Sponsor

Novartis

Generic Drug Name

Aliskiren

Therapeutic Area of Trial

Hypertension

Approved Indication

Hypertension

Study Number

CSPP100A2331

Title

An eight week, randomized, double-blind, parallel-group, multicenter study to evaluate the efficacy and safety of the combination of aliskiren/valsartan/HCTZ (300/320/25 mg), compared to the combinations of aliskiren/HCTZ (300/25 mg) and valsartan/HCTZ (320/25 mg) in patients with essential hypertension not adequately responsive to HCTZ 25 mg

Phase of Development

Phase III

Study Start/End Dates

31 Oct 2005 to 11 Jan 2007

Study Design/Methodology

An eight week, randomized, double-blind, parallel-group, multicenter, efficacy and safety study of the combination of aliskiren/valsartan/hydrochlorothiazide (HCTZ) (300/320/25 mg) versus

the combinations of aliskiren/HCTZ (300/25 mg) and valsartan/HCTZ (320/25 mg) in patients with essential hypertension not adequately responsive to HCTZ 25 mg. After a 4-week single-blind HCTZ run-in phase, patients were randomized to 8 week double-blind treatment with HCTZ 25 mg, aliskiren/HCTZ (150/25 mg for four weeks and 300/25 mg for another four weeks), valsartan/HCTZ (160/25 mg for four weeks and 320/25 mg for another four weeks), or aliskiren/valsartan/HCTZ (150/160/25 mg for four weeks and 300/320/25 mg for another four weeks).

Centres

112 centers in 3 countries: Germany (47 centers), Spain (17 centers), and the United States (48 centers).

Objectives

Primary objective(s)

• To assess the efficacy of the combination of aliskiren/valsartan/HCTZ (300/320/25 mg) compared to the combinations of aliskiren/HCTZ (300/25 mg) and valsartan / HCTZ (320/25 mg) in reducing mean sitting diastolic blood pressure (msDBP) from baseline to the end of 8 weeks of treatment in patients with hypertension not adequately responsive to HCTZ 25 mg.

Secondary objective(s)

• Evaluate the efficacy of the combination of aliskiren/valsartan/HCTZ (300/320/25 mg) compared to the combinations of aliskiren/HCTZ (300/25 mg) and valsartan/HCTZ (320/25 mg) in reducing mean sitting systolic blood pressure (msSBP) from baseline to the end of 8 weeks of treatment in patients with hypertension not adequately responsive to HCTZ 25 mg.
• Evaluate the efficacy of the combination of aliskiren/HCTZ (300/25 mg) compared to HCTZ alone in reducing msDBP and msSBP from baseline to the end of 8 weeks of treatment in patients with hypertension not adequately responsive to HCTZ 25 mg.
• Evaluate the efficacy of the combination of aliskiren/valsartan/HCTZ (150/160/25 mg) compared to the combinations of aliskiren/HCTZ (150/25 mg) and valsartan/HCTZ (160/25 mg) in reducing msDBP and msSBP from baseline to the end of 4 weeks of treatment in patients with hypertension not adequately responsive to HCTZ 25 mg.
• Evaluate the efficacy of the combination of aliskiren/HCTZ (150/25 mg) compared to HCTZ alone in reducing msDBP and msSBP from baseline to the end of 4 weeks of treatment in patients with hypertension not adequately responsive to HCTZ 25 mg.
• Evaluate the safety and tolerability profile of all treatment groups.

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

One oral tablet of Aliskiren 150 mg once each morning,
Two oral tablets of Aliskiren 150 mg once each morning

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

One oral capsule of Valsartan 160mg once each morning
Two oral capsules of Valsartan 160mg once each morning
One oral capsule of HCTZ 12.5mg or 25 mg once each morning

Criteria for Evaluation

Primary variables

Change from baseline at the Week 8 Endpoint in the mean sitting diastolic blood pressure (msDBP).

Secondary variables

- Change from baseline in msDBP and mean sitting systolic blood pressure (msSBP) at both Week 4 and Week 8 Endpoints.
- Blood Pressure (BP) control rate.

Safety and tolerability

- Adverse Events (AEs) and Serious Adverse Events (SAEs)
- Hematology / blood chemistry
- Vital signs
- Physical exams
- Electrocardiogram (ECG)
- Pregnancy tests.

Other

- Change from baseline to Week 8 Endpoint in biomarkers (PRA, PRC MCP-1, PAI-1, and plasma aldosterone) in a subset of study patients.

