Sponsor

Novartis

Generic Drug Name

Aliskiren

Therapeutic Area of Trial

Essential hypertension

Approved Indication

Investigational

Study Number

CSPP100A2302 (including amendment #3 CSPP100A2302E1)

Title

A 12 month, randomized, open-label, multicenter, study to assess the long term safety of aliskiren 150 mg alone and 300 mg alone or with the optional addition of hydrochlorothiazide (12.5 mg or 25 mg) in patients with essential hypertension (including amendment #3 – 4 month extension).

Phase of Development

Phase III

Study Start/End Dates

15 June 2004 to 13 October 2005 (Amendment #3, 13 February 2006)

Study Design/Methodology

This was an open-label, multicenter, randomized, parallel-group, dose escalation study of aliskiren 150 mg and 300 mg administered as monotherapy, and aliskiren 300 mg administered in combination with hydrochlorothiazide (HCTZ) 12.5 mg or 25 mg as needed for blood pressure (BP) control in patients with uncomplicated essential hypertension. The study was comprised of three periods (with an additional Period 4 in a subset of patients at selected centers). Amendment #3 added a four-month extension period for a subset of patients on the high dose combination of aliskiren/HCTZ (300 mg/25 mg).

Period 1 was a 1 to 2 week period during which patients taking antihypertensives tapered off their medication. Patients who were newly diagnosed with uncomplicated hypertension and who were not taking any antihypertensive medication(s), or those who had not been taking antihypertensive drugs for at least 1 week prior to Visit 1, could combine visits one and two and be enrolled directly into the two to four week screening period.

Period 2 was a 2 to 4 week drug-free screening period used to establish a baseline blood pressure and eligibility for randomization based on the inclusion and exclusion criteria.

Eligible patients were randomized to either aliskiren 150 mg or 300 mg once daily (3:2 ratio) for 52 weeks of open-label treatment (Period 3). HCTZ 12.5 mg or 25 mg was added to 300mg aliskiren as necessary, in order to reach a goal blood pressure of < 140/90mmHg.

Following eleven months of active, open-label treatment, the first 320 patients receiving aliskiren as monotherapy for the treatment of their hypertension who consented to participate at selected centers, were randomized to the one month, double-blind, placebo-controlled withdrawal phase (Period 4).

Following twelve months of active, open-label treatment (Visit 10 Month 12), a subset of approximately 250 patients who received the combination treatment (aliskiren 300 mg and HCTZ 25 mg) for at least 8 months, were eligible to enter the extension phase of the study. These patients continued receiving open-label, combination treatment for an additional 4-months providing long-term safety data (12 months) on the high dose combination.

Centres

185 centers in 12 countries: USA (50), Germany (48), Italy (18), Switzerland (12), Belgium (11), Peru (10), UK (9), Russia (8), Denmark (8), Netherlands (5), Canada (4), Iceland (2).

Publication

Aliskiren, an oral direct renin inhibitor, provides long-term antihypertensive efficacy and safety in patients with hypertension

Domenic Sica, Alan Gradman, Ole Lederballe, Maria Meyers, Jennifer Cai, Deborah Keefe

Am J Hypertens – to be submitted

Objectives

Primary outcome/efficacy objective(s)

The primary objective of this study was to assess the long-term safety and tolerability of aliskiren 150 mg and aliskiren 300 mg, with the optional addition of HCTZ 12.5 mg or 25 mg to aliskiren 300 mg, in patients with essential hypertension (mean sitting diastolic blood pressure [msDBP] ≥ 90 mmHg and < 110 mmHg).

Secondary outcome/efficacy objective(s)

- Assess the long-term blood pressure efficacy of aliskiren 150 mg and 300 mg with the optional addition of HCTZ 12.5 mg or 25 mg to aliskiren 300 mg, in patients with essential hypertension (msDBP ≥ 90 mmHg and < 110 mmHg).
- Assess the long-term efficacy of aliskiren monotherapy by comparing the change in msDBP and mean sitting systolic blood pressure (msSBP) from Month 11 (end of open-label period) to Month 12 (end of one month, double-blind, placebo-controlled, randomized withdrawal period).
- Evaluate overall the potential for rebound hypertension following abrupt withdrawal of aliskiren treatment at one week and two weeks in those patients randomized to placebo who completed 11 months of treatment.

- Evaluate the effect of treatment on plasma renin activity and plasma renin concentration (active renin) in a subset of patients (for U.S. patients only).
- Evaluate the 24-hour blood pressure profile of patients treated with aliskiren monotherapy versus placebo by utilizing 24 hour ambulatory blood pressure measurement (ABPM) in a subset of patients during the withdrawal period.
- Assess the long-term safety (12 months) of aliskiren 300 mg in combination with hydrochlorothiazide (HCTZ) 25mg in a subset of patients

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

Aliskiren 150 mg or 300 mg once daily, oral administration

HCTZ 12.5 mg or 25 mg once daily, oral administration (added to aliskiren 300 mg as necessary)

Aliskiren 300 mg / HCTZ 25 mg in combination (amendment #3, 4-month extension) once daily, oral administration

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

Placebo was administered in the same manner as aliskiren 150 mg and 300 mg.

