Sponsor

Novartis

Generic Drug Name

Aliskiren

Trial Indication(s)

Essential hypertension

Protocol Number

CSPP100A2306

Protocol Title

A 26 Week, Double-blind, Randomized, Multicenter, Parallel Group, Active-controlled Study Comparing Aliskiren to Ramipril With Optional Addition of Hydrochlorothiazide, Followed by a 4 Week Double-blind, Randomized, Placebo-controlled Withdrawal in Patients With Essential Hypertension

Clinical Trial Phase

Phase III

Study Start/End Dates

28-Feb-2005 to 08-Mar-2006

Reason for Termination

Not applicable.

Study Design/Methodology

This was a randomized, double-blind, parallel group, multicenter, active-controlled study in patients with essential hypertension (msDBP ≥ 95 mm Hg and < 110 mm Hg). The study had four periods: Period 1 (Washout period), Period 2

(Single-blind placebo run-in period), Period 3 (Double-blind active-controlled treatment period), and Period 4 (Double-blind placebo-controlled withdrawal period).

Centers

Approximately 80 centers worldwide.

Objectives:

Primary objective(s)

Evaluate the efficacy of an aliskiren-based antihypertensive regimen (aliskiren 150 mg, aliskiren 300 mg, aliskiren 300 mg with HCTZ 12.5 mg/25 mg) when compared to a ramipril-based antihypertensive regimen (ramipril 5 mg, ramipril 10 mg, ramipril 10 mg with HCTZ 12.5 mg/25 mg) by testing: (i) the hypothesis of non-inferiority for the aliskiren regimen versus the ramipril regimen on reduction in mean sitting diastolic blood pressure (msDBP) from baseline to Week 26 and (ii) the hypothesis of superiority for the aliskiren regimen versus the ramipril regimen on reduction in msDBP from baseline, if the hypothesis of non-inferiority was achieved.

Secondary objective(s)

- Evaluate the efficacy of an aliskiren-based antihypertensive regimen when compared to a ramipril-based antihypertensive regimen by testing: (i) the hypothesis of non-inferiority for the aliskiren regimen versus the ramipril regimen on reduction in mean sitting systolic blood pressure (msSBP) from baseline to Week 26 and (ii) the hypothesis of superiority for the aliskiren regimen versus the ramipril regimen on reduction in msSBP from baseline, if the hypothesis of non-inferiority was achieved.
- Demonstrate the efficacy of an aliskiren-based antihypertensive regimen by testing the hypothesis of superiority on the change (i.e. smaller change for the aliskiren regimen when compared to placebo) in msDBP and msSBP from Week 26, after a 4-week randomized, double-blind, placebo-controlled withdrawal period when compared to placebo.
- Compare the efficacy of aliskiren 150 mg to ramipril 5 mg in reduction of msDBP and msSBP from baseline at Week 6 (i.e. after 6 weeks of randomized, double-blind treatment).

- Compare the efficacy of aliskiren 300 mg to ramipril 10 mg in reduction of msDBP and msSBP from baseline at Week 12 (i.e. after 12 weeks of randomized, double-blind treatment). Note: This objective was clarified in the statistical analysis plan to read as follows: Compare the efficacy of the aliskiren regimen, which could have reached a dose of 300 mg, to the ramipril regimen, which could have reached a dose of 10 mg, in reduction of msDBP and msSBP from baseline at Week 12 (i.e. after 12 weeks of randomized, double-blind treatment).
- Evaluate the proportion of patients controlled to a target blood pressure of < 140/90 mm Hg on the aliskiren-based antihypertensive regimen compared to the ramipril-based regimen.
- Evaluate the proportion of patients controlled to a target blood pressure of < 140/90 mm Hg on the aliskiren monotherapy regimen compared to the ramipril monotherapy regimen.
- Evaluate the long term safety and tolerability of an aliskiren-based antihypertensive regimen compared to the ramipril-based regimen.
- Evaluate the effect of an aliskiren-based antihypertensive regimen compared to a ramipril-based antihypertensive regimen on Quality of Life (QOL) as assessed by the Psychological General Well-Being Index (PGWBI).

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

The following study drugs were provided:

- Aliskiren 150 mg tablets
- Aliskiren 300 mg tablets
- Placebo to match aliskiren 150 and 300 mg tablets
- Ramipril 5 mg capsules
- Ramipril 10 mg capsules
- Placebo to match ramipril 5 and 10 mg capsules
- HCTZ 12.5 mg capsules
- HCTZ 25 mg capsules
- Placebo to match HCTZ 12.5 and 25 mg capsules

Statistical Methods

The primary objective of this study was to evaluate the efficacy of an aliskiren-based antihypertensive regimen (aliskiren 150 mg, aliskiren 300 mg, aliskiren 300 mg with HCTZ 12.5 mg/25 mg) when compared to a ramipril-based antihypertensive regimen (ramipril 5 mg, ramipril 10 mg, ramipril 10 mg with HCTZ 12.5 mg/25 mg). by testing: (i) the hypothesis of non-inferiority for the aliskiren regimen versus the ramipril regimen on reduction in msDBP from baseline and (ii) the hypothesis of superiority for the aliskiren regimen versus the ramipril regimen on reduction in msDBP from baseline, if the hypothesis of non-inferiority was achieved.

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. Other protocol-defined inclusion exclusion criteria also apply.

