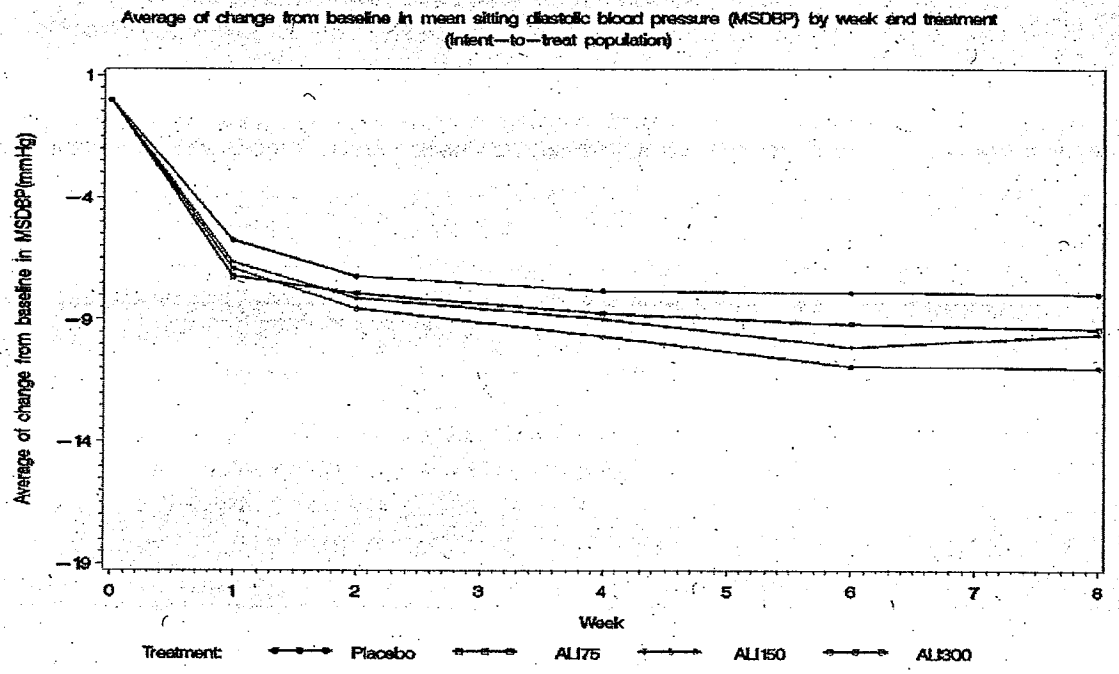
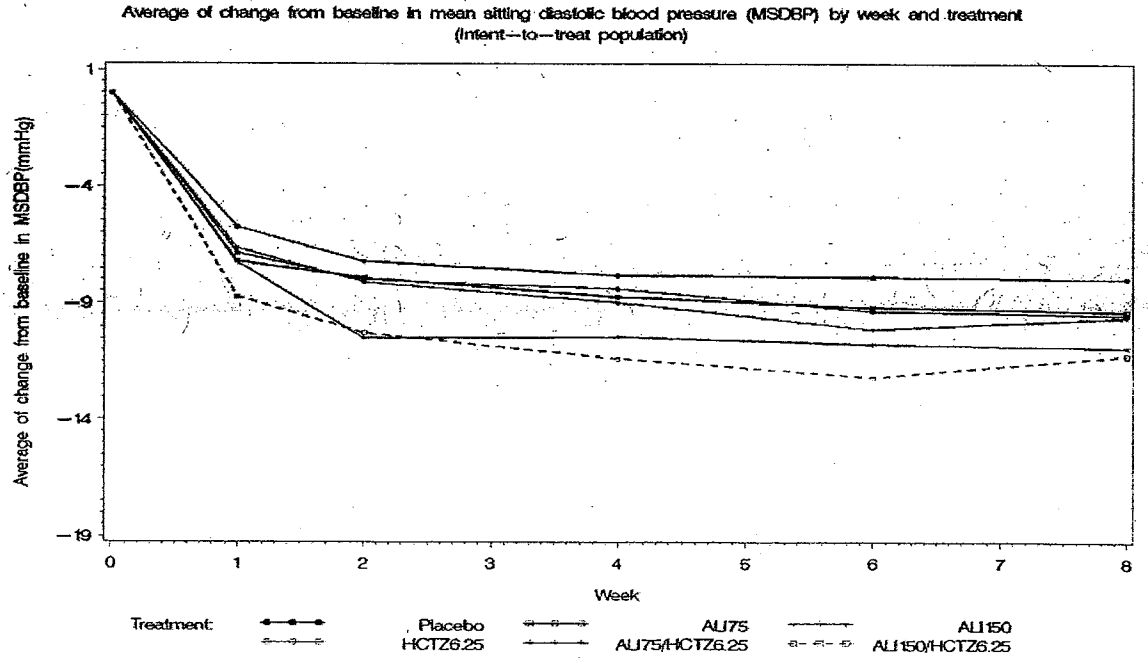
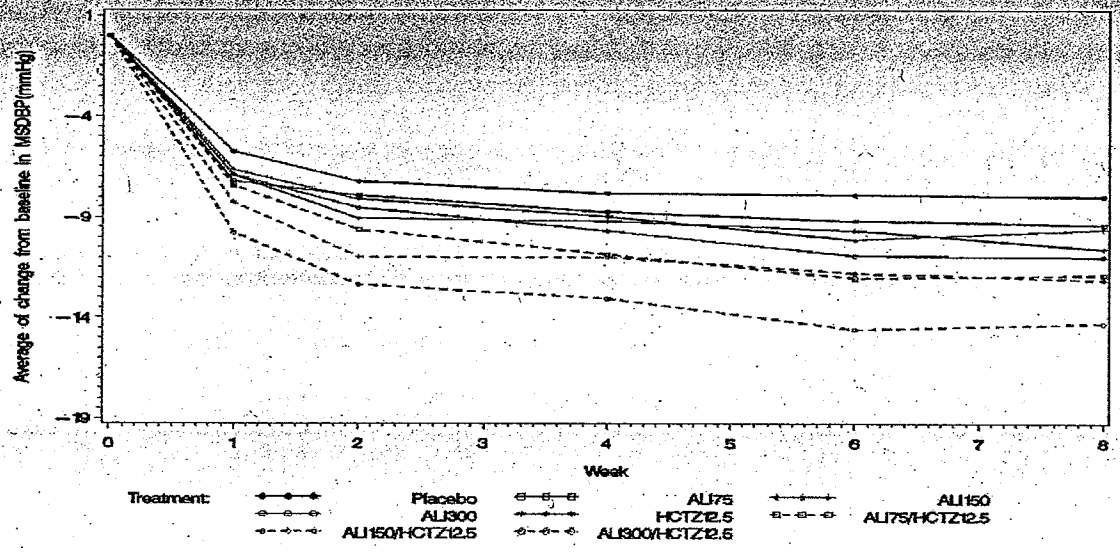
The antihypertensive effect of aliskiren/HCTZ was largely manifested within 1 week after initiating therapy and reach to the maximum effect by 4 weeks of therapy. A typical time course for BP reductions is shown the following Figures 1.