Criteria for Evaluation

Safety/tolerability (primary objective):

- Adverse events, physical examinations, vital signs, laboratory assessments, pregnancy tests and ECGs.

Secondary Objectives:

- Change from baseline in msDBP and msSBP at all visits and Endpoint (Month 12, Month 11, last observation carried forward)
- Change from baseline in standing diastolic and systolic blood pressures
- Long term blood pressure efficacy measured by response rates (percent of patients who achieved msDBP < 90 mmHg and/or ≥ 10 mmHg reduction from baseline)
- Long term blood pressure efficacy measured by control rate (percent of patients who achieved control [BP < 140/90])
- Changes in msSBP and msDBP from Month 11 to Month 12
- Changes from baseline in plasma renin activity, and plasma renin concentration (active renin) (for U.S. patients only)
- 24-hour ABPM was performed in a subset of patients participating in the randomized, double-blind withdrawal period
- Adverse events, physical examinations, vital signs, laboratory assessments and ECGs for all extension patients (amendment #3, 4 month extension)

Pharmacology:

Not applicable.

Other:

None.

Statistical Methods

Demographic and disease characteristics, study medication exposure, and prior and concomitant medication use were summarized. Summary statistics were provided for continuous variables, and frequency counts were provided for discrete variables. The regions were specified as country prior to the unblinding of the treatment codes.

Open label period: The primary objective was the reporting of any adverse events and SAE including death.

In addition, frequency distributions of safety parameters were summarized for the safety population. Laboratory data were summarized at baseline and endpoint for absolute values and change from baseline. Incidence counts of patients with pre-specified notable laboratory abnormalities were also provided.

Summary statistics for the post-baseline and change-from-baseline BP measurements and biomarkers were presented.

Randomized withdrawal period: The primary analysis model for treatment comparison of the BP measurements during the randomized withdrawal period was two-way analysis-of-covariance model (ANCOVA) with treatment (All Aliskiren vs. All Placebo), strata (150 mg vs. 300 mg), region as factors, and month 11 (Visit 10) as covariate. The regions were specified as country. If the pairwise comparison test was statistically significant in favor of All Aliskiren, All Aliskiren treatment is considered superior to All Placebo. Furthermore, the pairwise comparison with 95% confidence interval between All Aliskiren and All Placebo were provided.

Similar safety analyses were performed for the randomized withdrawal period.

Four month extension period: Safety analyses were performed including the reporting of any adverse events and SAE including death.

Study Population: Inclusion/Exclusion Criteria and Demographics

- Patients were male or female patients at least 18 years of age. Female patients had to be either post-menopausal for one year, surgically sterile, or using effective contraceptive methods such as oral contraceptives, barrier method with spermicide or an intrauterine device.
- Patients with essential hypertension (msDBP $\geq$ 90 mmHg and < 110 mmHg during the last two visits of the lead-in period of the study).
- Patients with an absolute difference of $\leq$ 10 mmHg in their average sitting DBP during the last two visits of the lead-in period of the study.
- Patients who were eligible and able to participate in the study, and who provided written informed consent.
- Patients who successfully completed study SPP100A2203: "A randomized, double-blind, multicenter, multifactorial, placebo-controlled, parallel-group study to confirm the efficacy and safety of aliskiren monotherapy, and evaluate efficacy and safety of combinations of aliskiren and valsartan in hypertension patients" (defined as completing all study visits without serious adverse events), after signing an informed consent, **could be** (not the only source) **enrolled** directly in the treatment portion of this study (visit 3), with no additional blood pressure qualification required.

Exclusion criteria (open-label period)

- Patients previously treated with aliskiren (with the exception of protocol SPP100A2203).
- Severe hypertension (grade 3 WHO classification; msDBP ≥ 110 mmHg and/or msSBP ≥ 180 mmHg).
- History or evidence of a secondary form of hypertension.
- Transient ischemic cerebral attack during the 12 months prior to Visit 1.
- Type 1 or Type 2 diabetes mellitus with poor glycemic control defined as fasting glycosylated hemoglobin (HbA1c) > 8% at Visit 1 or 2.
- Serum sodium and/or serum potassium less than the lower limit of normal, dehydration, or hyperkalemia > 5.5 at Visit 1 or 2.
- Pregnant or nursing women

Number of Subjects

	Aliskiren 150 mg (R)		Aliskiren 300 mg (R)		Total	
Disposition	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Patients randomized					1955	
Received active treatment	1179		776		1955	
Completed open label period	966	(81.9)	659	(84.9)	1625	(83.1)
Discontinued during open label period	213	(18.1)	117	(15.1)	330	(16.9)
Reason for discontinuation during the open label period						
Adverse event(s)	63	(5.3)	39	(5.0)	102	(5.2)
Subject withdrew consent	52	(4.4)	25	(3.2)	77	(3.9)
Unsatisfactory therapeutic effect	34	(2.9)	30	(3.9)	64	(3.3)
Lost to follow-up	32	(2.7)	12	(1.5)	44	(2.3)
Protocol violation	13	(1.1)	5	(0.6)	18	(0.9)
Abnormal laboratory value(s)	8	(0.7)	0	(0.0)	8	(0.4)
Administrative problems	6	(0.5)	1	(0.1)	7	(0.4)
Death	3	(0.3)	2	(0.3)	5	(0.3)
Subject's condition no longer requires study drug	1	(0.1)	2	(0.3)	3	(0.2)
Abnormal test procedure result(s)	1	(0.1)	1	(0.1)	2	(0.1)

Note: (R)- Randomized aliskiren treatment group.

