Sponsor

Novartis

Generic Drug Name

Aliskiren

Trial Indication(s)

Essential hypertension

Protocol Number

CSPP100A2204

Protocol Title

An 8-week, double-blind, multicenter, randomized, multifactorial, placebo-controlled, parallel-group study to evaluate the efficacy and safety of aliskiren administered alone and in combination with hydrochlorothiazide in patients with essential hypertension

Clinical Trial Phase

Phase II

Study Start/End Dates

27-Aug-2004 to 27-Jun-2005

Reason for Termination

Not applicable.

Study Design/Methodology

A multicenter, randomized, double-blind, double-dummy, parallel-group, multifactorial study with placebo and active comparators in patients with hypertension. The study had three periods: Washout period (Visit 1), Single-blind, placebo run-in period (Visits 2, and optional Visit 201), and a double-blind, double-dummy treatment period (Visits 3-8), with dose titration (Visit 4) for patients assigned to receive aliskiren (150 or 300 mg) in combination with HCTZ 25 mg. Initially, these patients were supplied with the assigned aliskiren dose and HCTZ 12.5 mg for one week prior to receiving the assigned aliskiren dose with HCTZ 25 mg.

Centers

This study was performed in 19 countries: Argentina (9), Brazil (6), Canada (12), Colombia (2), Finland (11), France (16), Germany (29), Guatemala (4), Italy (23), Netherlands (12), Norway (5), Peru (8), Poland (3), Russia (11), Slovakia (5), Spain (11), Sweden (6), Taiwan (6), and United States (34)

Objectives:

Primary objective(s)

- confirm the efficacy of aliskiren 75 mg, 150 mg and 300 mg in patients with essential hypertension by testing the hypothesis of superior reduction in mean sitting diastolic blood pressure (msDBP) from Baseline to study end when compared to placebo, and
- demonstrate the efficacy of the combination of aliskiren and HCTZ 75/6.25 mg, 75/12.5 mg, 75/25 mg, 150/6.25 mg, 150/12.5 mg, 150/25 mg, 300/12.5 mg and 300/25 mg in patients with essential hypertension by testing the hypothesis of superior reduction in msDBP from Baseline to study end when compared to the component monotherapies.

Secondary objective(s)

- confirm the efficacy of aliskiren 75 mg, 150 mg and 300 mg in patients with essential hypertension by testing the hypothesis of superior reduction in mean sitting systolic blood pressure (msSBP) from Baseline to study end when compared to placebo;

- demonstrate the efficacy of the combination of aliskiren and HCTZ 75/6.25 mg, 75/12.5 mg, 75/25 mg, 150/6.25 mg, 150/12.5 mg, 150/25 mg, 300/12.5 mg and 300/25 mg in patients with essential hypertension by testing the hypothesis of superior reduction in msSBP from Baseline to study end when compared to the component monotherapies;
- demonstrate the antihypertensive dose response effect of aliskiren alone and in combination with HCTZ by testing the hypothesis that the magnitude of msDBP and msSBP reduction are related to the dose level of aliskiren and HCTZ administered in this study population;
- assess the proportion of patients achieving a successful response (msDBP < 90 mm Hg or a reduction ≥ 10 mm Hg from Baseline) for all treatment groups;
- explore the safety and tolerability of aliskiren 75 mg, 150 mg and 300 mg, given alone and in combination with HCTZ, in patients with essential hypertension; and
- explore the impact of treatment on plasma renin activity (PRA) and plasma renin concentration

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

Single-blind study treatment consisted of placebo. Double-blind study treatments were monotherapy (aliskiren or HCTZ, each at three different doses), combination therapy (aliskiren/HCTZ at eight different dose combinations), or placebo. Titration from HCTZ 12.5 to 25 mg was performed at Visit 4 for patients assigned to receive higher dose combination therapy (aliskiren 150 or 300 mg with HCTZ 25). Aliskiren monotherapy was compared to placebo, and combination therapy (aliskiren and HCTZ) were compared to their respective monotherapy doses.

Assigned study medication (1 tablet/capsule from each of three bottles) was taken once daily (o.d.) in the morning, except on the morning of study visits.

Statistical Methods

The primary efficacy variable was the change from Baseline in msDBP at Endpoint (intent-to-treat; ITT population). The primary analysis model for treatment comparisons was the two-way analysis-of-covariance model (ANCOVA) with treatment and region as factors and Baseline as a covariate for the ITT population.

For the comparison of monotherapy to placebo at an overall two-sided significance level at 5%, Dunnett's procedure was used to adjust for the multiple comparisons of the aliskiren doses versus placebo. This test was used for the assessment of the primary objective. If the primary test was statistically significant in favor of aliskiren, aliskiren treatment was considered superior to placebo. Pairwise comparisons with 95% confidence intervals between each of the aliskiren doses and placebo were also provided. No inference was to be made for the pairwise comparisons if the primary test was not statistically significant.

For the comparison of combination therapy to the respective monotherapies, a two-way ANCOVA model with 4-level aliskiren and 4-level HCTZ treatments as factors and Baseline as a covariate was used. The pattern of the interaction was further examined using least-squares means, and the add-on effects for a given combination dose due to the respective monotherapy doses was quantified. The change from Baseline at Endpoint in msDBP was further analyzed using a two-way ANCOVA model with treatment and region (randomization strata) as factors, and Baseline as a covariate.

The main secondary variable, change from Baseline in trough msSBP, was analyzed as described above.

Other secondary efficacy variables included the responder rate (msDBP < 90 mm Hg and/or at least 10 mm Hg reduction from Baseline in msDBP), percent of patients with controlled blood pressure (msDBP < 90 mm Hg and msSBP < 140 mm Hg), changes from Baseline at Endpoint in standing DBP and standing SBP. Except the primary analysis for combination, the same two-way analysis of covariance (ANCOVA) model was used for both aliskiren monotherapy and combination analyses.

A first-order response surface analysis with the aliskiren and HCTZ doses as predictor variables was performed using the change from Baseline at Endpoint in msDBP to examine the relationship between the blood pressure lowering effect and the dose. The test for lack of fit was performed at a significance level of 0.1 for the first order model. If the first order lack of fit was statistically significant, then a second-order dose-response surface was considered.