Figure 1:The average of change from baseline in msDBP by time (four figures provided by sponsor).

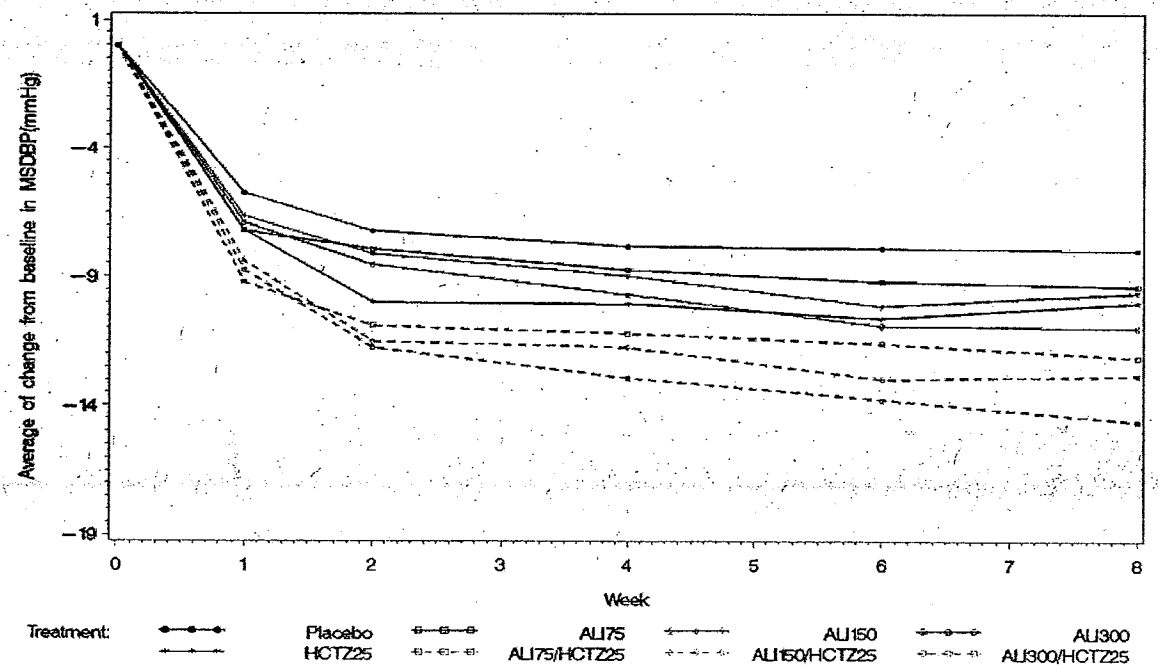




Average of change from baseline in mean sitting diastolic blood pressure (MSDBP) by week and treatment
(Intent–to–treat population)



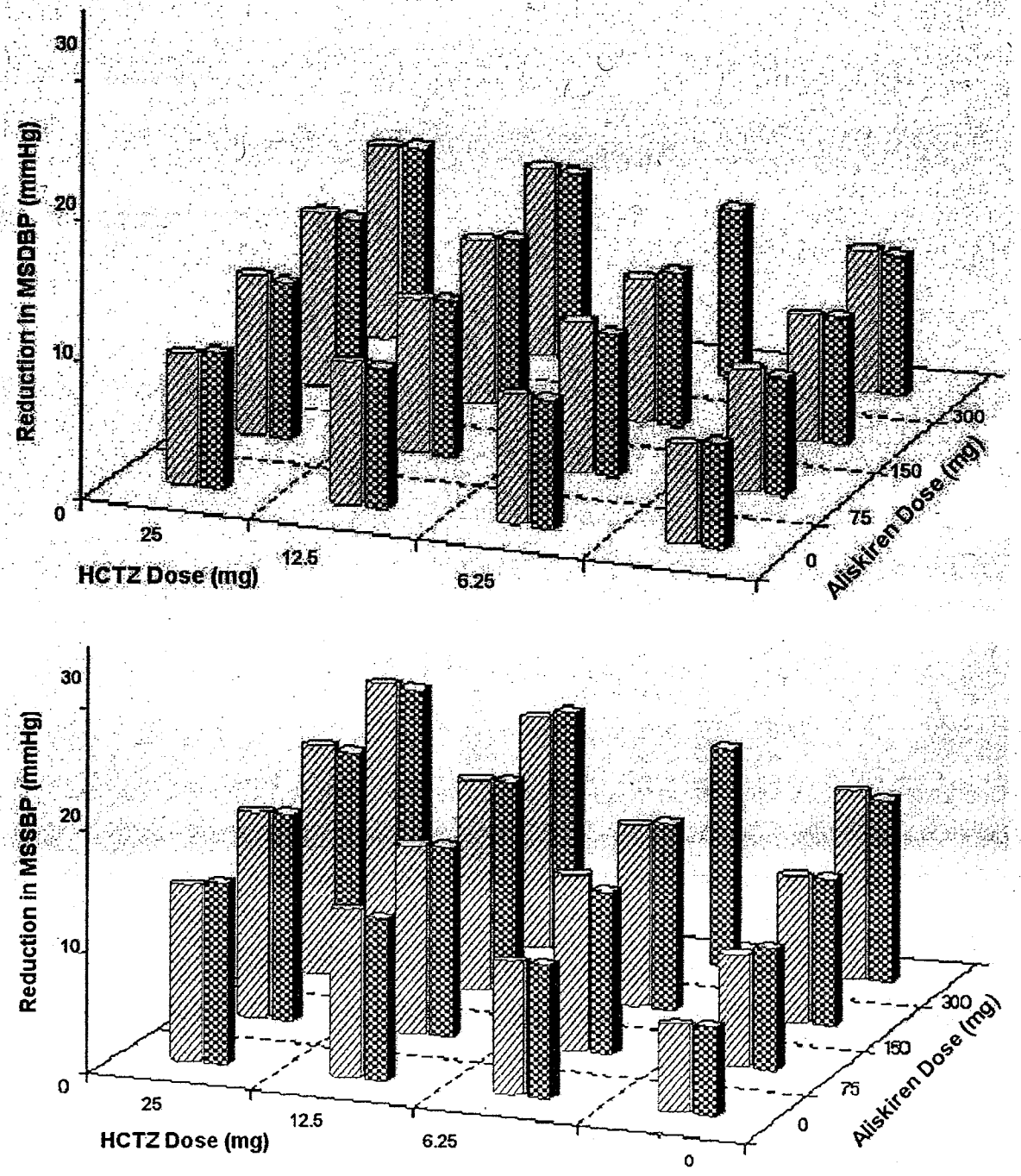
Average of change from baseline in mean sitting diastolic blood pressure (MSDBP) by week and treatment
(Intent–to–treat population)



In the dose-response relationships analysis, the reduction in msDBP was positively related to the dose of both aliskiren and HCTZ as shown graphically in the following Figure 2 (provided by sponsor).