Participant Flow Table

Patient disposition in active-controlled treatment period by treatment group (all enrolled patients)

Disposition/Reason	Aliskiren Regimen n (%)	Ramipril Regimen n (%)	Total n (%)
Enrolled			1082
Randomized	420	422	842
Completed	338 (80.5)	349 (82.7)	687 (81.6)
Discontinued	79 (18.8)	71 (16.8)	150 (17.8)
Reason for discontinuation			
Adverse event(s)	24 (5.7)	19 (4.5)	43 (5.1)
Abnormal laboratory value(s)	2 (0.5)	2 (0.5)	4 (0.5)

Abnormal test procedure result(s)	2 (0.5)	0 (0.0)	2 (0.2)
Unsatisfactory therapeutic effect	12 (2.9)	14 (3.3)	26 (3.1)
Protocol violation	6 (1.4)	3 (0.7)	9 (1.1)
Subject withdrew consent	28 (6.7)	28 (6.6)	56 (6.7)
Lost to follow-up	4 (1.0)	5 (1.2)	9 (1.1)
Administrative problems	1 (0.2)	0 (0.0)	1 (0.1)

Patient disposition in placebo-controlled treatment withdrawal period by treatment group (all withdrawal enrolled patients)

	Aliskiren Regimen			Ramipril Regimen		
	Aliskiren	**Placebo**	**Total**	**Ramipril**	**Placebo**	**Total**
Disposition/Reason	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Randomized	170	163	333	165	177	342
Completed	169 (99.4)	147 (90.2)	316 (94.9)	158 (95.8)	170 (96.0)	328 (95.9)
Discontinued	1 (0.6)	16 (9.8)	17 (5.1)	7 (4.2)	7 (4.0)	14 (4.1)
Reason for discontinuation						
Adverse event(s)	0 (0.0)	3 (1.8)	3 (0.9)	1 (0.6)	3 (1.7)	4 (1.2)
Abnormal laboratory value(s)	0 (0.0)	1 (0.6)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Abnormal test procedure result(s)	0 (0.0)	2 (1.2)	2 (0.6)	0 (0.0)	3 (1.7)	3 (0.9)
Unsatisfactory therapeutic effect	1 (0.6)	7 (4.3)	8 (2.4)	3 (1.8)	1 (0.6)	4 (1.2)
Protocol violation	0 (0.0)	1 (0.6)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Subject withdrew consent	0 (0.0)	1 (0.6)	1 (0.3)	2 (1.2)	0 (0.0)	2 (0.6)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.3)
Death	0 (0.0)	1 (0.6)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)

Baseline Characteristics

Patient background characteristics in active-controlled treatment period by treatment group (all randomized patients)

Demographic Characteristic Category/Statistic	Aliskiren Regimen N=420	Ramipril Regimen N=422	Total N=842
Sex n (%)			
Male	224 (53.3%)	256 (60.7%)	480 (57.0%)
Female	196 (46.7%)	166 (39.3%)	362 (43.0%)
Race n (%)			
Caucasian	312 (74.3%)	326 (77.3%)	638 (75.8%)
Black	84 (20.0%)	67 (15.9%)	151 (17.9%)
Asian	14 (3.3%)	13 (3.1%)	27 (3.2%)
Native American	0 (0.0%)	2 (0.5%)	2 (0.2%)
Other	10 (2.4%)	14 (3.3%)	24 (2.9%)
Ethnicity n (%)			
Hispanic or Latino	63 (15.0%)	63 (14.9%)	126 (15.0%)
Chinese	7 (1.7%)	7 (1.7%)	14 (1.7%)
Indian (India Subcontinent)	11 (2.6%)	10 (2.4%)	21 (2.5%)
Other	339 (80.7%)	342 (81.0%)	681 (80.9%)
Age (years)			
N	420	422	842
Mean (SD)	53.4 (10.78)	53.1 (11.21)	53.3 (10.99)
Age group n (%)			
< 65	356 (84.8%)	359 (85.1%)	715 (84.9%)
>=65	64 (15.2%)	63 (14.9%)	127 (15.1%)
>=75	13 (3.1%)	12 (2.8%)	25 (3.0%)
Duration of Hypertension (years)#			
n	410	411	821
Mean (SD)	7.4 (6.85)	8.1 (7.52)	7.8 (7.20)
naive patients n (%)	10 (2.4%)	11 (2.6%)	21 (2.5%)
Body Mass Index (kg/m2)**			
n	418	421	839
Mean (SD)	30.3 (5.89)	31.4 (6.79)	30.8 (6.38)
Obesity n (%)			
BMI >=30 (kg/m**2)	184 (43.8%)	221 (52.4%)	405 (48.1%)
BMI < 30 (kg/m**2)	234 (55.7%)	200 (47.4%)	434 (51.5%)
Metabolic Syndrome## n (%)			
Yes	171 (40.7%)	183 (43.4%)	354 (42.0%)
No	249 (59.3%)	238 (56.4%)	487 (57.8%)
Data not available	0 (0.0%)	1 (0.2%)	1 (0.1%)
Diabetes### n (%)			
Yes	42 (10.0%)	49 (11.6%)	91 (10.8%)
No	378 (90.0%)	373 (88.4%)	751 (89.2%)

Duration of hypertension = Visit 1 year - Year of hypertension diagnosis (from medical history) + 1.
Metabolic Syndrome=Yes, if any 3 of the following are true:
1. Waist circumference > 102 cm for men or > 88 cm for women; 2. Triglycerides >= 1.69 mmol/L; 3. HDL cholesterol < 1.04 mmol/L for men or < 1.29 mmol/L

for women; 4. Blood pressure: msSBP >= 130 mm Hg and/or msDBP >= 85 mm Hg; 5. Fasting glucose >= 6.1 mmol/L.
From medical history.
SD=standard deviation.

Patient background characteristics in placebo-controlled treatment withdrawal period by treatment group (all withdrawal randomized patients)