Demographic and Background Characteristics

Demographic variable	Statistic/category	Aliskiren 150 mg (R) N=1179	Aliskiren 300 mg (R) N=776	Mono*** N = 1085	Combo*** N = 870
Age (years)	Mean (SD)	55.7 (11.30)	55.9 (11.48)	54.8 (11.55)	57.0 (11.03)
	Range	19.0 - 88.0	22.0 - 86.0	19.0 - 88.0	22.0 - 86.0
Age group n (%)	< 65 years	912 (77.4)	604 (77.8)	862 (79.4)	654 (75.2)
	≥ 65 years	267 (22.6)	172 (22.2)	223 (20.6)	216 (24.8)
	< 75 years	1126 (95.5)	739 (95.2)	1041 (95.9)	824 (94.7)
	≥ 75 years	53 (4.5)	37 (4.8)	44 (4.1)	46 (5.3)
Sex n (%)	Male	613 (52.0)	414 (53.4)	546 (50.3)	481 (55.3)
	Female	566 (48.0)	362 (46.6)	539 (49.7)	389 (44.7)
Race n (%)	Caucasian	1020 (86.5)	667 (86.0)	921 (84.9)	766 (88.0)
	Black	69 (5.9)	46 (5.9)	59 (5.4)	56 (6.4)
	Asian	5 (0.4)	10 (1.3)	11 (1.0)	4 (0.5)
	Native American	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)
	Pacific Islander	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)
	Other	83 (7.0)	53 (6.8)	93 (8.6)	43 (4.9)
Ethnicity n (%)	Hispanic or Latino	226 (19.2)	144 (18.6)	254 (23.4)	116 (13.3)
	Indian (Indian subcontinent)	2 (0.2)	1 (0.1)	2 (0.2)	1 (0.1)
	Japanese	3 (0.3)	3 (0.4)	4 (0.4)	2 (0.2)
	Other	948 (80.4)	628 (80.9)	825 (76.0)	751 (86.3)
Body Mass Index (kg/m^2)	Mean (SD)	29.3 (4.93)	29.2 (5.20)	28.9 (4.97)	29.7 (5.09)
	Range	18.0 - 57.8	17.4 - 51.8	17.4 - 53.2	18.0 - 57.8
Obesity n (%)	BMI ≥ 30 (kg/m^2)	451 (38.3)	283 (36.5)	372 (34.3)	362 (41.6)
	BMI < 30 (kg/m^2)	727 (61.7)	491 (63.3)	710 (65.4)	508 (58.4)
Waist circumference (cm)	Mean (SD)	98.3 (14.12)	98.1 (14.82)	97.5 (14.43)	99.2 (14.31)
	Range	54.0 - 168.0	51.0 - 156.0	54.0 - 168.0	51.0 - 156.0
Duration of hypertension history (years)	Mean (SD)	7.0 (6.80)	7.6 (7.54)	6.5 (6.58)	8.2 (7.61)
	Range	1.0 - 43.0	1.0 - 42.0	1.0 - 41.0	1.0 - 43.0
Metabolic Syndrome # n (%)	Yes	536 (45.5)	331 (42.7)	452 (41.7)	415 (47.7)
	No	643 (54.5)	445 (57.3)	633 (58.3)	455 (52.3)
Diabetes n (%) ##	Yes	87 (7.4)	73 (9.4)	86 (7.9)	74 (8.5)
	No	1092 (92.6)	703 (90.6)	999 (92.1)	796 (91.5)

* Metabolic Syndrome=Yes, if any 3 of the following are true: 1. Waist circumference (> 102 cm (i.e. > 40 in) for men or > 88 cm (i.e. > 35 in) for women); 2. Triglycerides ≥150 mg/dL (i.e. ≥ 1.69 mmol/L); 3. HDL cholesterol (< 40 mg/dL (i.e. < 1.04 mmol/L) for men or < 50 mg/dL (i.e. < 1.29 mmol/L) for women); 4. Blood pressure≥ 130/ ≥ 85 mmHg; 5. Fasting glucose ≥ 110 mg/dL (i.e. ≥ 6.1 mmol/L).
**From medical history
SD = standard deviation.
Note: (R)- Randomized Aliskiren treatment group.
***Monotherapy patients are those who never took HCTZ. Combo = combination therapy (patients who took HCTZ at least once).