Figure 2: Dose-response surface analysis for change in sitting BP at endpoint

(primary ITT population, study 2204 provided by sponsor, left column = raw mean, right column = prediction from dose-response surface analysis)



For the response rate (defined as DBP < 90 mmHg or fall in DBP ≥ 10 mmHg compared to baseline) and the control rate (defined as DBP < 90 mmHg and SBP < 140 mmHg), all combinations containing aliskiren 150 or 300 mg with HCTZ 12.5 or 25 mg produced statistically greater effects than the corresponding monotherapy, except for the aliskiren/HCTZ 150/12.5 mg. Data were summarized in the following table 7.

Table 7: Responder rates (%) and control rates (%) at endpoint (primary ITT population – Study 2204)

	Responder rates (%) (secondary efficacy variable)			
	Placebo	**75 mg Aliskiren**	**150 mg Aliskiren**	**300 mg Aliskiren**
Placebo	45.8	51.9	51.9	63.9 [a]
HCTZ 6.25 mg	53.6	61.5 [a]	58.4 [a]	-
HCTZ 12.5 mg	60.6 [a]	63.5 [a,b]	69.6 [a,b]	80.6 [a,b,c]
HCTZ 25 mg	59.0 [a]	70.4 [a,b,c]	71.1 [a,b,c]	76.9 [a,b,c]
	Control rates (%) (secondary efficacy variable)			
	Placebo	**75 mg Aliskiren**	**150 mg Aliskiren**	**300 mg Aliskiren**
Placebo	28.1	29.0	38.3	46.7 [a]
HCTZ 6.25 mg	32.5	37.4	41.0 [a]	-
HCTZ 12.5 mg	37.8	42.9 [a,b]	49.5 [a,b,c]	59.4 [a,b,c]
HCTZ 25 mg	37.0	49.5 [a,b,c]	54.0 [a,b,c]	59.5 [a,b,c]

response = msDBP <90 or msDBP ≥10 mm Hg below baseline, control = msDBP <90 and msSBP <140 mm Hg
[a] statistically significant difference vs. placebo (p <0.05)
[b] statistically significant difference vs. aliskiren component (p <0.05)
[c] statistically significant difference vs. HCTZ component (p <0.05)

For the plasma level of renin activity (PRA), aliskiren monotherapy at all doses was associated with PRA reduction while HCTZ monotherapy was associated with PRA increase. All aliskiren/HCTZ combinations showed a decrease in PRA, indicating that the addition of aliskiren prevented the effect of HCTZ to stimulate PRA. Data were summarized in the following table 8.

Table 8: Summary statistics for Plasma Renin Activity by treatment group and visit (ITT population)

PRA	Statistics	Placebo (N=192)	ALI75 (N=183)	ALI150 (N=183)	ALI300 (N=180)
Baseline	n	41	40	42	42
	Mean	0.55	1.29	0.81	1.11
	SD	0.622	2.196	0.972	3.012
	Median	0.40	0.50	0.40	0.20
	Minimum	0.10	0.10	0.10	0.10
	Maximum	3.50	9.80	3.90	17.80
	Geometric Mean*	0.358	0.555	0.441	0.324
	Low 95%CI of Geo mean	0.270	0.379	0.314	0.218
	High 95%CI of Geo mean	0.475	0.811	0.619	0.481
Endpoint	n	41	40	42	42
	Mean	0.68	0.44	0.19	0.25
	SD	1.275	0.696	0.146	0.692
	Median	0.40	0.20	0.10	0.10
	Minimum	0.10	0.10	0.10	0.10
	Maximum	7.80	3.80	0.60	4.60
	Geometric Mean*	0.361	0.254	0.154	0.137
	Low 95%CI of Geo mean	0.265	0.191	0.128	0.112
	High 95%CI of Geo mean	0.492	0.338	0.185	0.169
Change from Baseline	n	41	40	42	42
	Mean	0.13	-0.85	-0.62	-0.87
	SD	1.462	2.289	0.960	2.805
	Median	0.00	-0.20	-0.20	-0.10
	Minimum	-3.30	-9.50	-3.90	-17.70
	Maximum	7.60	3.40	0.20	0.10
	Geometric Mean*	1.037	0.459	0.349	0.424
	Low 95%CI of Geo mean	0.675	0.314	0.252	0.304
	High 95%CI of Geo mean	1.593	0.668	0.485	0.593

PRA	Statistics	HCTZ6.25 (N=194)	HCTZ12.5 (N=188)	HCTZ25 (N=173)	ALI75/HCTZ6.25 (N=187)
Baseline	n	45	45	38	42
	Mean	1.14	0.59	0.65	0.71
	SD	1.402	0.639	0.711	0.593
	Median	0.60	0.40	0.45	0.40
	Minimum	0.10	0.10	0.10	0.10
	Maximum	7.00	3.10	3.80	1.90
	Geometric Mean*	0.646	0.377	0.397	0.461
	Low 95%CI of Geo mean	0.467	0.287	0.286	0.340
	High 95%CI of Geo mean	0.891	0.497	0.552	0.625
Endpoint	n	45	45	38	42
	Mean	1.35	0.72	1.19	0.33
	SD	3.032	0.491	1.787	0.397
	Median	0.70	0.60	0.70	0.10
	Minimum	0.10	0.10	0.10	0.10
	Maximum	20.10	1.90	10.60	2.10
	Geometric Mean*	0.668	0.546	0.683	0.210
	Low 95%CI of Geo mean	0.496	0.431	0.490	0.160
	High 95%CI of Geo mean	0.900	0.693	0.952	0.275
Change from Baseline	n	45	45	38	42
	Mean	0.21	0.13	0.54	-0.38
	SD	2.600	0.709	1.346	0.585
	Median	-0.10	0.10	0.20	-0.20
	Minimum	-6.50	-2.40	-1.10	-1.60
	Maximum	14.20	1.60	6.80	0.90
	Geometric Mean*	1.035	1.447	1.719	0.455
	Low 95%CI of Geo mean	0.765	1.075	1.280	0.340
	High 95%CI of Geo mean	1.399	1.948	2.308	0.611

PRA	Statistics	ALI75/HCTZ12.5 (N=189)	ALI75/HCTZ25 (N=186)	ALI150/HCTZ6.25 (N=173)	ALI150/HCTZ12.5 (N=184)
Baseline	n	40	43	36	42
	Mean	1.03	1.35	0.95	0.92
	SD	1.325	2.804	1.256	1.886
	Median	0.50	0.40	0.45	0.50
	Minimum	0.10	0.10	0.10	0.10
	Maximum	6.70	13.60	5.00	12.30
	Geometric Mean*	0.547	0.523	0.490	0.453
	Low 95%CI of Geo mean	0.384	0.362	0.336	0.325
	High 95%CI of Geo mean	0.780	0.757	0.713	0.633
Endpoint	n	40	43	36	42
	Mean	0.43	0.49	0.27	0.69
	SD	0.482	0.650	0.429	2.206
	Median	0.20	0.20	0.10	0.10
	Minimum	0.10	0.10	0.10	0.10
	Maximum	2.10	2.80	2.60	14.40
	Geometric Mean*	0.267	0.267	0.179	0.228
	Low 95%CI of Geo mean	0.199	0.194	0.138	0.161
	High 95%CI of Geo mean	0.358	0.366	0.231	0.325
Change from Baseline	n	40	43	36	42
	Mean	-0.60	-0.86	-0.67	-0.23
	SD	1.237	2.699	1.291	2.869
	Median	-0.25	-0.10	-0.20	-0.10
	Minimum	-6.20	-12.60	-4.90	-12.20
	Maximum	1.40	0.60	1.30	13.30
	Geometric Mean*	0.487	0.509	0.365	0.504
	Low 95%CI of Geo mean	0.358	0.356	0.251	0.347
	High 95%CI of Geo mean	0.664	0.729	0.529	0.733