Demographic Characteristic	Aliskiren Regimen			Ramipril Regimen		
Category/Statistic	Aliskiren N=170	Placebo N=163	Total N=333	Ramipril N=165	Placebo N=177	Total N=342
Sex n (%)						
Male	95 (55.9%)	81 (49.7%)	176 (52.9%)	101 (61.2%)	110 (62.1%)	211 (61.7%)
Female	75 (44.1%)	82 (50.3%)	157 (47.1%)	64 (38.8%)	67 (37.9%)	131 (38.3%)
Race n (%)						
Caucasian	133 (78.2%)	128 (78.5%)	261 (78.4%)	126 (76.4%)	144 (81.4%)	270 (78.9%)
Black	28 (16.5%)	27 (16.6%)	55 (16.5%)	23 (13.9%)	24 (13.6%)	47 (13.7%)
Asian	4 (2.4%)	6 (3.7%)	10 (3.0%)	9 (5.5%)	3 (1.7%)	12 (3.5%)
Native American	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.6%)	1 (0.6%)	2 (0.6%)
Other	5 (2.9%)	2 (1.2%)	7 (2.1%)	6 (3.6%)	5 (2.8%)	11 (3.2%)
Ethnicity n (%)						
Hispanic or Latino	27 (15.9%)	26 (16.0%)	53 (15.9%)	27 (16.4%)	24 (13.6%)	51 (14.9%)
Chinese	3 (1.8%)	3 (1.8%)	6 (1.8%)	4 (2.4%)	2 (1.1%)	6 (1.8%)
Indian (India Subcontinent)	4 (2.4%)	4 (2.5%)	8 (2.4%)	5 (3.0%)	4 (2.3%)	9 (2.6%)
Other	136 (80.0%)	130 (79.8%)	266 (79.9%)	129 (78.2%)	147 (83.1%)	276 (80.7%)
Age (years)						
n	170	163	333	165	177	342
Mean (SD)	54.2 (9.88)	53.2 (11.28)	53.7 (10.59)	53.3 (10.90)	52.9 (11.30)	53.1 (11.10)
Age group n (%)						
< 65	144 (84.7%)	138 (84.7%)	282 (84.7%)	140 (84.8%)	153 (86.4%)	293 (85.7%)
>=65	26 (15.3%)	25 (15.3%)	51 (15.3%)	25 (15.2%)	24 (13.6%)	49 (14.3%)
>=75	4 (2.4%)	5 (3.1%)	9 (2.7%)	5 (3.0%)	3 (1.7%)	8 (2.3%)
Duration of Hypertension (years)#						
n	164	160	324	164	168	332
Mean (SD)	6.6 (5.76)	7.9 (7.38)	7.3 (6.63)	7.8 (7.17)	7.4 (6.91)	7.6 (7.03)
Naive patients n (%)	6 (3.5%)	3 (1.8%)	9 (2.7%)	1 (0.6%)	9 (5.1%)	10 (2.9%)
Body Mass Index (kg/m2)**						
n	169	160	329	161	176	337
Mean (SD)	29.6 (6.01)	30.7 (5.85)	30.2 (5.95)	30.5 (6.41)	32.0 (6.98)	31.2 (6.74)
Obesity n (%)						
BMI >=30 (kg/m**2)	68 (40.0%)	79 (48.5%)	147 (44.1%)	74 (44.8%)	89 (50.3%)	163 (47.7%)
BMI < 30 (kg/m**2)	101 (59.4%)	81 (49.7%)	182 (54.7%)	87 (52.7%)	87 (49.2%)	174 (50.9%)

Metabolic Syndrome## n (%)						
Yes	60 (35.3%)	71 (43.6%)	131 (39.3%)	72 (43.6%)	81 (45.8%)	153 (44.7%)
No	110 (64.7%)	92 (56.4%)	202 (60.7%)	93 (56.4%)	96 (54.2%)	189 (55.3%)
Diabetes### n (%)						
Yes	14 (8.2%)	18 (11.0%)	32 (9.6%)	16 (9.7%)	26 (14.7%)	42 (12.3%)
No	156 (91.8%)	145 (89.0%)	301 (90.4%)	149 (90.3%)	151 (85.3%)	300 (87.7%)

Duration of hypertension = Visit 1 year - Year of hypertension diagnosis (from medical history) + 1.
Metabolic Syndrome=Yes, if any 3 of the following are true:
1. Waist circumference > 102 cm for men or > 88 cm for women; 2. Triglycerides >= 1.69 mmol/L; 3. HDL cholesterol < 1.04 mmol/L for men or < 1.29 mmol/L for women; 4. Blood pressure: msSBP >= 130 mm Hg and/or msDBP >= 85 mm Hg; 5. Fasting glucose >= 6.1 mmol/L.
From medical history.
SD=standard deviation.

Baseline (Week 0) values of blood pressures and biomarkers in active-controlled treatment period (all randomized patients)

Parameter Statistic	Aliskiren Regimen N=420	Ramipril Regimen N=422	Total N=842
msDBP (mm Hg)			
n	420	422	842
Mean (SD)	98.8 (3.38)	98.9 (3.45)	98.9 (3.42)
Median	98	98	98
Min	90	95	90
Max	109.3	109.3	109.3
msSBP (mm Hg)			
n	420	422	842
Mean (SD)	151.3 (11.70)	151.5 (11.73)	151.4 (11.71)
Median	150.7	150.7	150.7
Min	121.3	114	114
Max	189.3	178.7	189.3
Standing DBP (mm Hg)			
n	419	422	841
Mean (SD)	99.5 (5.55)	99.9 (5.47)	99.7 (5.51)
Median	100	100	100
Min	72	80	72
Max	120	118	120
Standing SBP (mm Hg)			
n	419	422	841
Mean (SD)	151.0 (12.80)	150.7 (13.12)	150.9 (12.96)
Median	150	150	150
Min	118	110	110
Max	184	198	198

Parameter Statistic	Aliskiren Regimen N=420	Ramipril Regimen N=422
PRA (ng/ml/h)		
n	103	100
Mean (SD)	1.406 (1.983)	1.722 (2.980)
Median	0.800	1.050
Min	0.160	0.160
Max	14.700	22.500
Geometric Mean*	0.828	0.956
Low 95%CI of Geo mean	0.682	0.781
High 95%CI of Geo mean	1.004	1.170
Renin concentration (mU/L)		
n	39	33
Mean (SD)	22.062 (23.339)	22.852 (26.603)
Median	13.600	13.900
Min	1.700	1.700
Max	123.500	133.600
Geometric Mean*	14.942	14.408
Low 95%CI of Geo mean	11.308	10.374
High 95%CI of Geo mean	19.742	20.012
Aldosterone (pmol/L)		
n	101	102
Mean (SD)	197.178 (124.574)	225.120 (142.084)
Median	186.000	197.000
Min	55.200	55.200
Max	588.000	697.000
Geometric Mean*	157.620	181.134
Low 95%CI of Geo mean	137.345	158.215
High 95%CI of Geo mean	180.888	207.373

hs-CRP (mg/L)		
n	103	100
Mean (SD)	2.950 (3.873)	3.651 (4.231)
Median	1.500	2.050
Min	0.080	0.080
Max	24.000	24.000
Geometric Mean*	1.517	2.031
Low 95%CI of Geo mean	1.199	1.617
High 95%CI of Geo mean	1.919	2.550
hs-IL6 (ng/L)		
n	102	99
Mean (SD)	2.915 (2.830)	2.858 (2.305)
Median	1.905	2.080
Min	0.360	0.600
Max	12.000	12.000
Geometric Mean*	2.140	2.275
Low 95%CI of Geo mean	1.852	2.001
High 95%CI of Geo mean	2.472	2.586
MCP-1 (ng/L)		
n	102	99
Mean (SD)	315.951 (128.984)	333.646 (129.853)
Median	290.000	333.000
Min	87.000	67.000
Max	817.000	855.000
Geometric Mean*	290.982	307.021
Low 95%CI of Geo mean	268.376	281.928
High 95%CI of Geo mean	315.491	334.347