Results of Primary Objective (See Safety section below)

Efficacy Result(s)

Change from baseline in msDBP (mmHg) at open-label visit by randomized treatment group (Open-label ITT population)

		Aliskiren 150 mg(R) N = 1162		Aliskiren 300 mg(R) N = 766	
Open label visit	(Month)	N*	Mean (SD)	N*	Mean (SD)
4	1	1161	-8.3 (7.6)	766	-9.3 (7.8)
5	2	1112	-9.0 (8.1)	744	-9.8 (7.8)
6	3	1080	-11.0 (8.1)	726	-12.0 (7.4)
7	4	1046	-12.3 (7.4)	715	-13.0 (7.6)
8	6	1031	-12.6 (7.1)	702	-13.3 (7.6)
9	9	1007	-13.6 (7.4)	683	-13.9 (7.4)
10	11/12	974	-13.5 (7.4)	665	-14.2 (7.7)
Endpoint**		1162	-12.4 (8.5)	766	-13.3 (8.3)

(*) N is the number of patients with values obtained at both baseline and post-baseline visit.
(**) Endpoint is Month 11/12, or last visit carried forward.
Note: A decrease in the mean change indicates improvement.
Note: (R)- Randomized aliskiren treatment group.

Summary of blood pressure results at Visit 10 (final visit, Month 11/12) of the open label period

	Monotherapy		Combo therapy		Aliskiren 150 mg(R)		Aliskiren 300 mg(R)	
	Mean change from BL (mmHg)	BP at Visit 10 (mmHg)	Mean change from BL (mmHg)	BP at Visit 10 (mmHg)	Mean change from BL (mmHg)	BP at Visit 10 (mmHg)	Mean change from BL (mmHg)	BP at Visit 10 (mmHg)
msDBP	-14.7	81.7	-12.8	85.6	-13.5	83.6	-14.2	83.4
msSBP	-19.5	130.5	-19.8	136.2	-19.3	133.2	-20.2	133.0

BL = baseline
Monotherapy patients were those who never took HCTZ
Combo patients were those who took HCTZ at least once during the open label period.
(R) = Randomized aliskiren treatment group.

Change from baseline in msSBP (mmHg) at open-label visit by randomized treatment group (Open-label ITT population)

		Aliskiren 150 mg(R) N = 1162		Aliskiren 300 mg(R) N = 766	
Open label Visit	(Month)	N*	Mean (SD)	N*	Mean (SD)
4	1	1161	-10.8 (12.5)	766	-12.4 (12.9)
5	2	1112	-12.7 (12.9)	744	-14.0 (12.8)
6	3	1080	-15.5 (13.4)	726	-17.4 (13.6)
7	4	1046	-17.7 (12.7)	715	-19.2 (13.7)
8	6	1031	-18.6 (13.2)	702	-19.6 (13.8)
9	9	1007	-19.9 (13.2)	683	-20.2 (13.4)
10	11/12	974	-19.3 (13.1)	665	-20.2 (13.3)
Endpoint**		1162	-17.5 (14.5)	766	-18.8 (14.6)

Note: (R)- Randomized aliskiren treatment group.
(*) N is the number of patients with values obtained at both baseline and post-baseline visit.
(**) Endpoint is Month 11/12, or last visit carried forward.
Note: A decrease in the mean change indicates improvement.

Change from baseline to endpoint in mean standing diastolic and systolic blood pressure by randomized treatment (intent-to-treat population)

Value	Aliskiren 150 mg(R) (mmHg)	Aliskiren 300 mg(R) mmHg	Total mmHg
mDBP	98.7/87.8 (-10.9)	99.1/87.5 (-11.6)	98.8/87.7 (-11.2)
mSBP	152.8/136.5 (-16.3)	153.0/135.8 (-17.1)	152.8/136.2 (-16.6)
Endpoint**			

(**) Endpoint is Month 11/12, or last visit carried forward.

Distribution of msDBP rebound effect (Randomized withdrawal ITT population)

Rebound effect	All Aliskiren (N=131) n (%)	All Placebo (N=128) n (%)
Visit 11 (Month 11+7 days)		
< baseline-10mmHg	95 (72.5)	85 (66.4)
baseline-10mmHg to baseline	34 (26.0)	37 (28.9)
baseline to baseline+5mmHg	2 (1.5)	4 (3.1)
baseline+5mmHg to baseline+10mmHg	0 (0.0)	2 (1.6)
≥ baseline+10mmHg	0 (0.0)	0 (0.0)
Visit 12 (Month 11+14 days)		
< baseline-10mmHg	89 (67.9)	65 (50.8)
baseline-10mmHg to baseline	35 (26.7)	55 (43.0)
baseline to baseline+5mmHg	2 (1.5)	2 (1.6)
baseline+5mmHg to baseline+10mmHg	3 (2.3)	2 (1.6)
≥ baseline+10mmHg	0 (0.0)	2 (1.6)
Visit 13 (Month 11+21 days)		
< baseline-10mmHg	88 (67.2)	63 (49.2)
baseline-10mmHg to baseline	36 (27.5)	44 (34.4)
baseline to baseline+5mmHg	1 (0.8)	13 (10.2)
baseline+5mmHg to baseline+10mmHg	2 (1.5)	0 (0.0)
≥ baseline+10mmHg	0 (0.0)	4 (3.1)
Visit 14 (Month 11+28 days)		
< baseline-10mmHg	86 (65.6)	62 (48.4)
baseline-10mmHg to baseline	34 (26.0)	45 (35.2)
baseline to baseline+5mmHg	3 (2.3)	9 (7.0)
baseline+5mmHg to baseline+10mmHg	2 (1.5)	7 (5.5)
≥ baseline+10mmHg	0 (0.0)	0 (0.0)