PBA	Statistics	ALI150/HCTZ25 (N=187)	ALI300/HCTZ12.5 (N=180)	ALI300/HCTZ25 (N=173)
Baseline	n	36	40	39
	Mean	0.89	0.68	1.52
	SD	0.765	0.720	4.869
	Median	0.70	0.50	0.60
	Minimum	0.10	0.10	0.10
	Maximum	3.20	3.10	30.90
	Geometric Mean*	0.605	0.418	0.597
	Low 95%CI of Geo mean	0.446	0.304	0.426
	High 95%CI of Geo mean	0.821	0.575	0.837
Endpoint	n	36	40	39
	Mean	0.62	0.42	0.34
	SD	0.988	0.880	0.321
	Median	0.30	0.15	0.20
	Minimum	0.10	0.10	0.10
	Maximum	5.60	5.50	1.20
	Geometric Mean*	0.326	0.214	0.225
	Low 95%CI of Geo mean	0.229	0.158	0.170
	High 95%CI of Geo mean	0.465	0.289	0.298
Change from Baseline	n	36	40	39
	Mean	-0.27	-0.26	-1.19
	SD	0.831	1.093	4.813
	Median	-0.20	-0.20	-0.30
	Minimum	-1.80	-2.70	-30.30
	Maximum	2.40	5.00	0.30
	Geometric Mean*	0.539	0.512	0.377
	Low 95%CI of Geo mean	0.394	0.367	0.279
	High 95%CI of Geo mean	0.737	0.714	0.508

* Geometric mean of endpoint/baseline.
Patients with both baseline and endpoint for this biomarker parameter are shown in this table.
/vob/CSPP100A_restricted/CSPP100A2204/report/pgm_eff/t_biogeo.sas - 20SEP2006:16:11:51

6.1.4.2 Long term efficacy

The long-term efficacy was evaluated in Study 100A 2302, Study 100A 2302E1 and Study 100A 2306 as summarized in the following Table 9.

Table 9:Summary of studies providing long-term efficacy data

Study no.	Study objective, population	Patients random. / treated	Treatment duration	Treatments and daily doses (mg)	Primary and key secondary efficacy endpoints
2302	Long-term safety/efficacy in hypertensive patients	1951 / 1955	52 weeks	Aliskiren 150 or 300 with optional addition of HCTZ 2.5 or 25	Change in msDBP, msSBP
2302E1	Extension to long-term safety/efficacy in hypertensive patients	n.a. / 198	16 weeks	Aliskiren 300 with HCTZ 25	Change in msDBP, msSBP
2306	Efficacy/safety in hypertensive patients	842 / 841	26 weeks + 4 weeks withdrawal	Aliskiren 150 or 300 with optional addition of HCTZ 2.5 or 25 Ramipril 5 or 10 with optional addition of HCTZ 2.5 or 25	Change in msDBP, msSBP

In Study 100A 2302, patients were initially randomized to aliskiren 150 or 300 mg. The dose of aliskiren was increased to 300 mg for those patients who initially received 150 mg and did not achieve a target BP < 140/90 mmHg. In both groups, patients who did not respond adequately to aliskiren 300 mg had the optional addition of HCTZ 12.5 mg with optional titration to 25 mg. Study 100A 2302 E1 was a 4-month, open label extension study for a subset of 198 patients who

completed at least eight months of open-label combination therapy with aliskiren 300 mg and HCTZ 25 mg in the Study 100A 2302. The extension was conducted to ensure that an adequate number of patients would be exposed to the combination of aliskiren and HCTZ for at least a full year. From the Study 100A 2302, both combination therapy and monotherapy produced clinically meaningful msDBP and msSBP reduction from baseline after four months treatment and the BP lowering effect was maintained throughout the whole study duration as shown in the following table 10. From the extension study of Study 100A 2302 E1, the BP reductions were generally maintained during the 4 months of the extension as shown in the following tables 11, 12. Since there was no direct comparison between the monotherapy and the fixed dose combination therapy, the data from efficacy aspect in this study is not very compelling.

Table 10: Mean change from baseline in msDBP and msSBP (mm Hg) (long term, open-label) (Study 2302, open-label ITT population)

Open-label		Monotherapy N = 1060			Combo N = 868		
			Change (SD)			Change (SD)	
Visit	Month	N	msDBP	msSBP	N	msDBP	msSBP
4	1	1059	-10.5 (7.8)	-13.6 (12.4)	868	-6.5 (7.1)	-8.9 (12.6)
5	2	990	-12.3 (7.3)	-16.9 (12.2)	866	-6.0 (7.5)	-9.0 (12.4)
6	3	946	-13.9 (7.1)	-19.5 (12.1)	860	-8.6 (7.7)	-12.8 (14.1)
7	4	912	-14.5 (6.6)	-20.1 (11.7)	849	-10.4 (7.8)	-16.4 (14.3)
8	6	901	-14.3 (6.6)	-19.8 (12.1)	832	-11.4 (7.7)	-18.1 (14.7)
9	9	890	-14.7 (6.9)	-19.9 (12.3)	800	-12.6 (7.7)	-20.3 (14.2)
10	11/12	875	-14.7 (7.2)	-19.5 (12.6)	764	-12.8 (7.8)	-19.8 (13.8)
Endpoint		1060	-13.3 (8.5)	-17.4 (14.5)	868	-12.1 (8.4)	-18.7 (14.6)

Note: A decrease in the mean change indicates improvement.
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
Monotherapy = patients never took HCTZ, Combo = patients who took HCTZ at least once

Table 11: Change from baseline in mean sitting diastolic blood pressure during the entire study (All extension population)

			Aliskiren+HCTZ300/25mg		
Visit	Open label month	N*	Baseline (SD)	Mean (SD)	Change (SD)
7	Month 4	198	99.25 (4.9)	89.9 (7.70)	-9.38 (7.9)
8	Month 6	198	99.25 (4.9)	88.3 (7.32)	-10.99 (7.6)
9	Month 9	198	99.25 (4.9)	88.2 (7.74)	-11.01 (7.8)
10	Month 12	198	99.25 (4.9)	88.1 (7.66)	-11.13 (7.8)
15	Month 16	195	99.25 (4.9)	89.0 (8.23)	-10.29 (8.5)
Endpoint**	Month 16	198	99.25 (4.9)	88.9 (8.22)	-10.40 (8.5)

