Sponsor

Novartis

Generic Drug Name

Aliskiren

Therapeutic Area of Trial

Hypertension

Approved Indication

Hypertension

Study Number

CSPP100A2310

Title

A 12 week randomized, double-blind, placebo controlled, parallel group study evaluating the efficacy and safety of aliskiren in patients with diabetes and hypertension not adequately responsive to the combination of valsartan 160 mg and hydrochlororothiazide 25 mg.

Phase of Development

Phase IV

Study Start/End Dates

01-Jun-2005 to 07-May-2007

Study Design/Methodology

Methodology: This was a double-blind, randomized, multicenter, parallel group study comparing the efficacy and safety of aliskiren as add-on therapy to valsartan and HCTZ in patients with hy-

pertension and diabetes mellitus inadequately treated with valsartan/HCTZ alone. The study comprised three periods and nine visits.

At Visit 1 (days -56 to -42) eligibility for study participation was assessed, and patients discontinued or tapered off their current antihypertensive medication(s), according to investigator instruction and manufacturer's labeling. Treated Patients underwent a one to two-week washout period, whilst patients who were newly diagnosed with uncomplicated hypertension and who were not taking any antihypertensive medication(s), or patients who had not been taking antihypertensive drugs for at least 1 week prior to Visit 1 were considered as non-treated.

Patients who did not meet the inclusion/exclusion criteria at the time of Visit 2 were allowed to extend the washout period up to a maximum of four weeks (optional Visit 101), in order to meet blood pressure eligibility criteria.

At Visit 2, (days -42 to -28) patients who fulfilled the inclusion/exclusion criteria and treatment criteria entered a six week single-blind active run-in period. To enter this period patients had to fulfill the blood pressure eligibility criteria of MSDBP >= 95 mmHg. At Visit 2 patients received single-blind valsartan 160 mg OD for two weeks. HCTZ 25 mg OD was then added for an additional four weeks.

At Visit 3 patients had to fulfill the blood pressure eligibility criteria of MSDBP >= 85 mmHg.

At Visit 5 patients not adequately responsive to valsartan 160 mg and HCTZ 25 mg (MSDBP > 85 mmHg) and who fulfilled the inclusion/exclusion criteria were randomized in a double-blind fashion to aliskiren 150 mg or placebo OD; at Visit 7 after 6 weeks of treatment with aliskiren 150 mg or placebo, aliskiren dose was increased to 300 mg. Double-blind treatment began at Visit 5 after the completion of all visit specific procedures and continued for 12 weeks. Patients who adequately responded to valsartan 160 mg and HCTZ 25 mg at Visit 5 (MSDBP < 85 mmHg) were permanently discontinued from the study.

Centers

94 centers in 7 countries: Belgium (7 centers),Romania (8 centers), Spain (18 centers), Sweden (10 centers), Switzerland (3 centers), Ukraine (9 centers), United States (39 centers)

Publication

Ongoing

Objectives

Primary objective(s)

The primary objective of this study was to evaluate the blood pressure lowering effects of aliskiren 300 mg when compared to placebo as add-on therapy to valsartan and HCTZ in patients with essential hypertension and diabetes mellitus, who did not adequately respond to valsartan 160 mg/HCTZ 25 mg alone, by testing the hypothesis of superior reduction in mean sitting diastolic blood pressure (MSDBP) from baseline to study end.

Secondary objective(s)

- Evaluate the effects of aliskiren 300 mg when compared to placebo as add-on therapy, by testing the hypothesis of superior reduction in mean sitting systolic blood pressure (MSSBP) from baseline to study end.
- Evaluate the effects of aliskiren 150 mg when compared to placebo as add-on therapy, by testing the hypotheses of superior reduction in MSDBP and MSSBP from baseline after 6 weeks of double-blind treatment.
- Compare the proportions of patients achieving a successful response (MSDBP of < 80 mmHg or a reduction of MSDBP > 10 mmHg from baseline), or achieving a target blood pressure control of MSSBP of < 130 mmHg and MSDBP < 80 mmHg, in each group at study end.
- Evaluate the safety and tolerability of aliskiren as an add-on therapy to valsartan and HCTZ compared to placebo.
- Explore the impact of treatment with aliskiren in combination with valsartan and HCTZ on selected biomarkers, pulse wave velocity (PWV), post ischemic forearm skin reactive hyperemia (SRH) and brachial artery flow-mediated vasodilatation (FMD).