Distribution of msSBP rebound effect (Randomized withdrawal ITT population)

Rebound effect	All Aliskiren (N=131) n (%)	All Placebo (N=128) n (%)
Visit 11 (Month 11+7 days)		
< baseline-20mmHg	56 (42.7)	56 (43.8)
baseline-20mmHg to baseline	66 (50.4)	62 (48.4)
baseline to baseline+10mmHg	6 (4.6)	7 (5.5)
baseline+10mmHg to baseline+20mmHg	3 (2.3)	3 (2.3)
≥ baseline+20mmHg	0 (0.0)	0 (0.0)
Visit 12 (Month 11+14 days)		
< baseline-20mmHg	57 (43.5)	49 (38.3)
baseline-20mmHg to baseline	62 (47.3)	61 (47.7)
baseline to baseline+10mmHg	8 (6.1)	13 (10.2)
baseline+10mmHg to baseline+20mmHg	2 (1.5)	3 (2.3)
≥ baseline+20mmHg	0 (0.0)	0 (0.0)
Visit 13 (Month 11+21 days)		
< baseline-20mmHg	53 (40.5)	39 (30.5)
baseline-20mmHg to baseline	69 (52.7)	66 (51.6)
baseline to baseline+10mmHg	4 (3.1)	16 (12.5)
baseline+10mmHg to baseline+20mmHg	0 (0.0)	3 (2.3)
≥ baseline+20mmHg	1 (0.8)	0 (0.0)
Visit 14 (Month 11+28 days)		
< baseline-20mmHg	48 (36.6)	37 (28.9)
baseline-20mmHg to baseline	67 (51.1)	65 (50.8)
baseline to baseline+10mmHg	9 (6.9)	17 (13.3)
baseline+10mmHg to baseline+20mmHg	1 (0.8)	3 (2.3)
≥ baseline+20mmHg	0 (0.0)	1 (0.8)

Control Rates and Responder Rates in the open-label period

Control rate by randomized treatment group at endpoint during the open label period (intent-to-treat population)

Visit	Aliskiren 150 mg(R) n/N (%)	Aliskiren 300 mg(R) n/N (%)	Total n/N (%)
Endpoint**	699/1162 (60.2)	481/766 (62.8)	1180/1928 (61.2)

(**) Endpoint is Month 11/12, or last visit carried forward.

Responder rate by randomized treatment group at endpoint during the open label period (intent-to-treat population)

Visit	Aliskiren 150 mg(R) n/N (%)	Aliskiren 300 mg(R) n/N (%)	Total n/N (%)
Endpoint**	924/1162 (79.5)	628/766 (82.0)	1552/1928 (80.5)

(**) Endpoint is Month 11/12, or last visit carried forward.

Plasma Renin Activity and Renin Concentration measured in patients during the open-label period

Change from baseline at endpoint for plasma renin activity during the open label period (intent-to-treat population)

		Monotherapy** (N=1060)			Comb** (N= 868)			Total (N=1928)		
Visit	**Statistics**	**Base**	**Post**	**Change**	**Base**	**Post**	**Change**	**Base**	**Post**	**Change**
Endpoint	n	138	138	138	159	159	159	297	297	297
	Mean	1.40	0.69	-0.71	1.56	0.29	-1.26	1.49	0.48	-1.01
	SD	1.71	1.71	2.33	5.00	0.39	4.89	3.83	1.22	3.92
	Median	0.80	0.20	-0.50	0.50	0.10	-0.30	0.60	0.20	-0.40
	Minimum	0.10	0.10	-12.50	0.10	0.10	-41.80	0.10	0.10	-41.80
	Maximum	12.60	15.90	15.40	42.00	3.30	1.20	42.00	15.90	15.40
	Geometric Mean	0.832	0.266	0.320	0.547	0.189	0.346	0.665	0.222	0.334
	Low 95% CI of Geo mean	0.701	0.219	0.256	0.453	0.166	0.287	0.583	0.198	0.289
	High 95% CI of Geo mean	0.988	0.323	0.399	0.661	0.216	0.417	0.758	0.249	0.385

* Change=Post - Base. Endpoint is the value at last visit of open label period or LOCF value.

At each time point, only patients with a value at both baseline and this time point are included.

** 'Monotherapy' is defined as patient who never took HCTZ during the open label period.

'Comb' is defined as patient who ever took HCTZ in open label period.