Statistical Methods

The primary efficacy analysis was performed for the intent-to-treat (ITT) population consisting of all randomized patients that received at least one dose of study drug and have a baseline and at least one post-baseline assessment of the primary efficacy variable (the change in msDBP from baseline). The per protocol (PP) population consisted of all patients in ITT population who completed the double blind period without any major protocol violations.

The primary efficacy variable was the change from baseline (Visit 4) in msDBP. The primary

time-point for efficacy analysis was the Week 8 Endpoint. The primary variable (at Week 8 Endpoint) was analyzed based on an analysis of covariance (ANCOVA) model with treatment regimen and region as factors and with baseline as a covariate. This model is considered as the primary model.

To assess the primary objective, the first null hypothesis to be tested was that the combination of aliskiren/valsartan/HCTZ was equally effective to the combination of aliskiren/HCTZ. The second null hypothesis was that the combination of aliskiren/valsartan/HCTZ was equally effective to the combination valsartan/HCTZ. The combination of aliskiren/valsartan/HCTZ was considered more effective than the combinations of aliskiren/HCTZ and valsartan/HCTZ if both tests were statistically significant in favor of the combination of aliskiren/valsartan/HCTZ. Ninety-five percent confidence interval (CI) was provided for the differences between the combination of aliskiren/valsartan/HCTZ and the combinations of aliskiren/HCTZ and valsartan/HCTZ. For the baseline, the post-baseline values, and the change from baseline in msDBP, descriptive statistics (n, mean, standard deviation, minimum, median, and maximum) were calculated by treatment group and visit.

For supportive purposes, the primary efficacy variable was analyzed on the primary model for the PP population to examine the effect due to premature dropouts and/or major protocol violations/ deviations. The analysis on the supplemental model with the two interaction terms added to the primary model was also performed for the ITT and PP populations. The changes in msDBP from baseline (Visit 4) to the Week 4 Endpoint and Week 8 were analyzed on the primary model for the ITT population.

For msSBP, changes from baseline to Week 4 Endpoint, Week 8 Endpoint and Week 8 were analyzed for the ITT population using the primary model, and change from baseline to Week 8 Endpoint were also analyzed for the PP population.

For standing DBP and SBP, changes from baseline to Week 4 Endpoint, Week 8 Endpoint, and Week 8 were analyzed on the primary model for the ITT population. The comparisons were the combination of aliskiren/valsartan/HCTZ vs. the combination of aliskiren/HCTZ and valsartan/HCTZ based on the model.

The proportions of responders at Week 4 Endpoint and Week 8 Endpoint in each treatment were compared for the combination of aliskiren/valsartan/HCTZ vs. aliskiren/HCTZ and valsartan/HCTZ using a logistic regression model with treatment and region as the factors and baseline msDBP value as a covariate. Number (%) of responders was presented by treatment group. The analyses were performed for ITT population only.

The control rates, defined as the proportion of patients achieving a target blood pressure of msSBP/msDBP < 140/90 mmHg, were compared for the combination of aliskiren / valsartan / HCTZ vs. aliskiren/HCTZ and valsartan/HCTZ at Week 4 Endpoint and Week 8 Endpoint. The comparisons were based on the same model as for the responders. The control rates were also presented by treatment group. The analyses were performed for ITT population only.

For safety data, occurrence of patients of AEs was summarized by treatment group, body system and preferred term. Serious adverse events were also summarized and narrated. Patients with or-

thostatic blood pressure changes were summarized by treatment group and visit. For lab data, summary statistics by treatment group at baseline, last visit, and change from baseline to last visit were provided. Occurrences of significant abnormalities in change from baseline were summarized.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria:

1. Outpatients 18 years of age and older.
2. Male or female patients are 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 a msDBP ≥ 100 mmHg and < 110 mmHg at Visit 1.
   - Patients treated with monotherapy of HCTZ or another thiazide diuretic must have a msDBP ≥ 95 mmHg and < 110 mmHg at Visit 1.
   - Patients treated with antihypertensive monotherapy, excluding HCTZ or another thiazide diuretic, or any combination(s) of antihypertensive medications must have a msDBP ≥ 85 mmHg and < 110 mmHg at Visit 1.
4. All patients must have a msDBP ≥ 95 mmHg and < 110 mmHg at Visit 4, the end of the HCTZ run-in period.
5. Patients who are eligible and able to participate in the study, and who consent to do so after the purpose and nature of the investigation has been clearly explained to them (written informed consent).