Frequency distributions of safety parameters were summarized for the safety population. Laboratory data were summarized at Baseline and Endpoint of the double-blind period for absolute values and changes from Baseline. Incidence counts of patients with pre-specified notable laboratory abnormalities were also provided.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

- Patients with essential hypertension
- Patients who are eligible and able to participate in the study

Exclusion Criteria:

- Severe hypertension
- History or evidence of a secondary form of hypertension
- History of hypertensive encephalopathy or cerebrovascular accident

Participant Flow Table

Patient disposition for each treatment group during the double-blind period (all enrolled patients)

Monotherapy - n (%)	Placebo	ALI75	ALI150	ALI300	HCTZ6.25	HCTZ12.5	HCTZ25	
Randomized*	195	184	185	183	194	188	176	
Completed†	171 (87.7)	169 (91.8)	169 (91.4)	164 (89.6)	181 (93.3)	178 (94.7)	159 (90.3)	
Discontinued†	22 (11.3)	15 (8.2)	16 (8.6)	17 (9.3)	13 (6.7)	10 (5.3)	14 (8.0)	
Adverse event(s)	7 (3.6)	1 (0.5)	0 (0.0)	8 (4.4)	2 (1.0)	1 (0.5)	5 (2.8)	
Abnormal lab value(s)	1 (0.5)	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Abnormal test/procedure result(s)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Unsatisfactory therapeutic effect	8 (4.1)	7 (3.8)	5 (2.7)	4 (2.2)	7 (3.6)	4 (2.1)	1 (0.6)	
Protocol violation	1 (0.5)	1 (0.5)	1 (0.5)	1 (0.5)	0 (0.0)	1 (0.5)	1 (0.6)	
Subject withdrew consent	3 (1.5)	4 (2.2)	5 (2.7)	1 (0.5)	4 (2.1)	4 (2.1)	5 (2.8)	
Lost to follow-up	1 (0.5)	1 (0.5)	3 (1.6)	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.6)	
Administrative problems	1 (0.5)	0 (0.0)	0 (0.0)	2 (1.1)	0 (0.0)	0 (0.0)	1 (0.6)	

† The 14 patients randomized in error were not treated and did not provide any post-Baseline double-blind study data. Therefore, these patients were not included in the other analysis populations.

Combination therapy - n (%)	ALI75 / HCTZ6.25	ALI75 / HCTZ12.5	ALI75 / HCTZ25	ALI150 / HCTZ6.25	ALI150 / HCTZ12.5	ALI150 / HCTZ25	ALI300 / HCTZ12.5	ALI300 / HCTZ25	Total
Randomized*	188	193	186	176	186	188	181	173	2776
Completed†	179 (95.2)	175 (90.7)	173 (93.0)	157 (89.2)	177 (95.2)	170 (90.4)	170 (93.9)	166 (96.0)	2558 (92.1)
Discontinued†	9 (4.8)	15 (7.8)	13 (7.0)	17 (9.7)	7 (3.8)	18 (9.6)	11 (6.1)	7 (4.0)	204 (7.3)
Adverse event(s)	3 (1.6)	7 (3.6)	4 (2.2)	7 (4.0)	4 (2.2)	6 (3.2)	3 (1.7)	5 (2.9)	63 (2.3)
Abnormal lab value(s)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	4 (0.1)
Abnormal test/procedure result(s)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.1)
Unsatisfactory therapeutic effect	2 (1.1)	4 (2.1)	4 (2.2)	5 (2.8)	0 (0.0)	1 (0.5)	2 (1.1)	2 (1.2)	56 (2.0)
Cond. no longer requires therapy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.0)
Protocol violation	1 (0.5)	0 (0.0)	3 (1.6)	0 (0.0)	1 (0.5)	1 (0.5)	1 (0.6)	0 (0.0)	13 (0.5)
Subject withdrew consent	2 (1.1)	3 (1.6)	1 (0.5)	2 (1.1)	2 (1.1)	4 (2.1)	2 (1.1)	0 (0.0)	42 (1.5)
Lost to follow-up	1 (0.5)	1 (0.5)	0 (0.0)	2 (1.1)	0 (0.0)	3 (1.6)	2 (1.1)	0 (0.0)	16 (0.6)
Administrative problems	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	5 (0.2)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.0)

† The 14 patients randomized in error were not treated and did not provide any post-Baseline double-blind study data. Therefore, these patients were not included in the other analysis populations.

Baseline Characteristics

Patient background characteristics by treatment group (all randomized patients)

	Monotherapy	Placebo N = 195	ALI75 N = 184	ALI150 N = 185	ALI300 N = 183	HCTZ6.25 N = 194	HCTZ12.5 N = 188	HCTZ25 N = 176
Sex–n (%)	Male	109 (55.9)	103 (56.0)	112 (60.5)	99 (54.1)	109 (56.2)	103 (54.8)	92 (52.3)
	Female	86 (44.1)	81 (44.0)	73 (39.5)	84 (45.9)	85 (43.8)	85 (45.2)	84 (47.7)
Age (years)	n	195	184	185	183	194	188	176
	Mean (SD)	54.4 (11.80)	55.0 (11.81)	53.5 (12.34)	54.2 (12.19)	55.2 (12.77)	55.4 (11.99)	55.1 (11.98)
Age group –n (%)	< 65	157 (80.5)	138 (75.0)	150 (81.1)	144 (78.7)	140 (72.2)	138 (73.4)	139 (79.0)
	≥ 65	38 (19.5)	46 (25.0)	35 (18.9)	39 (21.3)	54 (27.8)	50 (26.6)	37 (21.0)
	≥ 75	10 (5.1)	5 (2.7)	8 (4.3)	10 (5.5)	9 (4.6)	7 (3.7)	6 (3.4)
Hypertension duration (years)	n	187	178	178	177	187	183	170
	Mean (SD)	7.1 (7.24)	7.9 (7.37)	7.3 (7.36)	7.7 (7.23)	7.4 (7.23)	7.9 (8.20)	8.4 (8.58)
Treatment-naive [†] –n (%)		8 (4.1)	6 (3.3)	7 (3.8)	6 (3.3)	7 (3.6)	5 (2.7)	6 (3.4)

	Combination therapy	ALI75 / HCTZ6.25 N = 188	ALI75 / HCTZ12.5 N = 193	ALI75 / HCTZ25 N = 186	ALI150 / HCTZ6.25 N = 176	ALI150 / HCTZ12.5 N = 186	ALI150 / HCTZ25 N = 188	ALI300 / HCTZ12.5 N = 181	ALI300 / HCTZ25 N = 173	Total N =2776
Sex–n (%)	Male	108 (57.4)	101 (52.3)	101 (54.3)	96 (54.5)	98 (52.7)	104 (55.3)	89 (49.2)	98 (56.6)	1522 (54.8)
	Female	80 (42.6)	92 (47.7)	85 (45.7)	80 (45.5)	88 (47.3)	84 (44.7)	92 (50.8)	75 (43.4)	1254 (45.2)
Age (years)	n	188	193	186	176	186	188	181	173	2776
	Mean (SD)	55.1 (10.63)	54.4 (10.11)	54.7 (12.17)	53.9 (11.12)	54.7 (11.35)	53.7 (11.58)	55.5 (11.67)	54.8 (10.86)	54.6 (11.63)
Age group –n (%)	< 65	153 (81.4)	166 (86.0)	147 (79.0)	148 (84.1)	148 (79.6)	151 (80.3)	133 (73.5)	138 (79.8)	2190 (78.9)
	≥ 65	35 (18.6)	27 (14.0)	39 (21.0)	28 (15.9)	38 (20.4)	37 (19.7)	48 (26.5)	35 (20.2)	586 (21.1)
	≥ 75	6 (3.2)	3 (1.6)	9 (4.8)	5 (2.8)	6 (3.2)	7 (3.7)	6 (3.3)	2 (1.2)	99 (3.6)
Hypertension duration (years)	n	182	192	183	171	181	185	174	167	2695
	Mean (SD)	6.5 (5.84)	7.8 (8.19)	8.3 (7.43)	7.0 (6.55)	7.8 (7.59)	7.4 (7.10)	7.9 (7.76)	8.4 (7.37)	7.6 (7.43)
Treatment-naive [†] –n (%)		6 (3.2)	1 (0.5)	3 (1.6)	5 (2.8)	5 (2.7)	3 (1.6)	7 (3.9)	6 (3.5)	81 (2.9)