Parameter Statistic	Aliskiren Regimen N=420	Ramipril Regimen N=422
sICAM-1 (ug/L)		
n	102	99
Mean (SD)	249.039 (61.855)	255.667 (87.570)
Median	245.000	239.000
Min	79.000	48.000
Max	471.000	647.000
Geometric Mean*	240.648	240.695
Low 95%CI of Geo mean	228.074	223.736
High 95%CI of Geo mean	253.916	258.940
UACR (mg/mmol)		
n	73	78
Mean (SD)	4.151 (9.351)	9.656 (49.566)
Median	1.000	0.950
Min	0.100	0.200
Max	63.800	433.500
Geometric Mean*	1.284	1.390
Low 95%CI of Geo mean	0.926	0.985
High 95%CI of Geo mean	1.779	1.961

SD=standard deviation.
* Geometric mean is a value transformed back from the mean logarithm of the biomarker.

Withdrawal baseline (Week 26) values of blood pressures and biomarkers in placebo-controlled treatment withdrawal period (all withdrawal randomized patients)

	Aliskiren Regimen			Ramipril Regimen		
Parameter Statistic	Aliskiren N=170	Placebo N=163	Total N=333	Ramipril N=165	Placebo N=177	Total N=342
msDBP (mm Hg)						
n	170	163	333	164	177	341
Mean (SD)	83.8 (7.13)	85.1 (7.20)	84.4 (7.18)	86.3 (6.57)	85.3 (6.73)	85.8 (6.66)
Median	83.3	85.3	84.7	86.3	84.7	85.3
Min	64	60	60	68.7	68.7	68.7
Max	104	108	108	102	104.7	104.7
msSBP (mm Hg)						
n	170	163	333	164	177	341
Mean (SD)	130.7 (10.76)	132.3 (13.01)	131.5 (11.92)	134.0 (11.70)	133.6 (11.79)	133.8 (11.73)
Median	130.3	131.3	130.7	132.7	133.3	132.7
Min	107.3	100.7	100.7	106.7	109.3	106.7
Max	163.3	173.3	173.3	168.3	166	168.3
Standing DBP (mm Hg)						
n	170	163	333	164	177	341
Mean (SD)	86.1 (8.57)	87.9 (8.07)	87.0 (8.37)	89.2 (8.23)	87.9 (7.94)	88.5 (8.09)
Median	86	88	87	90	88	88
Min	62	68	62	64	64	64
Max	110	110	110	110	108	110
Standing SBP (mm Hg)						
n	170	163	333	164	177	341
Mean (SD)	132.1 (13.34)	133.8 (15.09)	132.9 (14.22)	134.2 (13.86)	133.7 (12.52)	133.9 (13.17)
Median	130	132	132	134	134	134
Min	100	104	100	100	104	100
Max	182	184	184	175	162	175

PRA (ng/ml/h)				
n	54	40	44	46
Mean (SD)	0.414 (0.389)	0.604 (1.296)	4.887 (4.995)	3.798 (4.992)
Median	0.25	0.2	4	2.2
Min	0.16	0.16	0.16	0.16
Max	2.2	6.7	28.08	29
Geometric Mean*	0.307	0.307	3.016	1.994
Low 95%CI of Geo mean	0.253	0.233	2.181	1.399
High 95%CI of Geo mean	0.373	0.404	4.169	2.841

Parameter **Statistic**		**Aliskiren** **N=170**	**Placebo** **N=163**	**Ramipril** **N=165**
Renin concentration (mU/L)				
n	22	16	12	19
Mean (SD)	99.714 (134.695)	95.163 (83.584)	76.425 (90.282)	53.758 (72.999)
Median	68.25	59.35	45.05	24.1
Min	4.2	23.8	5.7	5.4
Max	477.8	308.3	311	249.3
Geometric Mean*	44.395	66.952	40.486	30.066
Low 95%CI of Geo mean	24.842	43.737	20.183	18.943
High 95%CI of Geo mean	79.338	102.491	81.213	47.722

SD=standard deviation.
* Geometric mean is a value transformed back from the mean logarithm of the biomarker.

Summary of Efficacy

Primary Outcome Result(s)

Statistical analysis of change from baseline in msDBP at Week 26 endpoint in active-controlled treatment period (intent-to-treat population)

Treatment Regimen	N	LSM change from baseline(SE)
Aliskiren	414	-13.17 (0.39)
Ramipril	418	-11.96 (0.38)

Pairwise Comparison	LSM difference in Change from baseline (SE)	95% CI for LSM difference	P-value[1] Non-inferiority+	P-value[1] Superiority
Aliskiren vs. Ramipril	-1.21 (0.54)	(-2.27,-0.15)	<.0001*	0.0250*

SE = Standard Error; LSM = Least Squares Mean; CI = Confidence Interval.
+Non-inferiority margin used in the non-inferiority test is 2 mm Hg. One-sided significance level of 0.025 was only used for the non-inferiority test.
[1]P-Values and treatment comparisons were evaluated at the average baseline level.
* indicates statistical significance at 0.05 level.