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

Treatments in this study were a single-blind active run-in period comprising two weeks of valsartan 160 mg, followed by four weeks with the addition of HCTZ 25 mg. During the first two weeks placebo to HCTZ was taken. Patients eligible for the double-blind period of the trial were randomized to receive either aliskiren 150 mg (one 150 mg tablet plus one placebo) or placebo (two placebo tablets). Following six weeks of period 2, the aliskiren dose was increased to 300 mg (two 150 mg tablets). All study medication was supplied in blisters. In order to adequately blind the study, patients were required to take a total of two tablets and two capsules of study medication per day throughout the study.

The following study drugs were provided:

- Valsartan 160 mg capsules
- HCTZ 25 mg capsules
- Placebo matching to HCTZ 25 mg capsules
- Aliskiren 150 mg film-coated tablets
- Placebo matching to aliskiren 150 mg film-coated tablets

Each dose was taken orally with water at approximately 8:00 am, except on the morning of the next office/clinic visit which occurred approximately 24 hours following the last dose of study medication.

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

Placebo to both HCTZ and aliskiren were administered in a formulation matching the active therapy

Criteria for Evaluation

Primary variables

The primary efficacy variable was the change from baseline (Visit 5) in mean sitting diastolic blood pressure. The primary analysis endpoint was the Visit 9 endpoint.

Secondary variables

The secondary variables were change from baseline in mean sitting systolic blood pressure, biomarkers, post-ischaemic forearm hypersensitivity, brachial artery flow-mediated vasodilation and pulse wave velocity to endpoint. Blood pressure 6 weeks into the double-blind phase was also assessed.

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 measurement of vital signs and the performance of physical examinations and ECGs.

Statistical Methods

To assess the primary objective, the primary variable (mean sitting diastolic blood pressure, msDBP) at Visit 9 was analyzed using a two-way analysis of covariance model with treatment and region as two factors, and the baseline as a covariate. This model was considered the primary model. The regions were specified prior to unblinding treatment codes for analyses. The statistical test was made at the two-sided significance level of 0.05. Ninety-five percent confidence intervals were calculated. This analysis was performed in the ITT population.
The analysis time points were either the Visit 7 or the Visit 9 endpoints. For each patient, the last postbaseline measurement during the double-blind treatment period was carried forward to Visit 7 or Visit 9 as the endpoint measurement for the variable to be analyzed.

Summary statistics for the post-baseline and the changes-from-baseline measurements in msDBP were presented by treatment group and visit. Within-treatment analysis was performed for change from baseline (Visit 5) by a one-sample t-test at the Visit 9 endpoint. In addition, summary statistics by demographic subgroups such as age (< 65 years or >= 65 years), gender, race and ethnicity were provided.

For the change from baseline (Visit 5) to the Visit 9 endpoint in msSBP the statistical hypothesis,

model and method of analysis were analogous to those for the primary objective.
Reduction of msDBP and msSBP after 6 weeks were modelled and analyzed analogously to the primary objective and the first secondary objective, respectively.
The proportion of patients who achieved a msDBP of less than 80 mmHg at the Visit 9 endpoint, or a change from baseline (Visit 5) to the Visit 9 endpoint in msDBP of equal to or more than 10 mmHg ("responders") was tested with the null hypothesis that the proportion of responders was the same in each of the two treatment arms. A logistic regression model was fitted to assess this objective; the baseline msDBP was included in this model as a covariate, and treatment and region were included as factors.

The proportion of patients who achieved a msSBP of < 130 mmHg and msDBP < 80 mmHg at the Visit 9 endpoint ("controlled") was analyzed as for response rates.
For patients with assessments, pulse wave velocity (PWV) was summarized by treatment group and visit using descriptive statistics. Skin reactive hyperemia analysis was analogous to PWV.
Plasma/serum biomarkers (hs-CRP, sVCAM, sICAM, PRA, plasma renin concentration and aldosterone) and UACR were measured for the double-blind treatment period at baseline (Visit 5) and End of Study (Visit 9) in a subset of patients. Descriptive statistics of baseline and post-baseline values, change from baseline, as well as % change from baseline were summarized by treatment group and visit for these biomarkers in the double-blind treatment period. Differences between antihypertensive regimens for each biomarker were explored by the use of parametric and nonparametric analyses as appropriate.