[†] Treatment naïve patients - Newly diagnosed with uncomplicated hypertension and who are not taking any antihypertensive medication(s) at the time of enrollment.
SD=standard deviation

	Monotherapy	Placebo N = 195	ALI75 N = 184	ALI150 N = 185	ALI300 N = 183	HCTZ6.25 N = 194	HCTZ12.5 N = 188	HCTZ25 N = 176
Race–n (%)	Caucasian	164 (84.1)	153 (83.2)	157 (84.9)	155 (84.7)	161 (83.0)	160 (85.1)	155 (88.1)
	Black	7 (3.6)	9 (4.9)	11 (5.9)	7 (3.8)	13 (6.7)	9 (4.8)	9 (5.1)
	Asian	5 (2.6)	6 (3.3)	4 (2.2)	3 (1.6)	5 (2.6)	3 (1.6)	4 (2.3)
	Nat. American	3 (1.5)	4 (2.2)	3 (1.6)	5 (2.7)	6 (3.1)	4 (2.1)	2 (1.1)
	Pacific Islander	0 (0.0)	1 (0.5)	1 (0.5)	0 (0.0)	1 (0.5)	1 (0.5)	0 (0.0)
	Other	16 (8.2)	11 (6.0)	9 (4.9)	13 (7.1)	8 (4.1)	11 (5.9)	6 (3.4)
Ethnicity–n (%)	Hispanic/Latin	55 (28.2)	47 (25.5)	55 (29.7)	55 (30.1)	54 (27.8)	50 (26.6)	45 (25.6)
	Chinese	5 (2.6)	5 (2.7)	4 (2.2)	3 (1.6)	2 (1.0)	3 (1.6)	3 (1.7)
	Indian-subcon.	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
	Japanese	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
	Other	135 (69.2)	131 (71.2)	126 (68.1)	125 (68.3)	136 (70.1)	135 (71.8)	128 (72.7)

	Combination therapy	ALI75 / HCTZ6.25 N = 188	ALI75 / HCTZ12.5 N = 193	ALI75 / HCTZ25 N = 186	ALI150 / HCTZ6.25 N = 176	ALI150 / HCTZ12.5 N = 186	ALI150 / HCTZ25 N = 188	ALI300 / HCTZ12.5 N = 181	ALI300 / HCTZ25 N = 173	Total N =2776
Race–n (%)	Caucasian	165 (87.8)	165 (85.5)	165 (88.7)	149 (84.7)	158 (84.9)	163 (86.7)	153 (84.5)	149 (86.1)	2372 (85.4)
	Black	5 (2.7)	12 (6.2)	5 (2.7)	8 (4.5)	10 (5.4)	5 (2.7)	10 (5.5)	7 (4.0)	127 (4.6)
	Asian	7 (3.7)	4 (2.1)	4 (2.2)	5 (2.8)	5 (2.7)	4 (2.1)	5 (2.8)	5 (2.9)	69 (2.5)
	Nat. American	3 (1.6)	3 (1.6)	3 (1.6)	4 (2.3)	3 (1.6)	3 (1.6)	3 (1.7)	1 (0.6)	50 (1.8)
	Pacific Islander	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	7 (0.3)
	Other	7 (3.7)	8 (4.1)	9 (4.8)	10 (5.7)	10 (5.4)	12 (6.4)	10 (5.5)	11 (6.4)	151 (5.4)
Ethnicity–n (%)	Hispanic/Latin	46 (24.5)	45 (23.3)	53 (28.5)	55 (31.3)	52 (28.0)	50 (26.6)	50 (27.6)	49 (28.3)	761 (27.4)
	Chinese	4 (2.1)	4 (2.1)	4 (2.2)	4 (2.3)	4 (2.2)	4 (2.1)	4 (2.2)	3 (1.7)	56 (2.0)
	Indian-subcon.	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	3 (0.1)
	Japanese	2 (1.1)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	5 (0.2)
	Other	136 (72.3)	144 (74.6)	129 (69.4)	116 (65.9)	130 (69.9)	134 (71.3)	127 (70.2)	119 (68.8)	1951 (70.3)

	Monotherapy	Placebo N = 195	ALI75 N = 184	ALI150 N = 185	ALI300 N = 183	HCTZ6.25 N = 194	HCTZ12.5 N = 188	HCTZ25 N = 176
BMI (kg/m^2)	n	195	182	184	182	192	187	173
	Mean (SD)	29.6 (5.81)	29.7 (5.06)	29.0 (4.97)	29.9 (6.46)	30.0 (5.93)	29.3 (5.42)	28.9 (5.05)

BMI –n (%)	≥ 30 kg/m^2	79 (40.5)	77 (41.8)	60 (32.4)	71 (38.8)	80 (41.2)	73 (38.8)	57 (32.4)	
	< 30 kg/m^2	116 (59.5)	105 (57.1)	124 (67.0)	111 (60.7)	112 (57.7)	114 (60.6)	116 (65.9)	
Metabolic Synd ‡ –n (%)	Yes	75 (38.5)	62 (33.7)	65 (35.1)	65 (35.5)	64 (33.0)	72 (38.3)	62 (35.2)	
	No	120 (61.5)	122 (66.3)	120 (64.9)	118 (64.5)	130 (67.0)	116 (61.7)	114 (64.8)	
Diabetes* –n (%)	Yes	16 (8.2)	16 (8.7)	12 (6.5)	13 (7.1)	19 (9.8)	9 (4.8)	14 (8.0)	
	No	179 (91.8)	168 (91.3)	173 (93.5)	170 (92.9)	175 (90.2)	179 (95.2)	162 (92.0)	