Secondary Outcome Result(s)

Statistical analysis of change from baseline in msSBP at Week 26 endpoint in active-controlled treatment period (intent-to-treat population)

Treatment Regimen	N	LSM change from baseline(SE)
Aliskiren	414	-17.88 (0.65)
Ramipril	418	-15.24 (0.64)

Pairwise Comparison	LSM difference in Change from baseline (SE)	95% CI for LSM difference	P-value[1] Non-inferiority+	P-value[1] Superiority
Aliskiren vs. Ramipril	-2.64 (0.90)	(-4.41,-0.86)	<.0001*	0.0036*

SE = Standard Error; LSM = Least Squares Mean; CI = Confidence Interval.
+Non-inferiority margin used in the non-inferiority test is 4 mm Hg. One-sided significance level of 0.025 was only used for the non-inferiority test.
[1]P-Values and treatment comparisons were evaluated at the average baseline level.
* indicates statistical significance at 0.05 level.

Statistical analysis of change from baseline in msDBP at Week 6 endpoint in active-controlled treatment period (intent-to-treat population)

Treatment Regimen	N	LSM change from baseline(SE)
Aliskiren	414	-10.51 (0.39)
Ramipril	418	-9.52 (0.39)

			P-value[1]	
Pairwise Comparison	LSM difference in Change from baseline (SE)	95% CI for LSM difference	Non-inferiority+	Superiority
Aliskiren vs. Ramipril	-0.99 (0.54)	(-2.06, 0.08)	<.0001*	0.0689

SE = Standard Error; LSM = Least Squares Mean; CI = Confidence Interval.
+Non-inferiority margin used in the non-inferiority test is 2 mm Hg. One-sided significance level of 0.025 was only used for the non-inferiority test.
[1]P-Values and treatment comparisons were evaluated at the average baseline level.
* indicates statistical significance at 0.05 level..

Statistical analysis of change from baseline in msDBP at Week 12 endpoint in active-controlled treatment period (intent-to-treat population)

Treatment Regimen	N	LSM change from baseline(SE)
Aliskiren	414	-11.26 (0.40)
Ramipril	418	-9.71 (0.40)

			P-value[1]	
Pairwise Comparison	LSM difference in Change from baseline (SE)	95% CI for LSM difference	Non-inferiority+	Superiority
Aliskiren vs. Ramipril	-1.55 (0.56)	(-2.65,-0.45)	<.0001*	0.0056*

SE = Standard Error; LSM = Least Squares Mean; CI = Confidence Interval.
+Non-inferiority margin used in the non-inferiority test is 2 mm Hg. One-sided significance level of 0.025 was only used for the non-inferiority test.
[1]P-Values and treatment comparisons were evaluated at the average baseline level.
* indicates statistical significance at 0.05 level.

Statistical analysis of change from baseline in msSBP at Week 6 endpoint in active-controlled treatment period (intent-to-treat population)

Treatment Regimen	N	LSM change from baseline(SE)
Aliskiren	414	-12.93 (0.61)
Ramipril	418	-10.48 (0.61)

			P-value[1]	
Pairwise Comparison	LSM difference in Change from baseline (SE)	95% CI for LSM difference	Non-inferiority+	Superiority
Aliskiren vs. Ramipril	-2.45 (0.85)	(-4.12,-0.78)	<.0001*	0.0041*

SE = Standard Error; LSM = Least Squares Mean; CI = Confidence Interval.
+Non-inferiority margin used in the non-inferiority test is 4 mm Hg. One-sided significance level of 0.025 was only used for the non-inferiority test.
[1]P-Values and treatment comparisons were evaluated at the average baseline level.
* indicates statistical significance at 0.05 level.

Statistical analysis of change from baseline in msSBP at Week 12 endpoint in active-controlled treatment period (intent-to-treat population)

Treatment Regimen	N	LSM change from baseline(SE)
Aliskiren	414	-14.00 (0.64)
Ramipril	418	-11.32 (0.63)

			P-value[1]	
Pairwise Comparison	LSM difference in Change from baseline (SE)	95% CI for LSM difference	Non-inferiority+	Superiority
Aliskiren vs. Ramipril	-2.68 (0.89)	(-4.43,-0.93)	<.0001*	0.0027*

SE = Standard Error; LSM = Least Squares Mean; CI = Confidence Interval.
+Non-inferiority margin used in the non-inferiority test is 4 mm Hg. One-sided significance level of 0.025 was only used for the non-inferiority test.
[1]P-Values and treatment comparisons were evaluated at the average baseline level.
* indicates statistical significance at 0.05 level.

Number (%) of patients with blood pressure control at Week 26 endpoint in active-controlled treatment period by treatment group (intent-to-treat population)

Treatment Comparisons (A vs. B)	Treatment A n/N (%)	Treatment B n/N (%)	P-value
Aliskiren vs. Ramipril	254/414 (61.4)	222/418 (53.1)	0.0205*

Blood pressure control is defined as a patient with target msSBP < 140 mm Hg and msDBP < 90 mm Hg.
P-values were from a logistic regression model with treatment and region as factors and baseline as a covariate.
Baseline is the week 0 value.
N = Number of patients with baseline and endpoint msDBP values.
* indicates statistical significance at 0.05 level.

Number (%) of patients with blood pressure control at Week 6 endpoint in active-controlled treatment period by treatment group (intent-to-treat population)

Treatment Comparisons (A vs. B)	Treatment A n/N (%)	Treatment B n/N (%)	P-value
Aliskiren vs. Ramipril	181/414 (43.7)	170/418 (40.7)	0.4131

Blood pressure control is defined as a patient with target msSBP < 140 mm Hg and msDBP < 90 mm Hg.
P-values were from a logistic regression model with treatment and region as factors and baseline as a covariate.
Baseline is the week 0 value.
N = Number of patients with baseline and endpoint msDBP values.
* indicates statistical significance at 0.05 level.

Number (%) of patients with blood pressure control at Week 12 endpoint in active-controlled treatment period by treatment group (intent-to-treat population)

Treatment Comparisons (A vs. B)		Treatment A n/N (%)	Treatment B n/N (%)	P-value
Aliskiren	vs. Ramipril	197/414 (47.6)	178/418 (42.6)	0.1698

Blood pressure control is defined as a patient with target msSBP < 140 mm Hg and msDBP < 90 mm Hg.
P-values were from a logistic regression model with treatment and region as factors and baseline as a covariate.
Baseline is the week 0 value.
N = Number of patients with baseline and endpoint msDBP values.
* indicates statistical significance at 0.05 level.