Exclusion Criteria:

1. Previously treated in an aliskiren study and who qualified to be randomized or enrolled into the active drug treatment period.
2. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test (≥ 5 mIU/ml).
3. Women of child-bearing potential (WOCBP), defined as all women physiologically capable of becoming pregnant, including women whose career, lifestyle, or sexual orientation precludes intercourse with a male partner and women whose partners have been sterilized by vasectomy or other means, UNLESS they meet the following definition of post-menopausal: 12 months of natural (spontaneous) amenorrhea or 6 months of spontaneous amenorrhea with serum FSH levels > 40 mIU/m or 6 weeks post surgical bilateral oophorectomy with or without hysterectomy OR are using one or more of the following acceptable methods of contraception: surgical sterilization (e.g., bilateral tubal ligation), hormonal contraception (implantable, patch, oral), and double-barrier methods. Reliable contraception should be maintained throughout the study and for 7 days after study drug discontinuation.
4. Patients currently on antihypertensive medication(s) that require tapering of > 7 days at Visit 1.

5. Severe hypertension (an office cuff msDBP ≥ 110 mmHg and/or msSBP ≥ 180 mmHg).
6. History or evidence of a secondary form of hypertension.
7. Known Keith-Wagener grade III or IV hypertensive retinopathy.
8. Previous or current diagnosis of heart failure (NYHA Class II-IV).
9. History of hypertensive encephalopathy or cerebrovascular accident, transient ischemic cerebral attack (TIA), myocardial infarction, coronary bypass surgery, or any percutaneous coronary intervention (PCI).
10. Serum sodium < 135 mEq/ L (mmol/L) at Visit 1.
11. Serum potassium < 3.5 mEq/L (mmol/L) or ≥ 5.3 mEq/L (mmol/L) at Visit 1.
12. Type 1 or Type 2 diabetes mellitus with glycosylated hemoglobin (HbA1c) > 8.0 % at Visit 1.
13. Current angina pectoris requiring pharmacological therapy.
14. Second or third degree heart block without a pacemaker.
15. Atrial fibrillation or atrial flutter at Visit 1, or potentially life threatening or any symptomatic arrhythmia during the 12 months prior to Visit 1.
16. Clinically significant valvular heart disease.
17. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of study drugs including, but not limited to, any of the following:
    - History of major gastrointestinal tract surgery such as gastrectomy, gastroenterostomy, or bowel resection.
    - History of active inflammatory bowel disease during the 12 months prior to Visit 1.
    - Currently active gastritis, duodenal or gastric ulcers, or gastrointestinal 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 during the 12 months prior to Visit 1.
    - Evidence of hepatic disease as determined by any one of the following: ALT or AST values exceeding 3 x upper limit 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.
18. History of hypersensitivity to any of the study drugs or to drugs belonging to the same therapeutic class, angiontensin receptor blockers (ARB's), angiotensin converting enzyme inhibitors (ACE-I), thiazide diuretics, or other sulfonamide derived drugs) as the study drugs.
19. History of angioedema due to usage of an ARB or ACE-I.
20. History of malignancy of any organ system, treated or untreated, within the past 5 years whether or not there is evidence of local recurrence or metastases, with the exception of localized basal cell carcinoma of the skin.
21. History of gouty arthritis

22. History or evidence of drug or alcohol abuse within the last 12 months.
23. Any surgical or medical condition, which in the opinion of the investigator, may place the patient at higher risk from his/her participation in the study, or is likely to prevent the patient from complying with the requirements of the study or completing the study.
24. Use of other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives of enrollment, whichever is longer.
25. History of noncompliance to medical regimens or unwillingness to comply with the study protocol.
26. 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.
27. Persons directly involved in the execution of this protocol.