Combination therapy		**ALI75 / HCTZ6.25 N = 188**	**ALI75 / HCTZ12.5 N = 193**	**ALI75 / HCTZ25 N = 186**	**ALI150 / HCTZ6.25 N = 176**	**ALI150 / HCTZ12.5 N = 186**	**ALI150 / HCTZ25 N = 188**	**ALI300 / HCTZ12.5 N = 181**	**ALI300 / HCTZ25 N = 173**	**Total N =2776**
BMI (kg/m^2)	n	187	191	186	174	184	188	180	171	2756
	Mean (SD)	29.1 (4.85)	29.5 (5.63)	29.6 (5.70)	29.5 (5.14)	29.2 (5.59)	29.3 (5.44)	29.7 (5.48)	29.8 (5.66)	29.5 (5.49)
BMI –n (%)	≥ 30 kg/m^2	71 (37.8)	77 (39.9)	72 (38.7)	66 (37.5)	66 (35.5)	71 (37.8)	76 (42.0)	71 (41.0)	1067 (38.4)
	< 30 kg/m^2	116 (61.7)	114 (59.1)	114 (61.3)	108 (61.4)	118 (63.4)	117 (62.2)	104 (57.5)	100 (57.8)	1689 (60.8)
Metabolic Synd ‡ –n (%)	Yes	74 (39.4)	64 (33.2)	70 (37.6)	56 (31.8)	63 (33.9)	72 (38.3)	63 (34.8)	61 (35.3)	988 (35.6)
	No	114 (60.6)	129 (66.8)	116 (62.4)	120 (68.2)	123 (66.1)	116 (61.7)	118 (65.2)	112 (64.7)	1788 (64.4)
Diabetes * –n (%)	Yes	14 (7.4)	18 (9.3)	13 (7.0)	14 (8.0)	10 (5.4)	14 (7.4)	11 (6.1)	18 (10.4)	211 (7.6)
	No	174 (92.6)	175 (90.7)	173 (93.0)	162 (92.0)	176 (94.6)	174 (92.6)	170 (93.9)	155 (89.6)	2565 (92.4)

‡ Metabolic Syndrome - Any 3 of the following: 1. Waist circumference (cm) > 102 (males) or > 88 (females); 2. Triglycerides (mmol/L) ≥ 1.69; 3. HDL cholesterol (mmol/L) < 1.04 (males) or < 1.29; 4. Blood pressure (mm Hg) ≥ 130 / ≥ 85; 5. Fasting glucose (mmol/L) ≥ 6.1

* From medical history.

SD=standard deviation BMI=Body mass index

Summary of Efficacy

Primary Outcome Result(s)

Statistical analysis of change from Baseline in mean sitting diastolic blood pressure (mm Hg) at Endpoint (ITT population)

Monotherapy	N	LSM change from Baseline (SE)	Combination therapy	N	LSM change from Baseline (SE)
Aliskiren 75 mg	183	-8.68 (0.59)	Aliskiren 75 mg/HCTZ 6.25 mg	187	-10.76 (0.59)
Aliskiren 150 mg	183	-8.94 (0.59)	Aliskiren 75 mg/HCTZ 12.5 mg	189	-11.14 (0.59)
Aliskiren 300 mg	180	-10.26 (0.60)	Aliskiren 75 mg/HCTZ 25 mg	186	-11.46 (0.59)
HCTZ 6.25 mg	194	-9.07 (0.58)	Aliskiren 150 mg/HCTZ 6.25 mg	173	-10.36 (0.61)
HCTZ 12.5 mg	188	-10.11 (0.59)	Aliskiren 150 mg/HCTZ 12.5 mg	184	-11.90 (0.59)
HCTZ 25 mg	173	-9.37 (0.61)	Aliskiren 150 mg/HCTZ 25 mg	187	-12.65 (0.59)
Placebo	192	-6.93 (0.58)	Aliskiren 300 mg/HCTZ 12.5 mg	180	-13.87 (0.60)
			Aliskiren 300 mg/HCTZ 25 mg	173	-14.26 (0.61)

	Pairwise Comparison		LSM difference		
			Change from Baseline (SE)	95% CI	Nominal p-value
	Aliskiren 75 mg	vs. placebo	-1.75 (0.83)	(-3.37, -0.13)	0.0344*
	Aliskiren 150 mg	vs. placebo	-2.01 (0.83)	(-3.63, -0.39)	0.0152*
	Aliskiren 300 mg	vs. placebo	-3.33 (0.83)	(-4.95, -1.70)	< 0.0001*
	Aliskiren 75 mg/HCTZ 6.25 mg	vs. aliskiren 75 mg	-2.08 (0.83)	(-3.71, -0.45)	0.0126*
		vs. HCTZ 6.25 mg	-1.69 (0.82)	(-3.30, -0.08)	0.0394*
		vs. placebo	-3.83 (0.82)	(-5.44, -2.22)	< 0.0001*
	Aliskiren 75 mg/HCTZ 12.5 mg	vs. aliskiren 75 mg	-2.46 (0.83)	(-4.09, -0.83)	0.0031*
		vs. HCTZ 12.5 mg	-1.03 (0.83)	(-2.65, 0.59)	0.2124
		vs. placebo	-4.21 (0.82)	(-5.82, -2.60)	< 0.0001*
	Aliskiren 75 mg/HCTZ 25 mg	vs. aliskiren 75 mg	-2.77 (0.83)	(-4.41, -1.14)	0.0009*
		vs. HCTZ 25 mg	-2.09 (0.85)	(-3.75, -0.43)	0.0136*
		vs. placebo	-4.52 (0.82)	(-6.14, -2.91)	< 0.0001*
	Aliskiren 150 mg/HCTZ 6.25 mg	vs. aliskiren 150 mg	-1.41 (0.85)	(-3.08, 0.25)	0.0962
		vs. HCTZ 6.25 mg	-1.29 (0.84)	(-2.93, 0.36)	0.1249
		vs. placebo	-3.42 (0.84)	(-5.07, -1.78)	< 0.0001*
	Aliskiren 150 mg/HCTZ 12.5 mg	vs. aliskiren 150 mg	-2.96 (0.84)	(-4.60, -1.32)	0.0004*
		vs. HCTZ 12.5 mg	1.79 (0.83)	(-3.42, -0.16)	0.0314*
		vs. placebo	-4.97 (0.83)	(-6.59, -3.35)	< 0.0001*
	Aliskiren 150 mg/HCTZ 25 mg	vs. aliskiren 150 mg	-3.70 (0.83)	(-5.33, -2.07)	< 0.0001*
		vs. HCTZ 25 mg	-3.28 (0.85)	(-4.94, -1.62)	0.0001*

Monotherapy	N	LSM change from Baseline (SE)	Combination therapy	N	LSM change from Baseline (SE)	
		vs. placebo	-5.71 (0.82)	(-7.33, -4.10)		< 0.0001*
	Aliskiren 300 mg/HCTZ 12.5 mg	vs. aliskiren 300 mg	-3.61 (0.84)	(-5.26, -1.95)		< 0.0001*
		vs. HCTZ 12.5 mg	-3.76 (0.84)	(-5.39, -2.12)		< 0.0001*
		vs. placebo	-6.93 (0.83)	(-8.56, -5.31)		< 0.0001*
	Aliskiren 300 mg/HCTZ 25 mg	vs. aliskiren 300 mg	-4.00 (0.85)	(-5.68, -2.33)		< 0.0001*
		vs. HCTZ 25 mg	-4.90 (0.86)	(-6.59, -3.21)		< 0.0001*
		vs. placebo	-7.33 (0.84)	(-8.98, -5.68)		< 0.0001*

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

* indicates statistical significance at the 0.05 level.