Number (%) of responders at Week 26 endpoint in active-controlled treatment period by treatment group (intent-to treat population)

Treatment Comparisons (A vs. B)		Treatment A n/N (%)	Treatment B n/N (%)	P-value
Aliskiren	vs. Ramipril	318/414 (76.8)	297/418 (71.1)	0.0772

Responder is defined as patient with msDBP < 90 mm Hg or reduction in msDBP at least 10 mm Hg at endpoint.
P-values were from a logistic regression model with treatment and region as factors and baseline as a covariate.
Baseline is the week 0 value.
N = Number of patients with baseline and endpoint msDBP values.
* indicates statistical significance at 0.05 level.

Number (%) of responders at Week 6 endpoint in active-controlled treatment period by treatment group (intent-to treat population)

Treatment Comparisons (A vs. B)		Treatment A n/N (%)	Treatment B n/N (%)	P-value
Aliskiren	vs. Ramipril	256/414 (61.8)	232/418 (55.5)	0.0798

Responder is defined as patient with msDBP < 90 mm Hg or reduction in msDBP at least 10 mm Hg at endpoint.
P-values were from a logistic regression model with treatment and region as factors and baseline as a covariate.
Baseline is the week 0 value.
N = Number of patients with baseline and endpoint msDBP values.
* indicates statistical significance at 0.05 level.

Number (%) of responders at Week 12 endpoint in active-controlled treatment period by treatment group (intent-to treat population)

Treatment Comparisons (A vs. B)	Treatment A n/N (%)	Treatment B n/N (%)	P-value
Aliskiren vs. Ramipril	267/414 (64.5)	237/418 (56.7)	0.0275*

Responder is defined as patient with msDBP < 90 mm Hg or reduction in msDBP at least 10 mm Hg at endpoint.
P-values were from a logistic regression model with treatment and region as factors and baseline as a covariate.
Baseline is the week 0 value.
N = Number of patients with baseline and endpoint msDBP values.
* indicates statistical significance at 0.05 level.

Statistical analysis of change from baseline in msDBP at Week 30 endpoint in placebo-controlled treatment withdrawal period (withdrawal intent-to-treat population)

Subgroup Treatment Regimen	N	LSM change from baseline(SE)
Overall		
Aliskiren	170	0.36 (0.54)
Aliskiren-Placebo	163	6.24 (0.55)
Ramipril	163	1.56 (0.55)
Ramipril-Placebo	177	6.13 (0.53)
Monotherapy		
Aliskiren	80	1.32 (0.74)
Aliskiren-Placebo	77	5.58 (0.76)
Ramipril	74	2.32 (0.77)
Ramipril-Placebo	75	4.06 (0.77)
HCTZ Combination		
Aliskiren	90	-0.61 (0.76)
Aliskiren-Placebo	86	6.73 (0.77)
Ramipril	89	0.96 (0.76)
Ramipril-Placebo	102	7.59 (0.71)

Subgroup Pairwise Comparison	LSM difference in change from baseline (SE)	95% CI for LSM difference	P-value[1]
Overall			
Aliskiren vs. Placebo	-5.88 (0.76)	(-7.38, -4.38)	<.0001*
Ramipril vs. Placebo	-4.57 (0.75)	(-6.06, -3.09)	<.0001*
Monotherapy			
Aliskiren vs. Placebo	-4.25 (1.05)	(-6.31, -2.19)	<.0001*
Ramipril vs. Placebo	-1.74 (1.07)	(-3.84, 0.37)	0.1050
HCTZ combination			
Aliskiren vs. Placebo	-7.34 (1.07)	(-9.45, -5.23)	<.0001*
Ramipril vs. Placebo	-6.62 (1.03)	(-8.65, -4.59)	<.0001*

SE = Standard Error; LSM = Least Squares Mean; CI = Confidence Interval.
[1]P-Values and treatment comparisons were evaluated at the average withdrawal baseline level.
* indicates statistical significance at 0.05 level.

Statistical analysis of change from withdrawal baseline in msSBP at Week 30 endpoint in placebo-controlled treatment withdrawal period (withdrawal intent-to-treat population)

Subgroup Treatment Regimen	N	LSM change from baseline(SE)
Overall		
Aliskiren	170	0.78 (0.92)
Aliskiren-Placebo	163	10.06 (0.94)
Ramipril	163	1.36 (0.93)
Ramipril-Placebo	177	11.23 (0.90)
Monotherapy		
Aliskiren	80	2.23 (1.08)
Aliskiren-Placebo	77	7.10 (1.09)
Ramipril	74	1.95 (1.11)
Ramipril-Placebo	75	5.98 (1.12)
HCTZ Combination		
Aliskiren	90	-0.70 (1.37)
Aliskiren-Placebo	86	12.57 (1.40)
Ramipril	89	0.83 (1.37)
Ramipril-Placebo	102	14.92 (1.28)

Subgroup Pairwise Comparison	LSM difference in change from baseline (SE)	95% CI for LSM difference	P-value[1]
Overall			
Aliskiren vs. Placebo	-9.28 (1.30)	(-11.84, -6.72)	<.0001*
Ramipril vs. Placebo	-9.86 (1.29)	(-12.39, -7.34)	<.0001*
Monotherapy			
Aliskiren vs. Placebo	-4.87 (1.52)	(-7.86, -1.89)	0.0015*
Ramipril vs. Placebo	-4.02 (1.55)	(-7.07, -0.98)	0.0098*
HCTZ combination			
Aliskiren vs. Placebo	-13.27 (1.94)	(-17.09, -9.45)	<.0001*
Ramipril vs. Placebo	-14.10 (1.87)	(-17.77, -10.4)	<.0001*

SE = Standard Error; LSM = Least Squares Mean; CI = Confidence Interval.
[1]P-Values and treatment comparisons were evaluated at the average withdrawal baseline level.
* indicates statistical significance at 0.05 level.

