors and confidence intervals) were transformed back to the original scale.

Analysis of biomarkers at Week 52 (ITT population)

Plasma Renin Activity	**Treatment Group**	**N**	**LSM change from baseline (SE)**	
	Aliskiren	51	0.40(1.13)	
	HCTZ	48	2.68(1.14)	
	Pairwise Comparison	**LSM difference in change from baseline (SE)**	**95% CI for LSM difference**	**P-Value[1]**
	Aliskiren vs. HCTZ	0.15(1.19)	(0.10,0.21)	<0.0001
Renin Concentration	**Treatment Group**	**N**	**LSM change from baseline (SE)**	
	Aliskiren	43	7.46(1.16)	
	HCTZ	33	2.59(1.18)	
	Pairwise Comparison	**LSM difference in change from baseline (SE)**	**95% CI for LSM difference**	**P-Value[1]**
	Aliskiren vs. HCTZ	2.88(1.23)	(1.89,4.38)	<0.0001
Aldosterone	**Treatment Group**	**N**	**LSM change from baseline (SE)**	
	Aliskiren	74	0.99(1.06)	
	HCTZ	65	1.43(1.07)	
	Pairwise Comparison	**LSM difference in change from baseline (SE)**	**95% CI for LSM difference**	**P-Value[1]**
	Aliskiren vs. HCTZ	0.69(1.09)	(0.58,0.82)	<0.0001
hsCRP	**Treatment Group**	**N**	**LSM change from baseline (SE)**	
	Aliskiren	82	1.18(1.08)	
	HCTZ	74	1.58(1.08)	
	Pairwise Comparison	**LSM difference in change from baseline (SE)**	**95% CI for LSM difference**	**P-Value[1]**
	Aliskiren vs. HCTZ	0.74(1.11)	(0.60,0.92)	0.0059
sICAM	**Treatment Group**	**N**	**LSM change from baseline (SE)**	
	Aliskiren	81	1.00(1.02)	
	HCTZ	74	1.02(1.02)	
	Pairwise Comparison	**LSM difference in change from baseline (SE)**	**95% CI for LSM difference**	**P-Value[1]**
	Aliskiren vs. HCTZ	0.98(1.02)	(0.94,1.03)	0.5138

MCP-1	Treatment Group	N	LSM change from baseline (SE)	
	Aliskiren	79	1.02(1.05)	
	HCTZ	74	1.00(1.05)	
	Pairwise Comparison	**LSM difference in change from baseline (SE)**	**95% CI for LSM difference**	**P-Value[1]**
	Aliskiren vs. HCTZ	1.02(1.07)	(0.90,1.16)	0.7186
LpPLA2	**Treatment Group**	**N**	**LSM change from baseline (SE)**	
	Aliskiren	79	-28.29(5.20)	
	HCTZ	70	-31.38(5.58)	
	Pairwise Comparison	**LSM difference in change from baseline (SE)**	**95% CI for LSM difference**	**P-Value[1]**
	Aliskiren vs. HCTZ	3.09(7.55)	(-11.82,18.00)	0.6830
PAI-1	**Treatment Group**	**N**	**LSM change from baseline (SE)**	
	Aliskiren	77	1.08(1.08)	
	HCTZ	69	1.23(1.08)	
	Pairwise Comparison	**LSM difference in change from baseline (SE)**	**95% CI for LSM difference**	**P-Value[1]**
	Aliskiren vs. HCTZ	0.88(1.11)	(0.71,1.08)	0.2224
Fasting Plasma Glucose	**Treatment Group**	**N**	**LSM change from baseline (SE)**	
	Aliskiren	437	1.01(1.01)	
	HCTZ	400	1.03(1.01)	
	Pairwise Comparison	**LSM difference in change from baseline (SE)**	**95% CI for LSM difference**	**P-Value[1]**
	Aliskiren vs. HCTZ	0.98(1.01)	(0.96,1.00)	0.0293
Fasting Plasma Insulin	**Treatment Group**	**N**	**LSM change from baseline (SE)**	
	Aliskiren	351	0.95(1.04)	
	HCTZ	304	0.98(1.04)	
	Pairwise Comparison	**LSM difference in change from baseline (SE)**	**95% CI for LSM difference**	**P-Value[1]**
	Aliskiren vs. HCTZ	0.97(1.05)	(0.89,1.07)	0.5879
HOMA-IR	**Treatment Group**	**N**	**LSM change from baseline (SE)**	
	Aliskiren	347	0.96(1.04)	
	HCTZ	301	1.01(1.05)	
	Pairwise Comparison	**LSM difference in change from baseline (SE)**	**95% CI for LSM difference**	**P-Value[1]**
	Aliskiren vs. HCTZ	0.95(1.05)	(0.86,1.06)	0.3634
QUICKI	**Treatment Group**	**N**	**LSM change from baseline (SE)**	
	Aliskiren	347	1.01(1.01)	
	HCTZ	301	1.00(1.01)	
	Pairwise Comparison	**LSM difference in change from baseline (SE)**	**95% CI for LSM difference**	**P-Value[1]**
	Aliskiren vs. HCTZ	1.01(1.02)	(0.98,1.05)	0.4175

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

[1] P-Values and treatment comparisons were evaluated at the average baseline level.

Analyses of biomarkers (except LpPLA2) were done on log-transformed data. The output of the ANCOVA (LSM estimates, standard errors and confidence intervals) were transformed back to the original scale.