The assessment of safety was based primarily on the frequency of adverse events, laboratory abnormalities and serious adverse events suspected by the investigators to be related to study medications in the safety population. The incidence of adverse events (new or worsened) was summarized by primary system organ class, preferred term, severity and relationship to study drug. The adverse events occurring during the drug withdrawal period were summarized separately from the adverse events occurring during the double-blind treatment period. In addition, the incidence of death, serious adverse events (SAEs), and AEs leading to discontinuation was summarized separately by primary system organ class and preferred term.

Summary statistics by treatment group at baseline, at last visit, and of changes from baseline at last visit for laboratory values were provided. Occurrence of significant abnormality in change of laboratory values from baseline was summarized by treatment group.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria:

1. Outpatients 18 years of age and older.
2. If female, using effective contraceptive methods.
3. Documented to have a diagnosis of either type 1 or type 2 diabetes mellitus. The patient should have been in a stable condition.

4. Hypertensive. Non-treated patients must have had a MSDBP >= 95 mmHg at Visit 1 which was on the same day as Visit 2. Treated patients must have discontinued from their antihypertensive medication at Visit 1; then, after a minimum of one week without concomitant antihypertensive treatment they had to have a MSDBP >= 95 mmHg in order to enter the single-blind active run-in at Visit 2.
5. To be eligible for randomization into the double-blind treatment period at Visit 5 (day 1) all patients must have had an MSDBP >= 85 mmHg and <110 mmHg and an MSSBP < 180 mmHg.

Exclusion Criteria:

1. History or evidence of a secondary form of hypertension.
2. History of Keith-Wagener grade III or IV hypertensive retinopathy, hypertensive encephalopathy or cerebrovascular accident.
3. Current diagnosis of heart failure (NYHA Class II-IV), stable or unstable angina pectoris, Clinically significant valvular heart disease, or history of myocardial infarction, coronary bypass surgery, or any percutaneous coronary intervention (PCI).
4. Serum sodium less than the lower limit of normal, serum potassium < 3.5 mEq/L or >= 5.3 mEq/L at Visit 1, 3 and 4.
5. Second or third degree heart block without a pacemaker.
6. Concurrent potentially life threatening arrhythmia or symptomatic arrhythmia.
7. Type 1 or type 2 diabetes mellitus with glycosylated hemoglobin (HbA1c) >11% at Visit 1. Any surgical or medical condition or treatment which might significantly alter the absorption, distribution, metabolism, or excretion of study drugs.
8. History of malignancy including leukemia and lymphoma (but not basal cell skin cancer) within the past five years.
9. History or evidence of drug or alcohol abuse within the last 12 months.
10. Known or suspected contraindications to the study medications.

Number of Subjects

Patient disposition for each treatment group during the double-blind period (Enrolled population)

	Aliskiren 300 mg Valsartan 160 mg HCTZ 25 mg	Valsartan 160 mg HCTZ 25 mg	Total
Total number of patients - n (%)			
Enrolled			1241
Entered single-blind			570
Randomized	**184 (100)**	**179 (100)**	**363 (100)**
Completed	165 (89.7)	163 (91.1)	328 (90.4)
Discontinuations Double-blind – n (%)			
Total	**19 (10.3)**	**16 (8.9)**	**35 (9.6)**
Primary reason			
Abnormal laboratory value	3 (1.6)	0	3 (0.8)
Administrative problems	1 (0.5)	0	1 (0.3)
Adverse events	5 (2.7)	6 (3.4)	11 (3.0)
Death	0	1 (0.6)	1 (0.3)
Lost to follow-up	2 (1.1)	1 (0.6)	3 (0.8)
Protocol violation	0	1 (0.6)	1 (0.3)
Subject withdrew consent	2 (1.1)	2 (1.1)	4 (1.1)
Unsatisfactory therapeutic effect	6 (3.3)	5 (2.8)	11 (3.0)