Number of Subjects

	HCTZ	**Aliskiren / HCTZ**	**Valsartan / HCTZ**	**Aliskiren / Valsartan / HCTZ**
Planned N	156	156	156	156
Randomized n	152	166	155	168
Intent-to-treat population (ITT) n (%)	151 (99.3)	164 (98.8)	154 (99.4)	168 (100)
Completed n (%)	133 (87.5)	149 (89.8)	140 (90.3)	161 (95.8)
Withdrawn n (%)	19 (12.5)	17 (10.2)	15 (9.7)	7 (4.2)
Withdrawn due to adverse events n (%)	4 (2.6)	6 (3.6)	5 (3.2)	4 (2.4)
Withdrawn due to lack of efficacy n (%)	7 (4.6)	3 (1.8)	3 (1.9)	0 (0.0)
Withdrawn for other reasons n (%)	8 (5.3)	8 (4.8)	7 (4.5)	3 (1.8)

Demographic and Background Characteristics

	HCTZ	**Aliskiren / HCTZ**	**Valsartan / HCTZ**	**Aliskiren / Valsartan / HCTZ**
N (ITT)	151	164	154	168
Females : males	58:94	74:92	67:88	77:91
Mean age, years (SD)	52.6(9.93)	52.3(10.9)	55.0(11.4)	52.9(10.83)
Mean weight, kg (SD)	93.3(20.39)	90.4(19.63)	90.1(20.34)	91.9(19.66)
Race White n (%) Black n (%) Asian n (%) Other n (%)	 131(86.2) 13(8.6) 3(2.0) 5(3.3)	 141(84.9) 16(9.6) 5(3.0) 4(2.4)	 135(87.1) 14(9.0) 4(2.6) 2(1.3)	 147(87.5) 15(8.9) 1(0.6) 5(3.0)

Primary Objective Result(s)

Statistical analysis of change from baseline in mean sitting diastolic blood pressure at Week 8 endpoint (ITT population)

Treatment Group	N	LSM change from baseline (SE)
HCTZ	151	-6.38 (0.70)
Aliskiren/HCTZ	164	-10.53 (0.67)
Valsartan/HCTZ	154	-13.52 (0.70)
Aliskiren/valsartan/HCTZ	168	-15.94 (0.67)

Pairwise comparison		LSM difference in change from baseline (SE)	95% CI for LSM difference	p-value[1]
Aliskiren/valsartan/HCTZ	*vs.* Aliskiren/HCTZ	-5.41 (0.95)	(-7.27, -3.56)	<0.0001*
Aliskiren/valsartan/HCTZ	*vs.* Valsartan/HCTZ	-2.42 (0.96)	(-4.31, -0.52)	0.0124*
Aliskiren/HCTZ	*vs.* HCTZ	-4.14 (0.97)	(-6.05, -2.23)	<0.0001*
Valsartan/HCTZ	*vs.* HCTZ	-7.14 (0.99)	(-9.08, -5.20)	<0.0001*
Aliskiren/valsartan/HCTZ	*vs.* HCTZ	-9.56 (0.97)	(-11.46, -7.65)	<0.0001*

SE = Standard Error; LSM = Least Squares Mean; CI = Confidence Interval
Least square means, confidence intervals, and p-values were from an ANCOVA model containing treatment, region, and baseline.
[1] p-values and treatment comparisons were evaluated at the average baseline level.
* Indicates statistical significance at 0.05 level.
Note: Patients receiving the active treatments were treated with aliskiren (150 mg) and/or valsartan (160 mg) for 4 weeks followed by 4 weeks of aliskiren (300 mg) and/or valsartan (320 mg).

Secondary Objective Result(s)

Statistical analysis of change from baseline in mean sitting systolic blood pressure at Week 8 Endpoint (ITT population)

Treatment group		N	LSM change from baseline (SE)	
HCTZ		151	-6.3 (1.12)	
Aliskiren/HCTZ		164	-15.0 (1.08)	
Valsartan/HCTZ		154	-18.3 (1.12)	
Aliskiren/valsartan/HCTZ		168	-21.6 (1.07)	
Pairwise comparison		**LSM difference in change from baseline (SE)**	**95% CI for LSM difference**	**p-value[1]**
Aliskiren/valsartan/HCTZ	vs. Aliskiren/HCTZ	-6.5 (1.51)	(-9.51, -3.57)	<0.0001*
Aliskiren/valsartan/HCTZ	vs. Valsartan/HCTZ	-3.3 (1.55)	(-6.31, -0.23)	0.0350*
Aliskiren/HCTZ	vs. HCTZ	-8.7 (1.55)	(-11.79, -5.68)	<0.0001*
Valsartan/HCTZ	vs. HCTZ	-12.0 (1.58)	(-15.11, -8.90)	<0.0001*
Aliskiren/valsartan/HCTZ	vs. HCTZ	-15.3 (1.55)	(-18.31, -12.2)	<0.0001*

SE = Standard Error; LSM = Least Square Mean; CI = Confidence Interval.
Least square mean, confidence intervals, and p-values were from an ANCOVA model containing treatment, region, and baseline.
[1] p-values and treatment comparisons were evaluated at the average baseline level.
* Indicates statistical significance at 0.05 level.
Note: Patients receiving the active treatments were treated with aliskiren (150 mg) and/or valsartan (160 mg) for 4 weeks followed by 4 weeks of aliskiren (300 mg) and/or valsartan (320 mg).