Safety Results

Adverse Events by System Organ Class

Primary System Organ Class	Aliskiren N=566 n (%)	HCTZ N=558 n (%)	Total N=1124 n (%)
Any Adverse Events	369 (65.2)	343 (61.5)	712 (63.3)
Blood and lymphatic system disorders	3 (0.5)	1 (0.2)	4 (0.4)
Cardiac disorders	23 (4.1)	22 (3.9)	45 (4.0)
Congenital, familial and genetic disorders	1 (0.2)	1 (0.2)	2 (0.2)
Ear and labyrinth disorders	21 (3.7)	20 (3.6)	41 (3.6)
Endocrine disorders	2 (0.4)	1 (0.2)	3 (0.3)
Eye disorders	19 (3.4)	15 (2.7)	34 (3.0)
Gastrointestinal disorders	82 (14.5)	77 (13.8)	159 (14.1)
General disorders and administration site conditions	72 (12.7)	70 (12.5)	142 (12.6)
Hepatobiliary disorders	1 (0.2)	2 (0.4)	3 (0.3)
Immune system disorders	3 (0.5)	4 (0.7)	7 (0.6)
Infections and infestations	144 (25.4)	119 (21.3)	263 (23.4)
Injury, poisoning and procedural complications	31 (5.5)	23 (4.1)	54 (4.8)
Investigations	23 (4.1)	19 (3.4)	42 (3.7)
Metabolism and nutrition disorders	59 (10.4)	58 (10.4)	117 (10.4)
Musculoskeletal and connective tissue disorders	105 (18.6)	103 (18.5)	208 (18.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	19 (3.4)	15 (2.7)	34 (3.0)
Nervous system disorders	73 (12.9)	102 (18.3)	175 (15.6)
Psychiatric disorders	35 (6.2)	35 (6.3)	70 (6.2)
Renal and urinary disorders	9 (1.6)	12 (2.2)	21 (1.9)
Reproductive system and breast disorders	17 (3.0)	19 (3.4)	36 (3.2)
Respiratory, thoracic and mediastinal disorders	34 (6.0)	41 (7.3)	75 (6.7)
Skin and subcutaneous tissue disorders	55 (9.7)	41 (7.3)	96 (8.5)
Social circumstances	1 (0.2)	1 (0.2)	2 (0.2)
Surgical and medical procedures	8 (1.4)	1 (0.2)	9 (0.8)
Vascular disorders	14 (2.5)	18 (3.2)	32 (2.8)

Adverse events with onset while a patient received placebo during the first six weeks of the double-blind treatment period, are not taken into account.

Serious Adverse Events and Deaths

	Aliskiren N = 566 n (%)	HCTZ N = 558 n (%)
Deaths	0 (0.0) [a]	0 (0.0)
SAEs	26 (4.6)	22 (3.9)
AE discontinuations*	29 (5.1)	41 (7.3)
Drug-related AE discontinuation**	26 (4.6)	38 (6.8)
SAE discontinuations	4 (0.7)	9 (1.6)
Laboratory abnormality leading to discontinuation	0 (0.0)	0 (0.0)

*Including AE discontinuations while a patient received placebo during the first six weeks of the double-blind treatment period.

**Adverse events with onset while a patient received placebo during the first six weeks of the double-blind treatment period, are not taken into account.

[a] One patient died during the follow-up period after discontinuing due to an SAE.

Quality of life

There were no statistically significant differences in mean total scores for the PGWBI between the aliskiren and HCTZ regimens at any timepoint, from Week 26 through Week 52 , however the aliskiren regimen appeared to show improvement, accounted for mainly by decreases in the anxiety score.

Arterial Compliance

Between treatment analysis for change from baseline in Augmentation Index at Week 26 end-point (ITT population)

Treatment Group	N	LSM change from baseline (SE)
Aliskiren	38	-4.71 (1.165)
HCTZ	40	-3.91 (1.135)

Pairwise Comparison	LSM difference in change from baseline (SE)	95% CI for LSM difference	P-Value[1] Superiority
Aliskiren vs. HCTZ	-0.79 (1.627)	(-4.04, 2.45)	0.6273

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

Between treatment analysis for change from baseline in Augmentation Index at Week 52 (ITT Population)

Treatment Group	N	LSM change from baseline (SE)
Aliskiren	38	-4.71 (1.165)
HCTZ	40	-3.91 (1.135)

Pairwise Comparison	LSM difference in change from baseline (SE)	95% CI for LSM difference	P-Value[1] Superiority
Aliskiren vs. HCTZ	-0.79 (1.627)	(-4.04, 2.45)	0.6273

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

Between treatment analysis for change from baseline in Pulse Wave Velocity (PWV) at Week 26 endpoint (ITT population)

Treatment Group	N	LSM change from baseline (SE)
Aliskiren	38	-4.71 (1.165)
HCTZ	40	-3.91 (1.135)

Pairwise Comparison	LSM difference in change from baseline (SE)	95% CI for LSM difference	P-Value[1] Superiority
Aliskiren vs. HCTZ	-0.79 (1.627)	(-4.04, 2.45)	0.6273

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

Between treatment analysis for change from baseline in Pulse Wave Velocity (PWV) at Week 52 (ITT population)

Treatment Group	N	LSM change from baseline (SE)
Aliskiren	38	-4.71 (1.165)
HCTZ	40	-3.91 (1.135)

Pairwise Comparison	LSM difference in change from baseline (SE)	95% CI for LSM difference	P-Value[1] Superiority
Aliskiren vs. HCTZ	-0.79 (1.627)	(-4.04, 2.45)	0.6273

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

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