Table 12: Change from baseline in mean sitting systolic blood pressure during the entire study (All extension population)

			Aliskiren+HCTZ300/25mg		
Visit	Open label month	N*	Baseline (SD)	Mean (SD)	Change (SD)
7	Month 4	198	158.99 (11.44)	143.7 (13.42)	-15.25 (14.17)
8	Month 6	198	158.99 (11.44)	141.1 (13.59)	-17.89 (15.50)
9	Month 9	198	158.99 (11.44)	139.6 (13.84)	-19.35 (14.16)
10	Month 12	198	158.99 (11.44)	140.6 (13.98)	-18.41 (13.84)
15	Month 16	195	159.32 (11.17)	142.1 (14.70)	-17.22 (15.37)
Endpoint**	Month 16	198	158.99 (11.44)	141.7 (15.02)	-17.30 (15.27)

Study 100A 2306 was a 26-week, randomized, double-blind, parallel group study comparing aliskiren to ramipril in patients with mild to moderate hypertension. The addition of HCTZ was permitted in patients whose blood pressure was not adequately controlled (msSBP ≥ 140 or msDBP ≥ 90 mm Hg) after at least 12 weeks of monotherapy treatment and also receiving aliskiren 300 mg or ramipril 10 mg. A total of 193 patients (46.1%) in the aliskiren group and 210 patients (49.8 %) in the ramipril group received the addition of HCTZ. In this study, aliskiren with and without HCTZ produced statistically significant superior reductions in both msDBP and msSBP vs. the ramipril-based treatment regimen at the Week 26 endpoint as shown in the following table 13.

Table 13: Mean change from baseline in msDBP and msSBP at Week 26 endpoint in active-controlled treatment period (Study 2306 – ITT population)

Treatment Regimen	N	msDBP change (SE)	msSBPchange (SE)
Aliskiren	414	-13.17 (0.39)*	-17.88 (0.65)*
Ramipril	418	-11.96 (0.38)	-15.24 (0.64)

SE = Standard Error, change = Least Squares Mean change from baseline
* indicates statistical significance at 0.05 level for superiority of aliskiren regimen vs. ramipril regimen

6.1.4.3 Sub-groups of the study population

The subgroups of the study population were examined to search for differences in efficacy (decreases in msDBP and msSBP, responder rate and control rate) related to the age, gender, race/ethnicity or the disease factor of obesity in the multifactorial trial only.

There are similar reductions of BP between ages of <65 years (no children were included) and ≥65 years, gender, and baseline obesity of BMI< 30 kg/m^2 and BMI≥ 30 kg/m^2 after the combined therapy. Data were summarized in the following tables 14-19.

Table 14: Change from baseline to endpoint in msDBP by age group (primary ITT population – Study 2204)

Treatment	N		Baseline mean		Endpoint mean		Change from baseline: Mean		Change from baseline: Placebo subtracted	
	<65	≥65	<65	≥65	<65	≥65	<65	≥65	<65	≥65
msDBP										
Placebo	154	38	99.4	98.7	92.9	89.9	-6.6	-8.7		
Ali 75 mg	137	46	99.6	99.0	91.2	89.1	-8.4	-9.9	-1.9	-1.1
Ali 150 mg	148	35	98.9	98.5	89.8	89.3	-9.1	-9.2	-2.5	-0.5
Ali 300 mg	142	38	99.6	98.4	88.7	89.8	-10.9	-8.6	-4.3	0.1
HCTZ 6.25 mg	140	54	99.6	98.6	90.3	89.6	-9.3	-8.9	-2.7	-0.2
HCTZ 12.5 mg	138	50	99.3	98.5	89.4	87.6	-9.9	-11.0	-3.3	-2.2
HCTZ 25 mg	137	36	99.4	98.2	90.5	86.7	-8.9	-11.5	-2.3	-2.7
Ali/HCTZ 75/6.25 mg	152	35	99.0	98.5	87.8	89.1	-11.2	-9.4	-4.6	-0.7
Ali/HCTZ 75/12.5 mg	162	27	100.0	99.2	88.5	90.0	-11.5	-9.3	-4.9	-0.6
Ali/HCTZ 75/25 mg	147	39	99.2	98.3	88.0	85.3	-11.2	-13.1	-4.6	-4.3
Ali/HCTZ 150/6.25 mg	145	28	99.3	98.2	89.2	85.6	-10.1	-12.6	-3.5	-3.9
Ali/HCTZ 150/12.5 mg	146	38	99.4	97.9	87.7	84.8	-11.7	-13.1	-5.1	-4.4
Ali/HCTZ 150/25 mg	150	37	98.6	98.1	86.0	84.4	-12.6	-13.6	-6.0	-4.9
Ali/HCTZ 300/12.5 mg	133	47	99.9	98.7	85.6	85.5	-14.2	-13.1	-7.7	-4.4
Ali/HCTZ 300/25 mg	138	35	99.5	98.4	85.1	84.2	-14.4	-14.2	-7.8	-5.4

Table 15: Change from baseline to endpoint in msSBP by age group (primary ITT population – Study 2204)

Treatment	N		Baseline mean		Endpoint mean		Change from baseline: Mean		Change from baseline: Placebo subtracted	
	<65	≥65	<65	≥65	<65	≥65	<65	≥65	<65	≥65
msSBP										
Placebo	154	38	151.6	157.0	144.2	151.0	-7.4	-6.0		
Ali 75 mg	137	46	151.0	159.8	141.7	151.1	-9.3	-8.7	-2.0	-2.7
Ali 150 mg	148	35	151.2	163.2	139.6	148.1	-11.6	-15.1	-4.2	-9.1
Ali 300 mg	142	38	153.0	159.4	136.0	147.0	-16.9	-12.4	-9.6	-6.4
HCTZ 6.25 mg	140	54	150.4	161.1	139.8	149.8	-10.6	-11.3	-3.3	-5.3
HCTZ 12.5 mg	138	50	151.6	158.4	137.8	144.8	-13.8	-13.6	-6.4	-7.6
HCTZ 25 mg	137	36	153.0	160.6	139.1	143.7	-13.9	-16.9	-6.5	-10.9
Ali/HCTZ 75/6.25 mg	152	35	153.5	159.2	138.4	147.4	-15.1	-11.8	-7.8	-5.8
Ali/HCTZ 75/12.5 mg	162	27	152.7	160.7	137.5	142.5	-15.2	-18.2	-7.8	-12.2
Ali/HCTZ 75/25 mg	147	39	150.9	160.4	134.1	142.0	-16.7	-18.4	-9.4	-12.4
Ali/HCTZ 150/6.25 mg	145	28	152.5	158.1	137.0	144.3	-15.5	-13.8	-8.1	-7.8
Ali/HCTZ 150/12.5 mg	146	38	153.2	157.7	136.0	138.1	-17.2	-19.6	-9.8	-13.6
Ali/HCTZ 150/25 mg	150	37	151.6	160.4	133.2	137.3	-18.4	-23.1	-11.1	-17.1
Ali/HCTZ 300/12.5 mg	133	47	150.5	161.0	130.4	142.6	-20.1	-18.4	-12.7	-12.4
Ali/HCTZ 300/25 mg	138	35	153.7	158.5	131.2	140.7	-22.4	-17.8	-15.1	-11.8