Statistical analysis of change from baseline in mean sitting diastolic blood pressure at Week 4 Endpoint (ITT population)

Treatment group		N	LSM change from baseline (SE)	
HCTZ		151	-6.5 (0.71)	
Aliskiren/HCTZ		164	-10.0 (0.68)	
Valsartan/HCTZ		154	-12.1 (0.70)	
Aliskiren/valsartan/HCTZ		168	-14.6 (0.67)	
Pairwise comparison		**LSM difference in change from baseline (SE)**	**95% CI for LSM difference**	**p-value[1]**
Aliskiren/valsartan/HCTZ	vs. Aliskiren/HCTZ	-4.6 (0.95)	(-6.48, -2.74)	<0.0001*
Aliskiren/valsartan/HCTZ	vs. Valsartan/HCTZ	-2.5 (0.97)	(-4.37, -0.57)	0.0109*
Aliskiren/HCTZ	vs. HCTZ	-3.5 (0.98)	(-5.37, -1.52)	0.0005*
Valsartan/HCTZ	vs. HCTZ	-5.6 (0.99)	(-7.53, -3.63)	<0.0001*
Aliskiren/valsartan/HCTZ	vs. HCTZ	-8.1 (0.97)	(-9.97, -6.14)	<0.0001*

SE = Standard Error; LSM = Least Square Mean; CI = Confidence Interval.
Least square mean, confidence intervals, and p-values were from an ANCOVA model containing treatment, region, and baseline.
[1] p-values and treatment comparisons were evaluated at the average baseline level.
* Indicates statistical significance at 0.05 level.
Note: Patients receiving the active treatments were treated with aliskiren (150 mg) and/or valsartan (160 mg) for 4 weeks followed by 4 weeks of aliskiren (300 mg) and/or valsartan (320 mg).

Statistical analysis of change from baseline in mean sitting systolic blood pressure at Week 4 Endpoint (ITT population)

Treatment group	N	LSM change from baseline (SE)
HCTZ	151	-7.2 (1.08)
Aliskiren/HCTZ	164	-12.7 (1.03)
Valsartan/HCTZ	154	-14.6 (1.07)
Aliskiren/valsartan/HCTZ	168	-18.5 (1.02)

Pairwise comparison		LSM difference in change from baseline (SE)	95% CI for LSM difference	p-value[1]
Aliskiren/valsartan/HCTZ	vs. Aliskiren/HCTZ	-5.8 (1.45)	(-8.69, -2.99)	<0.0001*
Aliskiren/valsartan/HCTZ	vs. Valsartan/HCTZ	-3.9 (1.48)	(-6.76, -0.94)	0.0097*
Aliskiren/HCTZ	vs. HCTZ	-5.5 (1.49)	(-8.42, -2.57)	0.0002*
Valsartan/HCTZ	vs. HCTZ	-7.5 (1.52)	(-10.47, -4.51)	<0.0001*
Aliskiren/valsartan/HCTZ	vs. HCTZ	-11.3 (1.48)	(-14.25, -8.42)	<0.0001*

SE = Standard Error; LSM = Least Square Mean; CI = Confidence Interval.
Least square mean, confidence intervals, and p-values were from an ANCOVA model containing treatment, region, and baseline.
[1] p-values and treatment comparisons were evaluated at the average baseline level.
* Indicates statistical significance at 0.05 level
Note: Patients receiving the active treatments were treated with aliskiren (150 mg) and/or valsartan (160 mg) for 4 weeks followed by 4 weeks of aliskiren (300 mg) and/or valsartan (320 mg).