Demographic and Background Characteristics

Demographic summary by treatment group (Randomized population)

Demographic Characteristic	Category/statistic	Aliskiren 300mg Valsartan 160mg HCTZ 25mg N=184	Valsartan 160mg HCTZ 25mg N=179
Sex - n (%)	Female	85 (46.2)	82 (45.8)
	Male	99 (53.8)	97 (54.2)
Race - n (%)	Caucasian	166 (90.2)	158 (88.3)
	Black	14 (7.6)	12 (6.7)
	Asian	3 (1.6)	4 (2.2)
	Pacific Islander	0	1 (0.6)
	Other	1 (0.5)	4 (2.2)
Ethnicity - n (%)	Hispanic or Latino	24 (13.0)	25 (14.0)
	Indian (Indian subconti-nent)	2 (1.1)	1 (0.6)
	Other	158 (85.9)	153 (85.5)

Age (yrs)	n	184	179
	Mean	56.8	57.2
	SD	8.62	8.56
	Min-Max	33.0-79.0	36.0-80.0
Age Group – n (%)	< 65 yrs	142 (77.2)	139 (77.7)
	>= 65 - < 75 yrs	41 (22.3)	38 (21.2)
	>= 75 yrs	1 (0.5)	2 (1.1)
Height (cm) by gender			
Male	n	99	96
	Mean	174.4	175.6
	SD	6.40	7.35
	Min-Max	162.0-187.0	160.0-195.0
Female	n	85	82
	Mean	160.4	162.0
	SD	5.82	6.60
	Min-Max	146.0-176.0	147.0-175.0
Weight (kg)	n	184	178
	Mean	93.33	95.13
	SD	17.127	22.565
	Min-Max	60.00-148.00	59.00-188.00
Duration of Hypertension (yrs)	n	184	179
	Mean	10.3	10.4
	SD	7.37	8.64
	Min-Max	1.0-31.0	1.0-37.0
Body Mass Index (kg/m2)	n	184	178
	Mean	33.13	33.02
	SD	5.735	6.326
	Min-Max	22.68-52.07	20.17-59.34
Waist circumference (cm) by gender			
Male	n	98	93
	Mean	106.3	110.8
	SD	14.26	17.33
	Min-Max	58.0-148.0	81.0-170.0
Female	n	85	80
	Mean	105.0	100.7
	SD	14.10	13.16
	Min-Max	78.0-144.0	69.0-140.0

Primary Objective Result(s)

Between treatment analysis results for change from baseline in mean sitting diastolic blood pressure at Week 12 endpoint (ITT population)

Treatment Group	N	Least squares mean (LSM) change from baseline (SE)
Aliskiren 300mg	181	-5.8 (0.67)
Valsartan 160mg		
HCTZ 25mg		
Valsartan 160mg	177	-4.8 (0.69)
HCTZ 25mg		

Pairwise Comparison	LSM difference in change from baseline (SE)	95% CI for LSM difference	p-value1
Aliskiren 300mg Valsartan 160mg HCTZ 25mg	-0.9 (0.87)	(-2.64, 0.76)	0.2767
vs.			
Valsartan 160mg HCTZ 25mg			

1p-values and treatment com parisons were evaluated using an ANCOVA model containing treatment, country and baseline.

Secondary Objective Result(s)

Between treatment analysis results for change from baseline in mean sitting systolic blood pressure at Week 12 endpoint (ITT population)

Treatment Group	N	LSM change from baseline (SE)
Aliskiren 300mg Valsartan 160mg HCTZ 25mg	181	-7.3 (1.08)
Valsartan 160mg HCTZ 25mg	177	-4.8 (1.11)

Pairwise Comparison	LSM difference in change from base-line (SE)	95% CI for LSM difference	p-value1
Aliskiren 300mg Valsartan 160mg HCTZ 25mg vs. Valsartan 160mg HCTZ 25mg	-2.5 (1.39)	(-5.24, 0.23)	0.0725

1p-values and treatment comparisons were evaluated using an ANCOVA model containing treatment, country and baseline.