Table 16: Change from baseline to endpoint in msDBP by gender (primary ITT population – Study2204)

Treatment	N		Baseline mean		Endpoint mean		Change from baseline: Mean		Change from baseline: Placebo subtracted	
	M	F	M	F	M	F	M	F	M	F
msDBP										
Placebo	107	85	99.7	98.8	93.4	90.8	-6.2	-7.9		
Ali 75 mg	102	81	99.7	99.2	91.7	89.4	-8.0	-9.8	-1.8	-1.8
Ali 150 mg	111	72	99.0	98.6	90.7	88.1	-8.2	-10.5	-2.0	-2.5
Ali 300 mg	99	81	99.8	98.8	90.7	86.8	-9.1	-12.1	-2.8	-4.1
HCTZ 6.25 mg	109	85	99.5	99.1	90.8	89.3	-8.6	-9.9	-2.4	-1.9
HCTZ 12.5 mg	103	85	99.5	98.6	90.6	86.9	-9.0	-11.6	-2.7	-3.7
HCTZ 25 mg	90	83	99.5	98.8	91.0	88.3	-8.4	-10.5	-2.2	-2.6
Ali/HCTZ 75/6.25 mg	107	80	99.4	98.2	89.9	85.6	-9.5	-12.6	-3.3	-4.7
Ali/HCTZ 75/12.5 mg	98	91	100.9	98.9	90.3	87.0	-10.6	-11.8	-4.3	-3.9
Ali/HCTZ 75/25 mg	101	85	99.0	99.1	88.3	86.5	-10.8	-12.6	-4.5	-4.6
Ali/HCTZ 150/6.25 mg	95	78	99.4	98.8	90.7	86.0	-8.7	-12.8	-2.4	-4.8
Ali/HCTZ 150/12.5 mg	98	86	99.1	99.1	88.0	86.2	-11.1	-12.9	-4.9	-5.0
Ali/HCTZ 150/25 mg	104	83	99.2	97.5	87.1	84.0	-12.2	-13.5	-5.9	-5.6
Ali/HCTZ 300/12.5 mg	89	91	100.1	99.0	86.9	84.4	-13.2	-14.7	-7.0	-6.7
Ali/HCTZ 300/25 mg	98	75	99.4	99.2	86.2	83.4	-13.2	-15.8	-6.9	-7.9

Table 17: Change from baseline to endpoint in msSBP by gender (primary ITT population – Study 2204)

Treatment	N		Baseline mean		Endpoint mean		Change from baseline			
							Mean		Placebo subtracted	
	M	F	M	F	M	F	M	F	M	F
msSBP										
Placebo	107	85	151.5	154.0	145.4	145.8	-6.1	-8.3		
Ali 75 mg	102	81	153.9	152.4	145.3	142.5	-8.6	-9.9	-2.5	-1.6
Ali 150 mg	111	72	152.8	154.4	142.0	140.0	-10.8	-14.4	-4.7	-6.1
Ali 300 mg	99	81	153.8	154.9	141.3	134.7	-12.5	-20.2	-6.4	-11.9
HCTZ 6.25 mg	109	85	153.1	153.8	143.0	142.0	-10.1	-11.8	-3.9	-3.5
HCTZ 12.5 mg	103	85	153.9	152.9	142.5	136.2	-11.3	-16.7	-5.2	-8.4
HCTZ 25 mg	90	83	154.2	155.1	140.9	139.2	-13.3	-15.9	-7.1	-7.6
Ali/HCTZ 75/6.25 mg	107	80	154.2	154.9	141.6	138.0	-12.7	-16.9	-6.5	-8.6
Ali/HCTZ 75/12.5 mg	98	91	156.2	151.3	140.0	136.2	-16.1	-15.0	-10.0	-6.8
Ali/HCTZ 75/25 mg	101	85	151.3	154.8	135.1	136.6	-16.2	-18.2	-10.0	-9.9
Ali/HCTZ 150/6.25 mg	95	78	152.4	154.7	139.7	136.5	-12.7	-18.2	-6.6	-9.9
Ali/HCTZ 150/12.5 mg	98	86	154.2	154.0	138.7	133.9	-15.5	-20.2	-9.3	-11.9
Ali/HCTZ 150/25 mg	104	83	154.9	151.3	135.6	131.9	-19.3	-19.4	-13.1	-11.1
Ali/HCTZ 300/12.5 mg	89	91	152.2	154.3	133.5	133.8	-18.7	-20.6	-12.6	-12.3
Ali/HCTZ 300/25 mg	98	75	154.3	155.0	133.0	133.3	-21.3	-21.7	-15.2	-13.4

Table 18: Change from baseline for msDBP at endpoint in pooled treatment groups by obesity (Group A: short term, double-blind, placebo controlled studies, ITT population)

Obesity: BMI < 30 (kg/m2)

		Baseline					Endpoint					Change from baseline				
Treatment	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
Placebo	115	99.4	3.84	98.7	90.0	108.7	92.2	9.69	91.3	70.0	120.0	-7.2	8.53	-8.0	-35.0	12.7
Ali 75 mg	105	99.3	3.59	98.3	93.3	108.3	89.4	8.65	90.0	71.7	112.7	-9.9	7.78	-10.3	-28.0	10.0
Ali 150 mg	122	98.6	3.06	98.0	93.3	109.3	89.9	8.72	90.0	70.7	117.3	-8.7	7.56	-8.7	-29.3	16.7
Ali 300 mg	111	99.1	3.01	98.7	95.0	108.7	87.9	9.34	86.3	69.3	118.3	-11.2	8.75	-12.7	-38.0	22.7
HCTZ 6.25 mg	112	99.0	3.69	98.0	92.7	109.3	88.9	8.99	88.7	65.7	116.0	-10.1	8.44	-9.8	-33.7	8.7
HCTZ 12.5 mg	114	99.1	3.53	98.0	93.3	109.0	88.8	9.22	88.7	70.7	118.7	-10.3	8.40	-10.0	-27.3	18.7
HCTZ 25 mg	116	98.8	3.12	98.0	90.0	109.3	89.6	8.93	90.0	71.3	123.3	-9.3	8.21	-9.7	-28.0	18.7
Ali/HCTZ 75/6.25 mg	115	98.5	3.36	97.7	86.7	108.0	87.4	8.04	86.7	70.0	110.0	-11.2	8.07	-10.3	-34.0	11.3
Ali/HCTZ 75/12.5 mg	114	99.8	3.73	99.3	93.3	110.0	88.7	8.53	87.5	67.3	125.7	-11.1	7.76	-11.5	-29.3	27.7
Ali/HCTZ 75/25 mg	114	98.6	3.18	98.0	92.7	109.7	85.7	8.00	85.2	66.7	109.3	-12.9	7.55	-14.0	-29.3	9.0
Ali/HCTZ 150/6.25 mg	106	99.1	3.48	98.3	92.7	108.7	88.4	9.88	88.3	62.7	122.0	-10.7	8.56	-10.7	-35.3	16.7
Ali/HCTZ 150/12.5 mg	118	99.0	3.44	98.3	92.7	109.3	86.4	7.47	85.2	60.0	107.0	-12.6	6.85	-12.7	-36.0	5.7
Ali/HCTZ 150/25 mg	117	98.3	4.00	97.3	76.7	109.3	85.2	7.95	86.7	55.0	104.7	-13.2	7.82	-12.7	-41.7	1.3
Ali/HCTZ 300/12.5 mg	103	99.5	3.84	98.3	92.0	109.3	85.9	7.94	84.7	70.0	111.0	-13.6	6.71	-13.3	-26.7	5.7
Ali/HCTZ 300/25 mg	100	98.9	3.16	98.5	91.7	108.0	83.5	8.33	82.0	64.0	106.7	-15.5	7.90	-16.0	-39.3	6.0