Dunnett's procedure between aliskiren monotherapy and placebo: statistical significance between placebo and at least one aliskiren treatment; smallest Dunnett's adjusted p-value was 0.0002.

Secondary Outcome Result(s)

Statistical analysis of mean change from Baseline in mean sitting systolic blood pressure (mm Hg) at Endpoint (ITT population)

Monotherapy	N	LSM change from Baseline (SE)	Combination therapy	N	LSM change from Baseline (SE)
Aliskiren 75 mg	183	-9.37 (0.94)	Aliskiren 75 mg/HCTZ 6.25 mg	187	-14.29 (0.93)
Aliskiren 150 mg	183	-12.24 (0.94)	Aliskiren 75 mg/HCTZ 12.5 mg	189	-15.64 (0.93)
Aliskiren 300 mg	180	-15.74 (0.95)	Aliskiren 75 mg/HCTZ 25 mg	186	17.32 (0.93)
HCTZ 6.25 mg	194	-10.95 (0.92)	Aliskiren 150 mg/HCTZ 6.25 mg	173	-15.31 (0.97)
HCTZ 12.5 mg	188	-13.92 (0.93)	Aliskiren 150 mg/HCTZ 12.5 mg	184	-17.61 (0.94)
HCTZ 25 mg	173	-14.30 (0.97)	Aliskiren 150 mg/HCTZ 25 mg	187	-19.47 (0.93)
Placebo	192	-7.48 (0.92)	Aliskiren 300 mg/HCTZ 12.5 mg	180	-19.82 (0.95)
			Aliskiren 300 mg/HCTZ 25 mg	173	-21.22 (0.97)

Pairwise Comparison		LSM difference		
		Change from Baseline (SE)	95% CI	Nominal p-value
Aliskiren 75 mg	vs. placebo	-1.89 (1.31)	(-4.46, 0.69)	0.1512
Aliskiren 150 mg	vs. placebo	-4.76 (1.31)	(-7.34, -2.18)	0.0003*
Aliskiren 300 mg	vs. placebo	-8.25 (1.32)	(-10.84, -5.67)	< 0.0001*
Aliskiren 75 mg/HCTZ 6.25 mg	vs. aliskiren 75 mg	-4.93 (1.32)	(-7.52, -2.33)	0.0002*
	vs. HCTZ 6.25 mg	-3.34 (1.30)	(-5.90, -0.79)	0.0103*
	vs. placebo	-6.81 (1.31)	(-9.38, -4.25)	< 0.0001*
Aliskiren 75 mg/HCTZ 12.5 mg	vs. aliskiren 75 mg	-6.27 (1.32)	(-8.86, -3.69)	< 0.0001*
	vs. HCTZ 12.5 mg	-1.71 (1.31)	(-4.28, 0.85)	0.1905
	vs. placebo	-8.16 (1.30)	(-10.71, -5.60)	< 0.0001*
Aliskiren 75 mg/HCTZ 25 mg	vs. aliskiren 75 mg	-7.95 (1.32)	(-10.55, -5.36)	< 0.0001*
	vs. HCTZ 25 mg	-3.02 (1.34)	(-5.66, -0.39)	0.0246*
	vs. placebo	-9.84 (1.31)	(-12.40, -7.27)	< 0.0001*
Aliskiren 150 mg/HCTZ 6.25 mg	vs. aliskiren 150 mg	-3.07 (1.35)	(-5.71, -0.42)	0.0230*
	vs. HCTZ 6.25 mg	-4.36 (1.33)	(-6.97, -1.75)	0.0011*
	vs. placebo	-7.83 (1.33)	(-10.44, -5.21)	< 0.0001*
Aliskiren 150 mg/HCTZ 12.5 mg	vs. aliskiren 150 mg	-5.37 (1.33)	(-7.97, -2.77)	< 0.0001*
	vs. HCTZ 12.5 mg	-3.69 (1.32)	(-6.27, -1.10)	0.0052*
	vs. placebo	-10.13 (1.31)	(-12.70, -7.56)	< 0.0001*
Aliskiren 150 mg/HCTZ 25 mg	vs. aliskiren 150 mg	-7.23 (1.32)	(-9.82, -4.64)	< 0.0001*
	vs. HCTZ 25 mg	-5.17 (1.34)	(-7.81, -2.54)	0.0001*

Monotherapy	N	LSM change from Baseline (SE)	Combination therapy	N	LSM change from Baseline (SE)	
		vs. placebo	-11.99 (1.31)	(-14.55, -9.43)	< 0.0001*	
Aliskiren 300 mg/HCTZ 12.5 mg		vs. aliskiren 300 mg	-4.08 (1.34)	(-6.71, -1.45)	0.0024*	
		vs. HCTZ 12.5 mg	-5.89 (1.33)	(-8.49, -3.29)	< 0.0001*	
		vs. placebo	-12.33 (1.32)	(-14.92, -9.75)	< 0.0001*	
Aliskiren 300 mg/HCTZ 25 mg		vs. aliskiren 300 mg	-5.48 (1.35)	(-8.14, -2.83)	< 0.0001*	
		vs. HCTZ 25 mg	-6.92 (1.37)	(-9.60, -4.24)	< 0.0001*	
		vs. placebo	-13.74 (1.33)	(-16.35, -11.1)	< 0.0001*	

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

* indicates statistical significance at the 0.05 level.

Dunnett's procedure between aliskiren monotherapy and placebo: statistical significance between placebo and at least one aliskiren treatment; the smallest Dunnett's adjusted p-value was < 0.0001.