Number (%) of patients with blood pressure control at Week 30 endpoint in placebo-controlled treatment withdrawal period by treatment group (withdrawal intent-to-treat population)

Subgroup Treatment Comparisons (A vs. B)	Treatment A n/N (%)	Treatment B n/N (%)	P-value
Overall			
Aliskiren vs. Placebo	107/170 (62.9)	56/163 (34.4)	<.0001*
Ramipril vs. Placebo	86/163 (52.8)	46/177 (26.0)	<.0001*
Monotherapy			
Aliskiren vs. Placebo	59/ 80 (73.8)	37/ 77 (48.1)	0.0029*
Ramipril vs. Placebo	48/ 74 (64.9)	33/ 75 (44.0)	0.0061*
HCTZ combination			
Aliskiren vs. Placebo	48/ 90 (53.3)	19/ 86 (22.1)	<.0001*
Ramipril vs. Placebo	38/ 89 (42.7)	13/102 (12.7)	<.0001*

Blood pressure control is defined as a patient with target msSBP <140 mm Hg and msDBP <90 mm Hg.
P-values were from a logistic regression model with treatment and region as factors and withdrawal baseline as a covariate.
Baseline during the withdrawal period is the Week 26 value.
N = Number of patients with withdrawal baseline and endpoint msDBP values.
* indicates statistical significance at 0.05 level.

Summary of msSBP and msDBP in patients reallocated to placebo in the placebo-controlled treatment withdrawal period by visit (withdrawal intent-to-treat population)

		Aliskiren --> Placebo						Ramipril --> Placebo					
		msSBP			msDBP			msSBP			msDBP		
		(N=163)			(N=163)			(N=177)			(N=177)		
Visit	**Statistics**	**Base**	**Post**	**Change**	**Base**	**Post**	**Change**	**Base**	**Post**	**Change**	**Base**	**Post**	**Change**
Week 26	n	163			163			177			177		
	Mean	132.3			85.1			133.6			85.3		
	SD	13.01			7.2			11.79			6.73		
	Median	131.3			85.3			133.3			84.7		
	Minimum	100.7			60			109.3			68.7		
	Maximum	173.3			108			166			104.7		

		Aliskiren --> Placebo						Ramipril --> Placebo					
		msSBP			msDBP			msSBP			msDBP		
		(N=163)			(N=163)			(N=177)			(N=177)		
Visit	Statistics	Base	Post	Change	Base	Post	Change	Base	Post	Change	Base	Post	Change
Week 27	n	162	162	162	162	162	162	177	177	177	177	177	177
	Mean	132.4	137.6	5.2	85	87.5	2.4	133.6	141.6	8	85.3	90	4.6
	SD	13	13.9	10.74	7.22	7.59	6.18	11.79	13.52	11.48	6.73	8.01	7.09
	Median	131.3	135.3	4.8	85.3	87.7	2	133.3	140	6	84.7	90	2.7
	Minimum	100.7	111.3	-23.3	60	61.3	-16	109.3	112.7	-12	68.7	69.3	-12.7
	Maximum	173.3	190	39.3	108	106.7	18	166	184	46.7	104.7	113.3	27.3
Week 28	n	160	160	160	160	160	160	173	173	173	173	173	173
	Mean	131.9	138.7	6.8	85	88	3	133.6	142	8.4	85.3	90	4.7
	SD	12.68	13.93	12.31	7.08	8.62	7.07	11.82	13.41	12.67	6.73	8.25	7.49
	Median	130.7	136.7	6	85.3	87.3	2.2	133.3	141.3	7.3	84.7	90	3.7
	Minimum	100.7	108.7	-24.7	60	62.7	-16	109.3	109.3	-22	68.7	71.3	-12
	Maximum	173.3	184	54.7	108	111.3	22	166	176	54	104.7	110.7	27.3
Week 29	n	154	154	154	154	154	154	172	172	172	172	172	172
	Mean	131.5	140.2	8.7	84.8	88.3	3.5	133.7	142.6	8.8	85.3	90.3	5
	SD	12.45	12.57	11.56	6.98	7.96	7.42	11.81	13.53	13.1	6.75	7.94	7.26
	Median	130.7	138	8	85.3	88	3.3	133.3	141	8	84.7	90	4
	Minimum	100.7	112	-24.7	60	68	-13.3	109.3	110	-28	68.7	63.3	-16.7
	Maximum	173.3	181.3	51.3	108	111.3	24.7	166	176	54.7	104.7	108	26.7
Week 30	n	147	147	147	147	147	147	170	170	170	170	170	170
	Mean	131.1	140.6	9.5	84.7	90.5	5.8	133.6	143.8	10.2	85.3	90.8	5.5
	SD	12.33	14.16	12.96	6.52	7.67	6.99	11.86	14.89	13.51	6.78	8.33	8.3
	Median	130.7	138.7	8.7	85.3	90	5.7	133.3	143	8.3	84.7	90.7	5.3
	Minimum	100.7	110.7	-22.7	66.7	73	-13.3	109.3	110.3	-21.3	68.7	72	-18
	Maximum	173.3	206	64.7	104	110	23.3	166	197.3	56	104.7	113.3	27.3
Week 30 Endpoint	n	163	163	163	163	163	163	177	177	177	177	177	177
	Mean	132.3	142.4	10.1	85.1	91.3	6.2	133.6	144.5	10.9	85.3	91.3	6
	SD	13.01	15.84	13.27	7.2	8.53	7.24	11.79	15.39	13.86	6.73	8.62	8.6
	Median	131.3	139.3	9.3	85.3	90	6	133.3	143.3	8.7	84.7	90.7	5.3
	Minimum	100.7	110.7	-22.7	60	70	-13.3	109.3	110.3	-21.3	68.7	72	-18
	Maximum	173.3	206	64.7	108	111.3	24.7	166	197.3	56	104.7	113.3	27.3

		Aliskiren --> Placebo						Ramipril --> Placebo					
		msSBP			msDBP			msSBP			msDBP		
		(N=163)			(N=163)			(N=177)			(N=177)		
Visit	Statistics	Base	Post	Change	Base	Post	Change	Base	Post	Change	Base	Post	Change

- Base=Withdrawal baseline, Change=Post - Base. Withdrawal baseline is the Week 26 value, and endpoint is the value at the week or LOCF value.
- At each time point, only patients with a value at both baseline and this time point are included

Summary of Safety

Safety Results

Number (%) of patients with serious adverse events (SAEs) in active-controlled treatment period by preferred term (safety population)