Obesity: BMI >=30 (kg/m2)

		Baseline					Endpoint					Change from baseline				
Treatment	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
Placebo	77	99.1	3.50	98.7	91.7	109.3	92.4	8.62	92.0	76.7	117.3	-6.8	7.64	-7.3	-22.0	11.3
Ali 75 mg	76	99.7	3.93	98.7	93.3	109.3	92.4	9.52	91.7	70.0	116.0	-7.3	7.87	-7.3	-27.3	18.0
Ali 150 mg	60	99.2	2.97	98.7	95.0	107.0	89.2	9.32	90.7	69.3	118.7	-10.0	8.47	-10.0	-28.0	14.0
Ali 300 mg	69	99.8	3.34	99.3	95.0	109.3	90.7	8.89	88.7	70.7	111.3	-9.2	8.41	-11.3	-26.0	11.3
HCTZ 6.25 mg	80	99.8	3.38	99.3	93.3	109.3	92.1	9.20	90.7	73.3	121.3	-7.7	8.57	-8.0	-29.7	16.0
HCTZ 12.5 mg	73	99.0	3.37	98.7	95.0	107.7	89.3	8.91	89.3	69.3	113.3	-9.8	8.24	-9.3	-29.3	10.0
HCTZ 25 mg	57	99.7	3.44	99.3	95.3	108.0	90.0	8.06	90.0	63.0	110.0	-9.7	7.97	-10.0	-37.3	4.0
Ali/HCTZ 75/6.25 mg	71	99.4	3.81	99.3	84.0	108.7	89.1	9.38	90.0	70.0	111.3	-10.4	8.79	-10.0	-28.3	6.0
Ali/HCTZ 75/12.5 mg	75	100.1	3.53	99.7	94.0	109.7	88.7	9.08	89.3	68.0	116.0	-11.3	8.21	-10.7	-33.3	14.0
Ali/HCTZ 75/25 mg	72	99.8	4.32	99.2	88.7	109.0	90.2	9.46	89.7	69.3	114.7	-9.6	7.99	-10.2	-26.7	12.7
Ali/HCTZ 150/6.25 mg	66	99.2	3.70	98.7	90.0	108.0	88.7	9.61	88.8	68.7	113.3	-10.4	8.69	-10.0	-35.3	9.3
Ali/HCTZ 150/12.5 mg	65	99.1	3.27	98.0	94.7	108.0	88.3	8.53	87.3	64.7	108.7	-10.8	8.16	-10.7	-36.0	5.0
Ali/HCTZ 150/25 mg	70	98.7	3.95	98.7	77.7	107.3	86.6	7.91	87.3	65.3	108.0	-12.1	6.82	-12.2	-25.3	4.0
Ali/HCTZ 300/12.5 mg	76	99.6	3.40	99.3	95.0	109.3	85.2	9.45	84.3	68.0	114.7	-14.5	8.96	-15.3	-37.3	12.7
Ali/HCTZ 300/25 mg	71	99.7	3.39	99.3	95.0	108.0	86.9	9.15	87.3	62.7	121.7	-12.8	8.19	-13.3	-36.7	13.7

Table 19: Change from baseline for msSBP at endpoint in pooled treatment groups by obesity (Group A: short term, double-blind, placebo controlled studies, ITT population)

Obesity: BMI < 30 (kg/m2)

	Baseline					Endpoint					Change from baseline				
Treatment	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
Placebo	115	153.7	12.03	153.3	123.3	180.7	145.8	15.82	142.7	119.3	209.3	-7.9	13.75	-8.0	-46.7	51.3
Ali 75 mg	105	153.0	12.31	153.7	126.7	177.3	144.1	16.87	140.0	105.7	203.7	-8.9	13.20	-10.0	-35.3	26.3
Ali 150 mg	122	153.0	12.29	152.7	122.0	175.7	141.8	15.92	138.5	111.3	193.0	-11.2	13.90	-11.2	-42.0	33.3
Ali 300 mg	111	154.6	10.68	154.0	129.3	177.0	136.8	14.75	134.3	109.7	188.7	-17.9	12.72	-18.3	-47.0	14.7
HCTZ 6.25 mg	112	154.5	11.60	154.3	131.7	178.3	142.3	14.90	141.5	115.3	190.0	-12.2	13.69	-11.0	-51.3	24.0
HCTZ 12.5 mg	114	153.3	11.61	152.8	116.0	178.7	138.6	14.12	138.7	108.0	192.7	-14.7	12.02	-15.5	-44.3	15.3
HCTZ 25 mg	116	155.0	12.81	156.7	118.3	178.7	141.8	15.29	140.0	110.7	193.7	-13.3	13.16	-12.3	-45.0	19.0
Ali/HCTZ 75/6.25 mg	115	153.7	11.90	152.0	129.3	179.3	139.2	15.55	138.0	110.7	193.3	-14.5	14.96	-15.7	-56.7	34.0
Ali/HCTZ 75/12.5 mg	114	154.9	12.16	156.7	124.0	177.3	138.7	14.46	138.5	109.3	177.7	-16.3	13.07	-16.7	-54.3	17.3
Ali/HCTZ 75/25 mg	114	152.3	12.58	153.3	128.0	178.7	135.0	15.51	132.7	108.0	198.3	-17.3	14.41	-17.8	-48.0	38.7
Ali/HCTZ 150/6.25 mg	106	153.5	12.52	151.8	120.0	179.3	138.4	15.85	137.0	101.3	192.0	-15.1	13.14	-16.7	-44.3	30.3
Ali/HCTZ 150/12.5 mg	118	154.8	12.93	155.3	122.0	197.7	136.8	15.34	135.5	106.7	181.3	-18.0	13.25	-15.5	-56.0	7.3
Ali/HCTZ 150/25 mg	117	153.0	12.36	153.3	110.0	174.7	132.9	13.15	133.3	96.0	166.7	-20.1	12.55	-20.7	-55.7	17.3
Ali/HCTZ 300/12.5 mg	103	152.0	12.06	152.7	118.7	176.7	132.2	14.54	130.7	104.7	173.0	-19.8	12.82	-21.3	-58.7	10.0
Ali/HCTZ 300/25 mg	100	154.3	12.49	156.5	130.0	178.3	132.2	15.74	132.8	93.3	205.3	-22.1	14.70	-23.3	-61.3	44.0