Number (%) of responders in mean sitting diastolic blood pressure (mm Hg) at Endpoint by treatment group (ITT population)

Pairwise Comparison		Treatment A		Treatment B		p-value
A	vs. B	n/N	(%)	n/N	(%)	
Aliskiren 75 mg	vs. placebo	95/183	51.9	88/192	45.8	0.2181
Aliskiren 150 mg	vs. placebo	95/183	51.9	88/192	45.8	0.3728
Aliskiren 300 mg	vs. placebo	115/180	63.9	88/192	45.8	0.0005*
Aliskiren 75 mg/HCTZ 6.25 mg	vs. aliskiren 75 mg	115/187	61.5	95/183	51.9	0.0902
	vs. HCTZ 6.25 mg			104/194	53.6	0.1459
	vs. placebo			88/192	45.8	0.0033*
Aliskiren 75 mg/HCTZ 12.5 mg	vs. aliskiren 75 mg	120/189	63.5	95/183	51.9	0.0118*
	vs. HCTZ 12.5 mg			114/188	60.6	0.3660
	vs. placebo			88/192	45.8	0.0002*
Aliskiren 75 mg/HCTZ 25 mg	vs. aliskiren 75 mg	131/186	70.4	95/183	51.9	0.0005*
	vs. HCTZ 25 mg			102/173	59.0	0.0284*
	vs. placebo			88/192	45.8	< 0.0001*
Aliskiren 150 mg/HCTZ 6.25 mg	vs. aliskiren 150 mg	101/173	58.4	95/183	51.9	0.1566
	vs. HCTZ 6.25 mg			104/194	53.6	0.4013
	vs. placebo			88/192	45.8	0.0214*
Aliskiren 150 mg/HCTZ 12.5 mg	vs. aliskiren 150 mg	128/184	69.6	95/183	51.9	0.0002*
	vs. HCTZ 12.5 mg			114/188	60.6	0.0690
	vs. placebo			88/192	45.8	< 0.0001*
Aliskiren 150 mg/HCTZ 25 mg	vs. aliskiren 150 mg	133/187	71.1	95/183	51.9	0.0002*
	vs. HCTZ 25 mg			102/173	59.0	0.0302*
	vs. placebo			88/192	45.8	< 0.0001*
Aliskiren 300 mg/HCTZ 12.5 mg	vs. aliskiren 300 mg	145/180	80.6	115/180	63.9	0.0002*
	vs. HCTZ 12.5 mg			114/188	60.6	< 0.0001*
	vs. placebo			88/192	45.8	< 0.0001*
Aliskiren 300 mg/HCTZ 25 mg	vs. aliskiren 300 mg	133/173	76.9	115/180	63.9	0.0058*
	vs. HCTZ 25 mg			102/173	59.0	0.0003*
	vs. placebo			88/192	45.8	< 0.0001*

Responder: a patient with trough msDBP < 90 mm Hg and/or ≥ 10 mm Hg reduction from Baseline (Week 0).
p-values were from a logistic regression model with treatment and region as factors and Baseline as a covariate.
N = Number of patients with Baseline and Endpoint msDBP values.
* indicates statistical significance at 0.05 level.

Response surface analysis for change from Baseline in mean sitting diastolic blood pressure (mm Hg) at Endpoint (ITT population)

Treatment Group	N	Predicted Mean	Raw Mean
Placebo	192	-7.37	-7.00
Aliskiren 75 mg	183	-8.43	-8.78
Aliskiren 150 mg	183	-9.27	-9.13
Aliskiren 300 mg	180	-10.31	-10.42
HCTZ 6.25 mg	194	-9.04	-9.18
HCTZ 12.5 mg	188	-10.01	-10.17
HCTZ 25 mg	173	-9.81	-9.42
Aliskiren 75 mg/HCTZ 6.25 mg	187	-10.21	-10.84
Aliskiren 75 mg/HCTZ 12.5 mg	189	-11.28	-11.19
Aliskiren 75 mg/HCTZ 25 mg	186	-11.30	-11.60
Aliskiren 150 mg/HCTZ 6.25 mg	173	-11.15	-10.52
Aliskiren 150 mg/HCTZ 12.5 mg	184	-12.33	-11.96
Aliskiren 150 mg/HCTZ 25 mg	187	-12.57	-12.77
Aliskiren 300 mg/HCTZ 6.25 mg	0	-12.40	n.a.
Aliskiren 300 mg/HCTZ 12.5 mg	180	-13.80	-13.95
Aliskiren 300 mg/HCTZ 25 mg	173	-14.46	-14.34

n.a. not applicable

Note: The dose response surface was fitted in second-order [change from Baseline in msDBP] = -7.373734712 + -0.015505586 [aliskiren dose] + 0.0000191134*[aliskiren dose]^2 + -0323519696* [HCTZ dose] + -0.000229186*[Aliskiren dose * HCTZ dose] + 0.0090363501*[HCTZ dose]^2.

Summary of Safety

Safety Results

Incidence of deaths, serious adverse events, and adverse events and abnormal laboratory values leading to permanent treatment discontinuations during double-blind period (Safety population) (safety population)

Monotherapy - n (%)	Placebo N = 193	ALI75 N = 184	ALI150 N = 185	ALI300 N = 181	HCTZ6.25 N = 194	HCTZ12.5 N = 188	HCTZ25 N = 173
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Serious adverse events	0 (0.0)	1 (0.5)	1 (0.5)	1 (0.6)	1 (0.5)	3 (1.6)	2 (1.2)
Adverse event discontinuations	7 (3.6)	1 (0.5)	0 (0.0)	8 (4.4)	2 (1.0)	1 (0.5)	5 (2.9)
Serious adverse event discontinuations	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Discontinuations for abnormal lab values	1 (0.5)	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Combination therapy - n (%)	ALI75 / HCTZ6.25 N = 188	ALI75 / HCTZ12.5 N = 190	ALI75 / HCTZ25 N = 186	ALI150 / HCTZ6.25 N = 174	ALI150 / HCTZ12.5 N = 184	ALI150 / HCTZ25 N = 188	ALI300 / HCTZ12.5 N = 181	ALI300 / HCTZ25 N = 173	Total N =2762
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.0)
Serious adverse events	0 (0.0)	5 (2.6)	4 (2.2)	2 (1.1)	3 (1.6)	2 (1.1)	2 (1.1)	1 (0.6)	28 (1.0)
Adverse event discontinuations	3 (1.6)	7 (3.7)	4 (2.2)	7 (4.0)	4 (2.2)	7 (3.7)	3 (1.7)	5 (2.9)	64 (2.3)
Serious adverse event discontinuations	0 (0.0)	2 (1.1)	2 (1.1)	1 (0.6)	2 (1.1)	1 (0.5)	0 (0.0)	1 (0.6)	9 (0.3)
Discontinuations for abnormal lab values	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	4 (0.1)

Incidence of SAEs during double-blind period by treatment group and preferred term (safety population)

Monotherapy - n (%) Preferred term	Placebo N= 193	ALI75 N= 184	ALI150 N= 185	ALI300 N= 181	HCTZ6.25 N= 194	HCTZ12.5 N= 188	HCTZ25 N= 173
Serious Adverse Events	0 (0.0)	**1 (0.5)**	**1 (0.5)**	**1 (0.6)**	**1 (0.5)**	**3 (1.6)**	**2 (1.2)**
Bone pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**1 (0.6)**
Breast cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**1 (0.5)**	0 (0.0)
Deep vein thrombosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**1 (0.6)**
Diarrhea hemorrhagic	0 (0.0)	0 (0.0)	0 (0.0)	**1 (0.6)**	0 (0.0)	0 (0.0)	0 (0.0)
Erysipelas	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**1 (0.6)**

Hematuria	0 (0.0)	0 (0.0)	**1 (0.5)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hyperventilation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**1 (0.6)**
Joint injury	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**1 (0.5)**	0 (0.0)
Lymphadenopathy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**1 (0.6)**
Neoplasm skin	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**1 (0.5)**	0 (0.0)	0 (0.0)
Pregnancy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**1 (0.5)**	0 (0.0)
Renal colic	0 (0.0)	**1 (0.5)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Urinary retention	0 (0.0)	0 (0.0)	**1 (0.5)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Incidence rates are sorted in alphabetical order. A patient with multiple SAEs is counted only once in the overall SAE rate. Preferred terms without incidence in monotherapy treatment groups have been removed.