Effect of aliskiren add-on therapy at Week 6

At Week 6, endpoint, aliskiren add-on therapy resulted in a decreased in msDBP of over 1mmHg greater than placebo add-on in the ITT population. Using an ANCOVA model, this difference was not significant.
The LSM difference between aliskiren and placebo add-on therapy at Week 6 endpoint for msSBP was -1.4 (SE=1.26), with a p-value of 0.2720, indicating that although at this time point aliskiren add-on therapy resulted in a numerically greater mean decrease in msSBP, it was not significantly greater than the placebo add-on group.

Between treatment comparisons for proportion of diastolic responders at Week 12 endpoint (ITT population)

Responder type	Aliskiren 300mg Valsartan 160mg HCTZ 25mg n/N (%)	Valsartan 160mg HCTZ 25mg n/N (%)	p-value
Diastolic responder	124/181 (68.5)	129/177 (72.9)	0.8482
Diastolic responder is defined as a patient with a msDBP < 80 mmHg or at least a 10 mmHg reduction from baseline.			
p-values were from a logistic regression model with treatment and country as factors, and baseline as a covariate.			

Between treatment analysis for blood pressure control at Week 12 endpoint (ITT population)

	Aliskiren 300mg Valsartan 160mg HCTZ 25mg n/N (%)	Valsartan 160mg HCTZ 25mg n/N (%)	p-value
Blood pressure control	29/181 (16.0)	29/177 (16.4)	0.7511
Blood pressure control was defined as a msSBP < 130 mmHg and msDBP < 80 mmHg at the visit analyzed.			
Blood pressure control was analyzed using a logistic regression model with treatment and country as factors, and baseline as a covariate.			

Biomarkers

The albumin:creatinine ratio was normal at baseline and therefore would not be expected to change with treatment.

Mean plasma renin activity (PRA) in the alikiren add-on group was reduced by 81% at Week 12 compared to baseline (randomization visit). PRA was not significantly changed at 12 weeks compared to baseline in the placebo add-on treatment group. Plasma rennin concentration (PRC) in the treatment group receiving aliskiren add-on therapy was increased at 12 weeks versus baseline compared with no significant changes in patients in the placebo add-on treatment group. Increases in PRA and PRC that are routinely seen with ARB and diuretic therapy would have occurred during the active run-in period in the present study and thus were not captured. Aldosterone and highly sensitive C reactive protein levels did not change during the 12 week treatment period in either treatment group, nor did the inflammatory markers ICAM-1 and VCAM-1

Pulse wave velocity

Pulse wave velocity (PWV) was measured in a subset of patients. There was no significant effect of aliskiren add-on treatment on PWV measured either in the carotid-femoral artery, or the carotid-radial artery. The augmentation decreased slightly in the aliskiren add-on therapy arm (change of -2.0), but not significantly.

Post ischemic forearm skin reactive hyperemia

Skin reactive hyperemia (SRH) was measured in a subset of patients. Baseline blood flow measurements were similar between the two treatment groups. Mean SRH decreased at week 12 endpoint in both the aliskiren and placebo add-on treatment arms, but to a greater degree in the placebo add-on group. However this group also had a very large variation in response to occlusion, with a change in the maximum cutaneous blood flow post reactive hyperemia of 370%. This combined with the small patient numbers (less than ten), makes correlations difficult to draw. The same is true of the response to temperature, where the standard deviation was greater than the level of change.

Brachial artery flow-mediated dilation

Brachial arterial flow mediated dilation (FMD) was measured in a small subset of patients. Patients in the placebo add-on treatment group had a lower baseline brachial arterial diameter than those in the aliskiren add-on treatment arm. The change from baseline in arterial diameter was not significant for either treatment group, and there was no difference between treatment groups.