Plasma Renin Activity and Renin Concentration measured in patients during the open-label period (continued)

Change from baseline at endpoint for renin concentration during the open label period (intent-to-treat population)

		Monotherapy** (N=1060)			Comb** (N= 868)			Total (N=1928)		
Visit	**Statistics**	**Base**	**Post**	**Change**	**Base**	**Post**	**Change**	**Base**	**Post**	**Change**
Endpoint	n	100	100	100	131	131	131	231	231	231
	Mean	30.7	93.4	62.7	36.0	91.8	55.8	33.7	92.5	58.8
	SD	42.0	120.1	114.4	178.1	100.2	167.2	136.7	109.0	146.5
	Median	14.3	47.1	19.7	9.0	52.5	34.7	12.2	48.2	27.2
	Minimum	1.4	1.4	-143.6	1.4	1.4	-1507.0	1.4	1.4	-1507.0
	Maximum	206.3	684.2	682.9	1990.1	526.0	522.8	1990.1	684.2	682.9
	Geometric Mean	16.40	45.19	2.76	9.75	49.76	5.11	12.21	47.73	3.91
	Low 95% CI of Geo mean	13.21	34.98	2.13	7.85	40.31	4.07	10.43	40.56	3.28
	High 95% CI of Geo mean	20.36	58.38	3.56	12.11	61.44	6.41	14.30	56.17	4.65

* Change=Post - Base. Endpoint is the value at last visit of open label period or LOCF value.

At each time point, only patients with a value at both baseline and this time point are included.

** 'Monotherapy' is defined as patient who never took HCTZ during the open label period.

'Comb' is defined as patient who ever took HCTZ in open label period.

Efficacy results in the randomized withdrawal period

Mean sitting diastolic blood pressure in the randomized withdrawal period

Between treatment analysis results for changes in msDBP from Month 11 (Visit 10) to endpoint (month 12 or last visit carried forward) of the randomized withdrawal period (Randomized withdrawal ITT population)

Treatment Group	N	LSM change from baseline (SE)		
Placebo	128	3.78 (0.78)		
Aliskiren Monotherapy	131	-0.09 (0.79)		
Pairwise comparison		**LSM difference in change from baseline (SE)**	**95% CI for LSM difference**	**P-Value**
Aliskiren Monotherapy vs Placebo		-3.87 (0.88)	(-5.61,-2.13)	< .0001*

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

Between treatme nt analysis results for changes in msDBP from Month 11 (Visit 10) to Month 12 during the randomized withdrawal period (Randomized withdrawal ITT population)

Treatment Group	N	LSM change from baseline (SE)		
Placebo	123	3.67 (0.78)		
Aliskiren Monotherapy	125	-0.11 (0.79)		
Pairwise comparison		**LSM difference in change from baseline (SE)**	**95% CI for LSM difference**	**P-Value**
Aliskiren Monotherapy vs Placebo		-3.78 (0.89)	(-5.54,-2.03)	< .0001*

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

Mean sitting systolic blood pressure in the randomized withdrawal period

Between treatment analysis results for changes in msSBP from Month 11 (Visit 10) to randomized withdrawal endpoint (month 12 or last visit carried forward) (Randomized withdrawal ITT population)

Treatment Group	N	LSM change from baseline (SE)		
Placebo	128	4.82 (1.20)		
Aliskiren Monotherapy	131	-1.16 (1.22)		
Pairwise comparison		**LSM difference in change from baseline (SE)**	**95% CI for LSM difference**	**p-value**
Aliskiren Monotherapy vs Placebo		-5.99 (1.34)	(-8.63,-3.34)	< .0001*

Least squares mean, confidence intervals, and p-values were from an ANCOVA model containing treatment, region, strata as factors, msSBP at Month 11 (Visit 10) as a covariate.
[1] Nominal P-values and treatment comparisons were evaluated at the average msSBP at Month 11 (Visit 10).
* indicates statistical significance at 0.05 level.

Between treatment analysis results for changes in msSBP from Month 11 (Visit 10) to Month 12 of the randomizedwithdrawal period (Randomized withdrawal ITT population)

Treatment Group	N	LSM change from baseline (SE)		
Placebo	123	4.56 (1.19)		
Aliskiren Monotherapy	125	-0.96 (1.22)		
Pairwise comparison		**LSM difference in change from baseline (SE)**	**95% CI for LSM difference**	**p-value**
Aliskiren Monotherapy vs Placebo		-5.52 (1.35)	(-8.19,-2.85)	< .0001*

Least squares mean, confidence intervals, and p-values were from an ANCOVA model containing treatment, region, strata as factors, and msSBP at Month 11 (Visit 10) as a covariate.
[1] Nominal P-values and treatment comparisons were evaluated at the average msSBP at Month 11 (Visit 10).
* indicates statistical significance at 0.05 level.

Ambulatory BP measurements in the randomized withdrawal period

Mean change in 24-hour ambulatory DBP (mmHg) from Month 11 (Visit 10) to randomized withdrawal endpoint (month 12 or last visit carried forward) (Randomized withdrawal ITT population)

Treatment Group	N	LSM change from baseline (SE)		
All Placebo	73	2.88 (0.48)		
Aliskiren Monotherapy	72	-0.99 (0.50)		
Pairwise comparison		**LSM difference in change from baseline (SE)**	**95% CI for LSM difference**	**P-Value**
Aliskiren Monotherapy vs Placebo		-3.87 (0.59)	(-5.04,-2.70)	< .0001*

Mean change in 24-hour ambulatory SBP (mmHg) from Month 11 (Visit 10) to randomized withdrawal endpoint (month 12 or last visit carried forward) (Randomized withdrawal ITT population)