Combination therapy - n (%) Preferred term	ALI75 / HCTZ6.25 N = 188	ALI75 / HCTZ12.5 N = 190	ALI75 / HCTZ25 N = 186	ALI150 / HCTZ6.25 N = 174	ALI150 / HCTZ12.5 N = 184	ALI150 / HCTZ25 N = 188	ALI300 / HCTZ12.5 N = 181	ALI300 / HCTZ25 N = 173	Total N =2762
Serious adverse events	0 (0.0)	**5 (2.6)**	**4 (2.2)**	**2 (1.1)**	**3 (1.6)**	**2 (1.1)**	**2 (1.1)**	**1 (0.6)**	28 (1.0)
Angina pectoris	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**1 (0.6)**	1 (0.0)
Bone pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Breast cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Coronary artery disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**1 (0.6)**	1 (0.0)
Cerebral infarction	0 (0.0)	0 (0.0)	**1 (0.5)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Colitis ulcerative	0 (0.0)	0 (0.0)	0 (0.0)	**1 (0.6)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Deep vein thrombosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Diabetes mellitus (NIDDM)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**1 (0.6)**	0 (0.0)	1 (0.0)
Diarrhea hemorrhagic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Diplopia	0 (0.0)	**1 (0.5)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Dysarthria	0 (0.0)	0 (0.0)	**1 (0.5)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Erysipelas	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
IIIrd nerve paresis	0 (0.0)	**1 (0.5)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Hematuria	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Hyperventilation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Joint injury	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Lung disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**1 (0.6)**	0 (0.0)	1 (0.0)
Lung neoplasm	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**1 (0.5)**	0 (0.0)	0 (0.0)	1 (0.0)
Lymphadenopathy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Mood disorder d/t medical cond.	0 (0.0)	**1 (0.5)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)

Incidence rates are sorted in alphabetical order. A patient with multiple SAEs is counted only once in the overall SAE rate.

Combination therapy - n (%) Preferred term	ALI75 / HCTZ6.25 N = 188	ALI75 / HCTZ12.5 N = 190	ALI75 / HCTZ25 N = 186	ALI150 / HCTZ6.25 N = 174	ALI150 / HCTZ12.5 N = 184	ALI150 / HCTZ25 N = 188	ALI300 / HCTZ12.5 N = 181	ALI300 / HCTZ25 N = 173	Total N =2762
Serious adverse events	0 (0.0)	**5 (2.6)**	**4 (2.2)**	**2 (1.1)**	**3 (1.6)**	**2 (1.1)**	**2 (1.1)**	**1 (0.6)**	28 (1.0)
Myocardial infarction	0 (0.0)	0 (0.0)	**1 (0.5)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Neoplasm skin	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**0 (0.0)**	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Non-cardiac chest pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**1 (0.5)**	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Phlebothrombosis	0 (0.0)	**1 (0.5)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)

Physical disability	0 (0.0)	0 (0.0)	**1 (0.5)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Pneumonia	0 (0.0)	0 (0.0)	0 (0.0)	**1 (0.6)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Pregnancy	0 (0.0)	0 (0.0)	**1 (0.5)**	0 (0.0)	**1 (0.5)**	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.1)
Psychotic disorder	0 (0.0)	**1 (0.5)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Renal colic	0 (0.0)	0 (0.0)	**1 (0.5)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Road traffic accident	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**1 (0.5)**	0 (0.0)	0 (0.0)	1 (0.0)
Small intestinal obstruction	0 (0.0)	**1 (0.5)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Syncope	0 (0.0)	**1 (0.5)**	0 (0.0)	0 (0.0)	**1 (0.5)**	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Urinary retention	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)

Incidence rates are sorted in alphabetical order. A patient with multiple SAEs is counted only once in the overall SAE rate.

Incidence rate of adverse events (>= 2.0%) during the double-blind period by treatment group (safety population):

Monotherapy - n (%)	Placebo N = 193	ALI75 N = 184	ALI150 N = 185	ALI300 N = 181	HCTZ6.25 N = 194	HCTZ12.5 N = 188	HCTZ25 N = 173
Any Adverse Events (AE)	85 (44.0)	69 (37.5)	69 (37.3)	71 (39.2)	75 (38.7)	79 (42.0)	72 (41.6)
Headache	26 (13.5)	13 (7.1)	13 (7.0)	10 (5.5)	12 (6.2)	15 (8.0)	12 (6.9)
Nasopharyngitis	10 (5.2)	9 (4.9)	5 (2.7)	3 (1.7)	6 (3.1)	9 (4.8)	6 (3.5)
Influenza	3 (1.6)	1 (0.5)	7 (3.8)	3 (1.7)	0 (0.0)	3 (1.6)	3 (1.7)
Vertigo	1 (0.5)	2 (1.1)	0 (0.0)	1 (0.6)	1 (0.5)	4 (2.1)	1 (0.6)
Diarrhea	1 (0.5)	3 (1.6)	3 (1.6)	4 (2.2)	3 (1.5)	5 (2.7)	3 (1.7)
Dizziness	2 (1.0)	1 (0.5)	1 (0.5)	3 (1.7)	4 (2.1)	3 (1.6)	6 (3.5)
Edema peripheral	1 (0.5)	4 (2.2)	3 (1.6)	2 (1.1)	2 (1.0)	3 (1.6)	1 (0.6)
Abdominal pain upper	1 (0.5)	1 (0.5)	1 (0.5)	3 (1.7)	3 (1.5)	3 (1.6)	2 (1.2)
Arthralgia	1 (0.5)	4 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.1)	1 (0.6)
Asthenia	0 (0.0)	3 (1.6)	2 (1.1)	2 (1.1)	3 (1.5)	2 (1.1)	1 (0.6)
Back pain	5 (2.6)	3 (1.6)	4 (2.2)	1 (0.6)	1 (0.5)	1 (0.5)	4 (2.3)
Muscle spasms	1 (0.5)	4 (2.2)	3 (1.6)	3 (1.7)	0 (0.0)	2 (1.1)	3 (1.7)
Rhinitis	0 (0.0)	1 (0.5)	1 (0.5)	2 (1.1)	0 (0.0)	2 (1.1)	4 (2.3)
Upper respiratory tract infection	2 (1.0)	2 (1.1)	0 (0.0)	5 (2.8)	0 (0.0)	2 (1.1)	2 (1.2)
Cough	1 (0.5)	1 (0.5)	2 (1.1)	1 (0.6)	1 (0.5)	1 (0.5)	2 (1.2)
Flatulence	1 (0.5)	1 (0.5)	0 (0.0)	2 (1.1)	0 (0.0)	2 (1.1)	1 (0.6)
Nausea	4 (2.1)	1 (0.5)	1 (0.5)	2 (1.1)	3 (1.5)	3 (1.6)	1 (0.6)
Palpitations	3 (1.6)	0 (0.0)	1 (0.5)	1 (0.6)	2 (1.0)	4 (2.1)	0 (0.0)
Bronchitis	1 (0.5)	0 (0.0)	3 (1.6)	4 (2.2)	2 (1.0)	1 (0.5)	1 (0.6)
Constipation	3 (1.6)	4 (2.2)	0 (0.0)	3 (1.7)	1 (0.5)	1 (0.5)	1 (0.6)
Urinary tract inf.	3 (1.6)	2 (1.1)	2 (1.1)	1 (0.6)	2 (1.0)	1 (0.5)	2 (1.2)
Vomiting	4 (2.1)	0 (0.0)	1 (0.5)	0 (0.0)	2 (1.0)	0 (0.0)	1 (0.6)