Safety Results

Adverse Events by System Organ Class

Number (%) of patients with adverse events overall during the double-blind period by system organ class (Safety population)

	Aliskiren 300mg Valsartan 160mg HCTZ 25mg N=183	Valsartan 160mg HCTZ 25mg N=179
	n (%)	n (%)
Total	**63 (34.4)**	**59 (33.0)**
Infections and infestations	22 (12.0)	15 (8.4)
Nervous system disorders	12 (6.6)	16 (8.9)
Metabolism and nutrition disorders	10 (5.5)	8 (4.5)
Musculoskeletal and connective tissue disorders	11 (6.0)	6 (3.4)
General disorders and administration site conditions	9 (4.9)	4 (2.2)
Gastrointestinal disorders	5 (2.7)	7 (3.9)
Injury, poisoning and procedural complications	6 (3.3)	6 (3.4)
Investigations	2 (1.1)	5 (2.8)
Respiratory, thoracic and mediastinal disorders	3 (1.6)	3 (1.7)
Cardiac disorders	2 (1.1)	3 (1.7)
Skin and subcutaneous tissue disorders	3 (1.6)	2 (1.1)
Vascular disorders	3 (1.6)	2 (1.1)
Ear and labyrinth disorders	2 (1.1)	2 (1.1)
Renal and urinary disorders	4 (2.2)	0
Hepatobiliary disorders	1 (0.5)	2 (1.1)
Blood and lymphatic system disorders	1 (0.5)	0
Endocrine disorders	1 (0.5)	0
Eye disorders	0	1 (0.6)
Immune system disorders	0	1 (0.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.5)	0
Psychiatric disorders	0	1 (0.6)
Reproductive system and breast disorders	0	1 (0.6)
Body systems are sorted according to descending frequency in total.		

Adverse events overall and most frequent events during the double-blind period - n (%) of patients (>= 2% in any group, Safety population)

	Aliskiren 300mg Valsartan 160mg HCTZ 25mg N=183	Valsartan 160mg HCTZ 25mg N=179
	n (%)	n (%)
Any Adverse Events	**63 (34.4)**	**59 (33.0)**
Headache	2 (1.1)	11 (6.1)
Dizziness	8 (4.4)	3 (1.7)
Nasopharyngitis	5 (2.7)	5 (2.8)
Influenza	2 (1.1)	6 (3.4)
Fatigue	4 (2.2)	2 (1.1)
Arthralgia	4 (2.2)	0
Hypokalaemia	0	4 (2.2)
Nausea	0	4 (2.2)

Preferred terms are sorted according to descending order of frequency in the total column.

Serious Adverse Events and Deaths

Deaths, other serious or clinically significant adverse events or related discontinuations during the double-blind period – n (%) of patients (Safety population)

	Aliskiren 300mg Valsartan 160mg HCTZ 25mg N=183	Valsartan 160mg HCTZ 25mg N=179	Total N=362
	n (%)	n (%)	n (%)
Deaths	0	1 (0.6)	1 (0.3)
SAEs	3 (1.6)	3 (1.7)	6 (1.7)
AE discontinuations	5 (2.7)	7 (3.9)	12 (3.3)
Discontinuations for abnormal lab values	3 (1.6)	0	3 (0.8)

1 Musculoskeletal chest pain, non cardiac chest pain
1 Diabetic autonomic neuropathy, Constipation, Abdominal pain
1 Renal failure and hyperkalemia
1 Fall , Tendon rupture
1 Cholelithiasis,
1 Angina unstable, Limb discomfort, Chest pain, Coronary artery thrombosis, Throat irritation, Coronary artery occlusion, Coronary artery disease, Disease progression

Other Relevant Findings

Laboratory values over time

There was no change in the mean or median value for any of the hematology variables assessed between baseline and end of study for either treatment arm.
There was a slight tendency for creatinine and blood urea nitrogen levels to increase over the 12 week treatment period in the aliskiren add-on group, although this increase was small (change from baseline in aliskiren add-on and placebo add-on groups of 3.4 and 0.7 µmol/L for creatinine, and 0.73 0.06 mmol/L for BUN). Mean levels increased over the treatment period, but the dose escalation did not appear to increase the rate of this rise.
Bicarbonate levels showed a slight decrease in both treatment groups over time, but again the degree of change was very small (a change of -0.98 and -0.68 mmol/L from baseline in the aliskiren and placebo add-on groups, respectively).

Individual patient changes

The majority of patients remained at their baseline categorization, or normalized. The aliskiren add-on therapy arm, and placebo add-on arm had 6.3% and 9.3% of patients moving from a normal to a high basophil count, and 5.6% and 7.9% of patients moving from a normal to a high eosinophil count.