Treatment Group	N	LSM change from baseline (SE)		
All Placebo	73	3.06 (0.67)		
Aliskiren Monotherapy	72	-1.08 (0.69)		
Pairwise comparison		**LSM difference in change from baseline (SE)**	**95% CI for LSM difference**	**P-Value**
Aliskiren Monotherapy vs Placebo		-4.14 (0.82)	(-5.76,-2.52)	< .0001*

Safety Results

Adverse Events by System Organ Class During the Entire Study (Safety population)

Primary system organ class	Aliskiren 150 mg N=1174 n (%)	Aliskiren 300 mg N=1443 n (%)	Ali/HCTZ 300/12.5 mg N=843 n (%)	Ali/HCTZ 300/25 mg N=453 n (%)	Monotherapy* N=1085 n (%)	Combo* N=870 n (%)	Total N=1955 n (%)
Any primary system organ class	544 (46.3)	608 (42.1)	323 (38.3)	189 (41.7)	693 (63.9)	575 (66.1)	1268 (64.9)
Infections and infestations	204 (17.4)	246 (17.0)	126 (14.9)	67 (14.8)	317 (29.2)	268 (30.8)	585 (29.9)
Nervous system disorders	156 (13.3)	126 (8.7)	56 (6.6)	34 (7.5)	182 (16.8)	162 (18.6)	344 (17.6)
Musculoskeletal and connective tissue disorders	115 (9.8)	133 (9.2)	77 (9.1)	44 (9.7)	168 (15.5)	172 (19.8)	340 (17.4)
Gastrointestinal disorders	129 (11.0)	113 (7.8)	50 (5.9)	21 (4.6)	169 (15.6)	116 (13.3)	285 (14.6)
General dis orders and administration site conditions	63 (5.4)	67 (4.6)	32 (3.8)	13 (2.9)	93 (8.6)	71 (8.2)	164 (8.4)
Injury, poisoning and procedural complications	40 (3.4)	47 (3.3)	31 (3.7)	18 (4.0)	66 (6.1)	64 (7.4)	130 (6.6)
Respiratory, thoracic and mediastinal disorders	38 (3.2)	49 (3.4)	31 (3.7)	15 (3.3)	60 (5.5)	66 (7.6)	126 (6.4)
Skin and subcutaneous tissue disorders	45 (3.8)	36 (2.5)	22 (2.6)	10 (2.2)	56 (5.2)	51 (5.9)	107 (5.5)
Psychiatric disorders	35 (3.0)	35 (2.4)	16 (1.9)	8 (1.8)	43 (4.0)	47 (5.4)	90 (4.6)
Metabolism and nutrition disorders	21 (1.8)	27 (1.9)	20 (2.4)	17 (3.8)	35 (3.2)	47 (5.4)	82 (4.2)
Cardiac disorders	23 (2.0)	26 (1.8)	10 (1.2)	18 (4.0)	37 (3.4)	39 (4.5)	76 (3.9)
Ear and labyrinth disorders	22 (1.9)	18 (1.2)	13 (1.5)	11 (2.4)	30 (2.8)	32 (3.7)	62 (3.2)
Eye disorders	14 (1.2)	26 (1.8)	11 (1.3)	12 (2.6)	22 (2.0)	40 (4.6)	62 (3.2)
Vascular disorders	20 (1.7)	21 (1.5)	7 (0.8)	12 (2.6)	29 (2.7)	28 (3.2)	57 (2.9)
Reproductive system and breast disorders	21 (1.8)	18 (1.2)	9 (1.1)	7 (1.5)	31 (2.9)	24 (2.8)	55 (2.8)
Renal and urinary disorders	18 (1.5)	17 (1.2)	10 (1.2)	5 (1.1)	24 (2.2)	26 (3.0)	50 (2.6)
Investigations	12 (1.0)	15 (1.0)	7 (0.8)	5 (1.1)	21 (1.9)	18 (2.1)	39 (2.0)

*Monotherapy patients are those who never took HCTZ. Combo = combination therapy (patients who took HCTZ at least once).