	Aliskiren Regimen N=419 n (%)	Ramipril Regimen N=422 n (%)
Any Serious Adverse Events	8 (1.9)	6 (1.4)
Preferred term		
Acute coronary syndrome	1 (0.2)	0 (0.0)
Anaemia	1 (0.2)	0 (0.0)
Angina pectoris	1 (0.2)	0 (0.0)
Angina unstable	1 (0.2)	0 (0.0)
Angioneurotic oedema	1 (0.2)	0 (0.0)
Blood pressure increased	1 (0.2)	0 (0.0)
Cerebrovascular accident	1 (0.2)	1 (0.2)
Cough	1 (0.2)	0 (0.0)
Dehydration	1 (0.2)	0 (0.0)
Laryngeal cancer	1 (0.2)	0 (0.0)
Lung infection	1 (0.2)	0 (0.0)

Nausea	1 (0.2)	0 (0.0)
Productive cough	1 (0.2)	0 (0.0)
Pyrexia	1 (0.2)	0 (0.0)
Staphylococcal infection	1 (0.2)	0 (0.0)
Anxiety	0 (0.0)	1 (0.2)
Nephrolithiasis	0 (0.0)	1 (0.2)
Procedural pain	0 (0.0)	1 (0.2)
Rib fracture	0 (0.0)	1 (0.2)
Syncope	0 (0.0)	1 (0.2)

Preferred terms are sorted by descending frequency, as reported in the Aliskiren Regimen column.
One patient (PID 0042-00018) accounted for 7 of the SAEs noted under the aliskiren regimen. All other SAEs in the aliskiren treatment group were reported in a single patient each.

Number (%) of patients with serious adverse events (SAEs) in placebo-controlled treatment withdrawal period by preferred term (withdrawal safety population)

	Aliskiren Regimen			Ramipril Regimen		
	Aliskiren N=170 n (%)	**Placebo N=163 n (%)**	**Total N=333 n (%)**	**Ramipril N=165 n (%)**	**Placebo N=177 n (%)**	**Total N=342 n (%)**
Any Serious Adverse Events	1 (0.6)	2 (1.2)	3 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
Preferred term						
Anaemia	0 (0.0)	1 (0.6)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Blue toe syndrome	1 (0.6)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Pulmonary embolism	0 (0.0)	1 (0.6)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)

Preferred terms are sorted by descending frequency, as reported in the Aliskiren Total column.
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.

Number (%) of patients with common adverse events (> or = 2% in any treatment group) in active-controlled treatment period by the order of the frequency (safety population)

	Aliskiren Regimen	Ramipril Regimen
	N=419	N=422
	n (%)	n (%)
Any Adverse Events	257 (61.3)	255 (60.4)
Preferred term		
Headache	47 (11.2)	35 (8.3)
Nasopharyngitis	25 (6.0)	26 (6.2)
Dizziness	23 (5.5)	20 (4.7)
Fatigue	18 (4.3)	15 (3.6)
Cough	17 (4.1)	40 (9.5)
Diarrhoea	16 (3.8)	7 (1.7)
Oedema peripheral	16 (3.8)	13 (3.1)
Back pain	15 (3.6)	13 (3.1)
Pain in extremity	15 (3.6)	8 (1.9)
Bronchitis	13 (3.1)	4 (0.9)
Upper respiratory tract infection	12 (2.9)	17 (4.0)
Nausea	11 (2.6)	8 (1.9)
Dyspepsia	10 (2.4)	4 (0.9)
Sinusitis	8 (1.9)	10 (2.4)
Influenza	6 (1.4)	11 (2.6)

Preferred terms are sorted by descending frequency, as reported in the Aliskiren Regimen column.
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.

Number (%) of patients with common adverse events (> or = 2% in any treatment group) in placebo-controlled treatment withdrawal period (withdrawal safety population)

	Aliskiren Regimen			Ramipril Regimen		
	Aliskiren N=170 n (%)	Placebo N=163 n (%)	Total N=333 n (%)	Ramipril N=165 n (%)	Placebo N=177 n (%)	Total N=342 n (%)
Any Adverse Events	38 (22.4)	31 (19.0)	69 (20.7)	49 (29.7)	52 (29.4)	101 (29.5)
Preferred term						
Headache	3 (1.8)	7 (4.3)	10 (3.0)	3 (1.8)	14 (7.9)	17 (5.0)
Upper respiratory tract infection	3 (1.8)	2 (1.2)	5 (1.5)	7 (4.2)	2 (1.1)	9 (2.6)
Nasopharyngitis	2 (1.2)	1 (0.6)	3 (0.9)	8 (4.8)	9 (5.1)	17 (5.0)

Preferred terms are sorted by descending frequency, as reported in the Aliskiren Total column.
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.

Incidence of deaths, serious adverse events, and adverse events and abnormal laboratory values leading to permanent treatment discontinuations in active-controlled treatment period (safety population)

	Aliskiren Regimen N=419 n (%)	Ramipril Regimen* N=422 n (%)
Deaths	0 (0.0)	0 (0.0)**
SAEs	8 (1.9)	6 (1.4)
AE leading to discontinuations	24 (5.7)	20 (4.7)
SAE discontinuations	5 (1.2)	2 (0.5)
Discontinuations for abnormal lab values	2 (0.5)	2 (0.5)

Incidence of deaths, serious adverse events, and adverse events and abnormal laboratory values leading to permanent treatment discontinuations in placebo-controlled treatment withdrawal period (withdrawal safety population)

	Aliskiren Regimen			Ramipril Regimen*		
	Aliskiren N=170 n (%)	Placebo N=163 n (%)	Total N=333 n (%)	Ramipril N=165 n (%)	Placebo N=177 n (%)	Total N=342 n (%)
Deaths	0 (0.0)	1 (0.6)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
SAEs	1 (0.6)	2 (1.2)	3 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
AE leading to discontinuations	0 (0.0)	4 (2.5)	4 (1.2)	1 (0.6)	3 (1.7)	4 (1.2)
SAE discontinuations	0 (0.0)	2 (1.2)	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Discontinuations for abnormal lab values	0 (0.0)	1 (0.6)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)

Date of Clinical Trial Report

15 Dec 2008