Eleven patients (6.5%) in the aliskiren add-on arm experienced a shift from normal to high platelet counts, whilst this was 2.4% in the placebo add-on arm. Red blood cell count, hematocrit and

hemoglobin all saw a shift of between 4.1% and 8.7% from normal to low values in each treatment group. All other shifts were in less than 5% of patients.
A greater than 50% increase in a hematological variable was only seen for white blood cell count (2.4% and 4.2% of patients in the aliskiren add-on arm and placebo add-on arm respectively), and platelet count (greater than 75% increase in 0.6% of patients in the aliskiren, and 1.2% of patients in the placebo add-on arm respectively). These increases resulted in only two patients in total being classed as having "high" values. Greater than 20% decreases were seen in one or two patients in each treatment arm for hemoglobin, hematocrit and red blood cell count. 1.8% of aliskiren add-on, and 2.4% of placebo add-on patients experienced a greater than 50% decrease in white blood cell count. With the exception of white blood cell count these decreases resulted in those patients having a "low" level.

Shift tables of laboratory values show that as expected in a diabetic population, glucose, glycosylated hemoglobin, triglycerides, cholesterol and low density lipoprotein were "high" in a large proportion of the patient population. These variables were also likely to shift to a "high" level from a baseline "normal" (which may not have been a large increase in actual value).

Creatinine, potassium and BUN all showed a tendency to shift from "normal" to "high" for both treatment groups, but for a slightly greater percentage of patients in the aliskiren add-on treatment group. AST and ALT also had a greater than 5% shift from "normal" to "high" in the aliskiren add-on arm, but slightly less for AST in the placebo add-on arm.
Bicarbonate and chloride levels showed a tendency to shift to "low" levels in both treatment arms.

Individual clinically significant abnormalities

The incidence of notable potassium values was similar between treatment groups, however the aliskiren add-on treatment arm experienced a higher percentage of blood urea nitrogen and creatinine elevations.

Number (%) of patients exceeding pre-specified thresholds at any timepoint post-baseline in laboratory values (Safety population)

		Aliskiren 300mg Valsartan 160mg HCTZ 25mg N=183	**Valsartan 160mg HCTZ 25mg N=179**
		n/N* (%)	**n/N* (%)**
Abnormal electrolyte parameters			
Potassium	>= 6.0 mmol/L	4/181 (2.2)	3/177 (1.7)
	> 5.5 mmol/L	12/181 (6.6)	10/177 (5.6)
	< 3.5 mmol/L	4/181 (2.2)	6/177 (3.4)
Abnormal kidney parameters			
Blood Urea Nitrogen (BUN)	> 14.28 mmol/L	7/181 (3.9)	1/177 (0.6)
Creatinine	> 176.8 mmol/L	7/181 (3.9)	1/177 (0.6)
N* is the number of patients with evaluable criterion.			
Percentages were calculated using the total row for each parameter as denominator.			

Vital signs, physical findings, and other observations related to safety

Vital signs

The number of patients with orthostatic hypotension is shown in the table below. There was no difference in occurrence between treatment arms.

Number (%) of patients with orthostatic blood pressure change from baseline to Week 12 (Safety population)

	Aliskiren 300mg Valsartan 160mg HCTZ 25mg N=183	Valsartan 160mg HCTZ 25mg N=179
Visit	**n/N (%)**	**n/N (%)**
Baseline	22/182 (12.1)	28/179 (15.6)
Week 2	43/180 (23.9)	29/177 (16.4)
Week 6	30/173 (17.3)	36/172 (20.9)
Week 8	35/170 (20.6)	33/168 (19.6)
Week 12	28/167 (16.8)	43/166 (25.9)
Any visit post-baseline	81/181 (44.8)	84/177 (47.5)
Orthostatic hypotension was defined as a decrease of at least 20 mmHg in systolic blood pressure or a decrease of at least 10 mmHg in diastolic blood pressure when a patient moved from sitting to standing.		

Both sitting and standing blood pressures decreased from baseline at Week 12 Endpoint, as expected. Sitting and standing pulse did not show a significant change from baseline.

Other safety evaluations

There were no other evaluations.

Date of Clinical Trial Report

30 October 2007

Date Inclusion on Novartis Clinical Trial Results Database

10 June 2008

Date of Latest Update

09 June 2008