Between treatment comparison for blood pressure control rate at Week 8 Endpoint by treatment group (ITT population)

Pairwise comparison		Treatment A	Treatment B	
A	vs. B	n/N (%)	n/N (%)	p-value
Aliskiren/valsartan/HCTZ	vs. Aliskiren/HCTZ	112/168 (66.7)	67/164 (40.9)	<0.0001*
Aliskiren/valsartan/HCTZ	vs. Valsartan/HCTZ	112/168 (66.7)	75/154 (48.7)	0.0026*
Aliskiren/HCTZ	vs. HCTZ	67/164 (40.9)	31/151 (20.5)	0.0020*
Valsartan/HCTZ	vs. HCTZ	75/154 (48.7)	31/151 (20.5)	<0.0001*
Aliskiren/valsartan/HCTZ	vs. HCTZ	112/168 (66.7)	31/151 (20.5)	<0.0001*

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.
Note: Patients receiving the active treatments were treated with aliskiren (150 mg) and/or valsartan (160 mg) for 4 weeks followed by 4 weeks of aliskiren (300 mg) and/or valsartan (320 mg).
* Indicates statistical significance at 0.05 level.

Between treatment comparison for blood pressure control at Week 4 Endpoint by treatment group (ITT population)

Pairwise comparison		Treatment A	Treatment B	
A	vs. B	n/N (%)	n/N (%)	p-value
Aliskiren/valsartan/HCTZ	vs. Aliskiren/HCTZ	94/168 (56.0)	60/164 (36.6)	0.0003*
Aliskiren/valsartan/HCTZ	vs. Valsartan/HCTZ	94/168 (56.0)	65/154 (42.2)	0.0288*
Aliskiren/HCTZ	vs. HCTZ	60/164 (36.6)	30/151 (19.9)	0.0025*

Valsartan/HCTZ	vs. HCTZ	65/154 (42.2)	30/151 (19.9)	<0.0001*
Aliskiren/valsartan/HCTZ	vs. HCTZ	94/168 (56.0)	30/151 (19.9)	<0.0001*

A patient with control in BP is defined as having as 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.
Note: Patients receiving the active treatments were treated with aliskiren (150 mg) and/or valsartan (160 mg) for 4 weeks.
* Indicates statistical significance at 0.05 level.

Safety Results

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

Primary system organ class	HCTZ N = 152 n (%)	Aliskiren / HCTZ N = 165 n (%)	Valsartan / HCTZ N = 154 n (%)	Aliskiren / Valsartan / HCTZ N = 168 n (%)
Any body system	64 (42.1)	60 (36.4)	72 (46.8)	62 (36.9)
Nervous system disorders	13 (8.6)	8 (4.8)	28 (18.2)	21 (12.5)
Infections and infestations	24 (15.8)	16 (9.7)	15 (9.7)	17 (10.1)
Gastrointestinal disorders	10 (6.6)	9 (5.5)	16 (10.4)	10 (6.0)
Musculoskeletal and connective tissue disorders	11 (7.2)	7 (4.2)	7 (4.5)	10 (6.0)
General disorders and administration site conditions	8 (5.3)	5 (3.0)	7 (4.5)	8 (4.8)
Metabolism and nutrition disorders	6 (3.9)	6 (3.6)	6 (3.9)	7 (4.2)
Respiratory, thoracic and mediastinal disorders	6 (3.9)	4 (2.4)	8 (5.2)	7 (4.2)
Investigations	4 (2.6)	1 (0.6)	0 (0.0)	6 (3.6)
Ear and labyrinth disorders	1 (0.7)	3 (1.8)	2 (1.3)	5 (3.0)
Injury, poisoning and procedural complications	6 (3.9)	0 (0.0)	2 (1.3)	3 (1.8)
Skin and subcutaneous tissue disorders	5 (3.3)	6 (3.6)	7 (4.5)	3 (1.8)
Vascular disorders	0 (0.0)	4 (2.4)	4 (2.6)	3 (1.8)
Renal and urinary disorders	2 (1.3)	6 (3.6)	4 (2.6)	2 (1.2)
Reproductive system and breast disorders	0 (0.0)	1 (0.6)	4 (2.6)	2 (1.2)
Eye disorders	2 (1.3)	1 (0.6)	1 (0.6)	1 (0.6)
Psychiatric disorders	2 (1.3)	0 (0.0)	2 (1.3)	1 (0.6)
Blood and lymphatic system disorders	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Cardiac disorders	2 (1.3)	2 (1.2)	2 (1.3)	0 (0.0)
Endocrine disorders	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Hepatobiliary disorders	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Immune system disorders	1 (0.7)	1 (0.6)	0 (0.0)	0 (0.0)

Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0.0)	0 (0.0)	2 (1.3)	0 (0.0)
Social circumstances	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Surgical and medical procedures	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)

Organ systems are sorted in descending frequency, as reported in the Aliskiren/Valsartan/HCTZ column. A patient with multiple adverse events within a primary system organ class is counted only once.