10 Most Frequently Reported Adverse Events by Preferred Term During the Entire Study (Safety population)

Preferred term	Aliskiren 150 mg N=1174 n (%)	Aliskiren 300 mg N=1443 n (%)	Ali/HCTZ 300/12.5 mg N=843 n (%)	Ali/HCTZ 300/25 mg N=453 n (%)	Monotherapy* N=1085 n (%)	Combo* N=870 n (%)	Total N=1955 n (%)
Any primary system organ class	544 (46.3)	608 (42.1)	323 (38.3)	189 (41.7)	693 (63.9)	575 (66.1)	1268 (64.9)
Nasopharyngitis	56 (4.8)	80 (5.5)	38 (4.5)	13 (2.9)	92 (8.5)	85 (9.8)	177 (9.1)
Headache	89 (7.6)	67 (4.6)	13 (1.5)	8 (1.8)	91 (8.4)	77 (8.9)	168 (8.6)
Dizziness	41 (3.5)	34 (2.4)	22 (2.6)	11 (2.4)	57 (5.3)	49 (5.6)	106 (5.4)
Back pain	33 (2.8)	36 (2.5)	21 (2.5)	6 (1.3)	48 (4.4)	47 (5.4)	95 (4.9)
Bronchitis	24 (2.0)	40 (2.8)	13 (1.5)	15 (3.3)	51 (4.7)	36 (4.1)	87 (4.5)
Diarrhea	32 (2.7)	38 (2.6)	12 (1.4)	4 (0.9)	49 (4.5)	36 (4.1)	85 (4.3)
Influenza	23 (2.0)	28 (1.9)	16 (1.9)	10 (2.2)	37 (3.4)	38 (4.4)	75 (3.8)
Upper resp tract infection	14 (1.2)	27 (1.9)	13 (1.5)	2 (0.4)	28 (2.6)	27 (3.1)	55 (2.8)
Arthralgia	18 (1.5)	17 (1.2)	9 (1.1)	11 (2.4)	26 (2.4)	28 (3.2)	54 (2.8)
Fatigue	17 (1.4)	24 (1.7)	10 (1.2)	2 (0.4)	29 (2.7)	22 (2.5)	51 (2.6)
Cough	13 (1.1)	17 (1.2)	15 (1.8)	4 (0.9)	18 (1.7)	30 (3.4)	48 (2.5)

A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
*'Monotherapy' is defined as patient who never took HCTZ in the entire study (exclude placebo in the Randomized withdrawal period).
'Combo' is defined as patient who took HCTZ at least once during the entire study.

Serious Adverse Events and Deaths

Number (%) of patients who died or had other serious or significant adverse events during the open-label period (Open-label safety population)

	Aliskiren 150 mg N=1174 n (%)	Aliskiren 300 mg N=1443 n (%)	Ali/HCTZ 300/12.5 mg N=843 n (%)	Ali/HCTZ 300/25 mg N=453 n (%)	Total N=1955 n (%)
Death	1 (0.1)	3 (0.2)	0 (0.0)	1 (0.2)	5 (0.3)
SAEs	33 (2.8)	35 (2.4)	10 (1.2)	16 (3.5)	93 (4.8)
AE discontinuations	46 (3.9)	41 (2.8)	9 (1.1)	16 (3.5)	111 (5.7)
SAE discontinuations	10 (0.9)	13 (0.9)	1 (0.1)	7 (1.5)	31 (1.6)
Discontinuations for abnormal lab value(s)	7 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)	8 (0.4)

Note: 1 patient had SAEs on two different regimens, and appears in the Aliskiren 150 mg and Ali/HCTZ 300/25 mg columns. PID 63/00017 appears in the Aliskiren 150 and 300 mg columns for AE discontinuations.

Number (%) of patients who died or had other serious or significant adverse events during the randomized withdrawal period (Randomized withdrawal safety population)

	All Aliskiren N=132		All Placebo N=129	
	n	(%)	n	(%)
Death	0	(0.0)	0	(0.0)
SAEs	0	(0.0)	0	(0.0)
AE discontinuations	0	(0.0)	0	(0.0)
SAE discontinuations	0	(0.0)	0	(0.0)
Discontinuations for abnormal laboratory value(s)	0	(0.0)	0	(0.0)

Safety Results (Amendment #3, four month extension period)

Adverse events during high dose combination therapy Aliskiren + HCTZ 300/25 mg by primary system organ class (All extension population)

Primary system organ class	Aliskiren + HCTZ 300/25 mg N=198 n (%)
Any primary system organ class	97 (49.0)
Infections and infestations	40 (20.2)
Musculoskeletal and connective tissue disorders	33 (16.7)
Nervous system disorders	23 (11.6)
Injury, poisoning and procedural complications	14 (7.1)
Gastrointestinal disorders	14 (7.1)

Respiratory, thoracic and mediastinal disorders	8 (4.0)
Eye disorders	7 (3.5)
Cardiac disorders	7 (3.5)
Ear and labyrinth disorders	6 (3.0)
Renal and urinary disorders	5 (2.5)
Psychiatric disorders	4 (2.0)
Vascular disorders	4 (2.0)
Skin and subcutaneous tissue disorders	3 (1.5)
General disorders and administration site conditions	3 (1.5)
Reproductive system and breast disorders	2 (1.0)
Blood and lymphatic system disorders	1 (0.5)
Hepatobiliary disorders	1 (0.5)
Investigations	1 (0.5)

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

Number (%) of patients who died or had other serious or significant adverse events during the high dose combination therapy Aliskiren/HCTZ 300/25 mg (All extension population)

	Aliskiren + HCTZ 300/25 mg N=198
Event	**n (%)**
Deaths	0 (0.0)
SAEs	6 (3.0)
AE discontinuations	2 (1.0)
SAE discontinuations	0 (0.0)
Discontinuations for abnormal laboratory values	0 (0.0)

Other Relevant Findings

none

Date of Clinical Trial Report

21 December 2005

27 April 2006 (Amendment #3, four month extension period)

Date Inclusion on Novartis Clinical Trial Results Database

04 April 2007

Date of Latest Update

06 October 2006