Incidence rates: presented in descending frequency in the Aliskiren 300 mg/HCTZ 25 column. A patient with multiple AEs within a preferred term is counted only once.

Combination therapy - n (%)	ALI75 / HCTZ6.25	ALI75 / HCTZ12.5	ALI75 / HCTZ25	ALI150 / HCTZ6.25	ALI150 / HCTZ12.5	ALI150 / HCTZ25	ALI300 / HCTZ12.5	ALI300 / HCTZ25	Total N =2762

	N = 188	N = 190	N = 186	N = 174	N = 184	N = 188	N = 181	N = 173	
Any Adverse Events	65 (34.6)	75 (39.5)	77 (41.4)	66 (37.9)	72 (39.1)	83 (44.1)	82 (45.3)	71 (41.0)	1111 (40.2)
Headache	11 (5.9)	14 (7.4)	11 (5.9)	8 (4.6)	15 (8.2)	9 (4.8)	16 (8.8)	14 (8.1)	199 (7.2)
Nasopharyngitis	9 (4.8)	6 (3.2)	10 (5.4)	5 (2.9)	3 (1.6)	7 (3.7)	7 (3.9)	9 (5.2)	104 (3.8)
Influenza	5 (2.7)	5 (2.6)	4 (2.2)	3 (1.7)	1 (0.5)	6 (3.2)	2 (1.1)	7 (4.0)	53 (1.9)
Vertigo	2 (1.1)	2 (1.1)	1 (0.5)	0 (0.0)	1 (0.5)	3 (1.6)	3 (1.7)	5 (2.9)	27 (1.0)
Diarrhea	0 (0.0)	2 (1.1)	3 (1.6)	3 (1.7)	1 (0.5)	6 (3.2)	6 (3.3)	3 (1.7)	46 (1.7)
Dizziness	2 (1.1)	5 (2.6)	5 (2.7)	2 (1.1)	6 (3.3)	3 (1.6)	9 (5.0)	3 (1.7)	55 (2.0)
Edema peripheral	1 (0.5)	3 (1.6)	0 (0.0)	0 (0.0)	2 (1.1)	1 (0.5)	3 (1.7)	3 (1.7)	29 (1.0)
Abdominal pain upper	1 (0.5)	1 (0.5)	1 (0.5)	0 (0.0)	3 (1.6)	4 (2.1)	1 (0.6)	2 (1.2)	27 (1.0)
Arthralgia	2 (1.1)	2 (1.1)	6 (3.2)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.6)	2 (1.2)	22 (0.8)
Asthenia	1 (0.5)	2 (1.1)	5 (2.7)	2 (1.1)	2 (1.1)	3 (1.6)	2 (1.1)	2 (1.2)	32 (1.2)
Back pain	2 (1.1)	7 (3.7)	1 (0.5)	1 (0.6)	2 (1.1)	3 (1.6)	3 (1.7)	2 (1.2)	40 (1.4)
Muscle spasms	3 (1.6)	1 (0.5)	3 (1.6)	1 (0.6)	1 (0.5)	0 (0.0)	0 (0.0)	2 (1.2)	27 (1.0)
Rhinitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	2 (1.1)	2 (1.1)	2 (1.2)	17 (0.6)
Upper respiratory tract infection	2 (1.1)	0 (0.0)	2 (1.1)	3 (1.7)	3 (1.6)	2 (1.1)	2 (1.1)	2 (1.2)	29 (1.0)
Cough	3 (1.6)	3 (1.6)	2 (1.1)	2 (1.1)	2 (1.1)	4 (2.1)	2 (1.1)	1 (0.6)	28 (1.0)
Flatulence	1 (0.5)	0 (0.0)	4 (2.2)	1 (0.6)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.6)	15 (0.5)
Nausea	2 (1.1)	5 (2.6)	0 (0.0)	1 (0.6)	2 (1.1)	4 (2.1)	2 (1.1)	1 (0.6)	32 (1.2)
Palpitations	1 (0.5)	2 (1.1)	1 (0.5)	1 (0.6)	2 (1.1)	5 (2.7)	2 (1.1)	1 (0.6)	26 (0.9)
Bronchitis	1 (0.5)	2 (1.1)	0 (0.0)	4 (2.3)	2 (1.1)	1 (0.5)	1 (0.6)	0 (0.0)	23 (0.8)
Constipation	3 (1.6)	2 (1.1)	2 (1.1)	0 (0.0)	1 (0.5)	2 (1.1)	2 (1.1)	0 (0.0)	25 (0.9)
Urinary tract inf.	1 (0.5)	0 (0.0)	0 (0.0)	2 (1.1)	3 (1.6)	0 (0.0)	5 (2.8)	0 (0.0)	24 (0.9)
Vomiting	0 (0.0)	1 (0.5)	2 (1.1)	0 (0.0)	3 (1.6)	2 (1.1)	0 (0.0)	0 (0.0)	16 (0.6)

Incidence rates: presented in descending frequency in the Aliskiren/HCTZ 300/25 mg column. A patient with multiple AEs within a preferred term is counted only once.

Date of Clinical Trial Report

25-Oct-2005