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

Preferred term	HCTZ N = 152 n (%)	Aliskiren / HCTZ N = 165 n (%)	Valsartan / HCTZ N = 154 n (%)	Aliskiren / Valsartan / HCTZ N = 168 n (%)
Any adverse event	64 (42.1)	60 (36.4)	72 (46.8)	62 (36.9)
Dizziness	3 (2.0)	3 (1.8)	13 (8.4)	10 (6.0)
Headache	8 (5.3)	4 (2.4)	9 (5.8)	5 (3.0)
Fatigue	4 (2.6)	2 (1.2)	3 (1.9)	4 (2.4)
Back pain	1 (0.7)	2 (1.2)	2 (1.3)	4 (2.4)
Vertigo	0 (0.0)	2 (1.2)	1 (0.6)	4 (2.4)
Nasopharyngitis	10 (6.6)	5 (3.0)	4 (2.6)	3 (1.8)
Cough	2 (1.3)	2 (1.2)	4 (2.6)	3 (1.8)
Hyperlipidemia	3 (2.0)	2 (1.2)	3 (1.9)	3 (1.8)
Diarrhea	4 (2.6)	2 (1.2)	3 (1.9)	2 (1.2)
Bronchitis	3 (2.0)	0 (0.0)	2 (1.3)	2 (1.2)
Upper respiratory tract infection	3 (2.0)	3 (1.8)	2 (1.3)	1 (0.6)
Eczema	3 (2.0)	1 (0.6)	1 (0.6)	1 (0.6)
Edema peripheral	3 (2.0)	0 (0.0)	1 (0.6)	1 (0.6)
Pollakiuria	0 (0.0)	4 (2.4)	2 (1.3)	0 (0.0)

Preferred terms are sorted in descending frequency, as reported in the Aliskiren/Valsartan/HCTZ column.
A patient with multiple occurrences of any adverse events within a preferred term is counted only once.

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

	HCTZ N = 152 n (%)	Aliskiren / HCTZ N = 165 n (%)	Valsartan / HCTZ N = 154 n (%)	Aliskiren / Valsartan / HCTZ N = 168 n (%)	Total N = 639 n (%)
Deaths	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.2)
SAEs	1 (0.7)	1 (0.6)	5 (3.3)	0 (0.0)	7 (1.1)
AE discontinuation	4 (2.6)	5 [a] (3.0)	5 [a] (3.2)	4 (2.4)	18 (2.8)
Drug-related AE discontinuation	0 (0.0)	4 (2.4)	1 (0.7)	3 (1.8)	8 (1.3)
SAE discontinuation	1 (0.7)	1 (0.6)	3 (2.0)	0 (0.0)	5 (0.8)

[a] During the double-blind period, 1 patients (valsartan/HCTZ) and 1 patient (aliskiren/HCTZ) discontinued due to AEs that began during the single-blind period. These patients are not included in this table since the AEs did not worsen in severity during the double-blind period but are counted as discontinuing due to AEs.

[*] Cause of SAE or death was not captured in this study.

Other Relevant Findings

Percentage of patients exceeding pre-specified lab criteria by laboratory parameter and treatment group (safety population)

Biochemistry variable		HCTZ N = 152		Aliskiren / HCTZ N = 165		Valsartan / HCTZ N = 154		Aliskiren / Valsartan / HCTZ N = 168	
		N	n (%)	N	n (%)	N	n (%)	N	n (%)
Potassium	≥ 6.0 mmol/L	150	0 (0.0)	160	0 (0.0)	153	0 (0.0)	167	1 (0.6) [a]
	> 5.5 mmol/L	150	0 (0.0)	160	0 (0.0)	153	0 (0.0)	167	1 (0.6) [a]
	< 3.5 mmol/L	150	14 (9.3)	160	8 (5.0)	153	13 (8.5)	167	10 (6.0)
Blood urea nitrogen	> 14.28 mmol/L	150	0 (0.0)	161	0 (0.0)	153	1 (0.7)	167	0 (0.0)

[a] One patient with elevated potassium of 6.8 mmol/L.

Date of Clinical Trial Report

20 Apr 2007

Date Inclusion on Novartis Clinical Trial Results Database

30 Jan 2008

Date of Latest Update

27 October 2009