Obesity: BMI >=30 (kg/m2)

	Baseline					Endpoint					Change from baseline				
Treatment	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
Placebo	77	151.0	11.04	150.0	123.7	179.7	145.1	15.80	141.3	109.3	205.7	-5.9	12.74	-7.3	-29.3	33.0
Ali 75 mg	76	153.5	13.14	151.7	129.3	176.0	143.9	16.58	143.3	108.7	184.7	-9.6	11.94	-10.0	-40.0	24.0
Ali 150 mg	60	154.5	13.57	152.2	120.7	178.7	140.0	14.48	139.0	116.0	184.7	-14.6	12.23	-12.7	-38.7	6.0
Ali 300 mg	69	153.8	11.29	153.3	132.0	178.7	140.9	16.54	138.3	108.7	196.0	-12.9	15.60	-14.3	-58.3	26.0
HCTZ 6.25 mg	80	152.2	13.79	152.0	123.3	179.0	143.5	14.40	141.3	117.3	180.7	-8.7	12.24	-8.7	-51.7	19.3
HCTZ 12.5 mg	73	153.5	11.69	152.7	121.7	177.3	141.2	16.73	141.3	108.0	196.7	-12.3	14.76	-14.0	-54.7	19.3
HCTZ 25 mg	57	153.7	10.62	151.3	134.7	179.3	136.7	9.99	136.0	117.3	171.3	-17.0	11.63	-15.3	-47.3	8.7
Ali/HCTZ 75/6.25 mg	71	156.0	12.35	156.0	130.7	179.3	141.6	15.15	140.0	112.0	202.7	-14.4	14.36	-15.7	-42.7	26.7
Ali/HCTZ 75/12.5 mg	75	152.1	12.47	151.7	118.7	178.7	137.5	13.20	137.3	108.7	175.3	-14.6	13.67	-13.3	-47.7	35.3
Ali/HCTZ 75/25 mg	72	153.7	12.82	154.5	130.0	177.7	137.0	14.76	137.3	107.3	178.0	-16.7	13.31	-18.3	-47.7	20.0
Ali/HCTZ 150/6.25 mg	66	153.2	11.51	153.0	128.3	177.3	137.9	15.35	138.5	103.3	178.3	-15.3	13.28	-14.0	-56.7	11.3
Ali/HCTZ 150/12.5 mg	65	152.7	11.93	152.7	130.0	176.7	136.0	13.93	137.3	106.7	168.7	-16.7	11.32	-19.3	-45.3	11.3
Ali/HCTZ 150/25 mg	70	153.9	12.55	153.3	110.0	176.0	135.8	13.95	133.2	112.0	178.0	-18.1	12.18	-17.7	-44.7	8.7
Ali/HCTZ 300/12.5 mg	76	155.0	10.81	154.3	130.0	177.3	135.5	16.51	133.0	109.3	185.3	-19.5	13.82	-21.7	-44.7	29.3
Ali/HCTZ 300/25 mg	71	155.0	12.95	154.0	129.3	178.0	134.5	15.34	133.3	107.3	182.7	-20.5	14.75	-20.0	-60.0	13.3

Due to the paucity of non-Caucasian patients in the studies, the subgroup analysis for race/ethnicity (Caucasian, Black, Asian, Native American, Pacific Islander, and Other) was not performed. Comparisons of BP reduction in both Caucasian and Black patients with the combination of aliskiren/HCTZ to the component monotherapies were shown in the following table 20. In the table, due to the inadequate number of Black patients, an analysis was not performed. A significantly additional BP reduction in the Black patients with the combination therapy, compared to the component monotherapies, was not observed.

Table 20: Changes from baseline to endpoint in msDBP and msSBP in aliskiren, HCTZ, and the combination groups by race in Study 2204

	msDBP (mm Hg)				msSBP (mm Hg)			
	Black		Caucasian		Black		Caucasian	
	N	Mean change	N	Mean change	N	Mean change	N	Mean change
Placebo	7	-0.7	161	-7.2	7	8.3	161	-7.7
Ali 75 mg	9	-3.1	153	-8.7	9	-2.0	153	-8.9
Ali 150 mg	11	-6.6	155	-9.1	11	-10.5	155	-12.3
Ali 300 mg	6	-7.8	154	-10.2	6	-10.8	154	-15.2
HCTZ 6.25 mg	13	-10.7	161	-9.0	13	-14.1	161	-10.8
HCTZ 12.5 mg	9	-9.0	160	-10.2	9	-10.7	160	-13.7
HCTZ 25 mg	9	-5.6	153	-9.4	9	-7.6	153	-14.4
Ali/HCTZ 75/6.25 mg	5	-3.7	164	-11.5	5	-1.1	164	-15.7
Ali/HCTZ 75/12.5 mg	12	-15.7	161	-11.0	12	-15.8	161	-15.7
Ali/HCTZ 75/25 mg	5	-4.5	165	-12.1	5	-12.1	165	-17.7
Ali/HCTZ 150/6.25	8	-3.9	146	-10.4	8	-9.6	146	-14.8
Ali/HCTZ 150/12.5	10	-14.2	157	-11.7	10	-18.6	157	-17.5
Ali/HCTZ 150/25	5	-9.3	162	-13.1	5	-9.6	162	-19.8
Ali/HCTZ 300/12.5 mg	10	-15.3	152	-13.8	10	-16.8	152	-20.0
Ali/HCTZ 300/25 mg	7	-10.6	149	-13.9	7	-18.2	149	-20.3

6.1.4.4 Other supportive trials or Data

Two short term active-controlled studies (Study 2303, 2309) using aliskiren/HCTZ combinations were conducted as summarized in the following table 21.

Table 21: Summary of two active-controlled studies

Study no.	Study objective, population	Patients random. / treated	Treatment duration	Treatments and daily doses (mg)	Primary efficacy endpoint
2309	Efficacy/safety in obese (BMI ≥30) hypertensive patients not responsive to HCTZ 25 mg	493* / 493	12 weeks	Aliskiren 150 or 300 with HCTZ 25 Irbesartan 150 or 300 with HCTZ 25 Amlodipine 5 or 10 with HCTZ 25 HCTZ 25	Change in msDBP
2303	Safety/Efficacy in uncomplicated severe hypertension patients	183 / 183	8 weeks	Aliskiren 150 titrated to 300 with optional addition of HCTZ 25 Lisinopril 20 titrated to 40 with optional addition of HCTZ 25	Change in msDBP and msSBP

* includes 4 patients in the safety analysis, which have been excluded from the efficacy analysis

Study 2309 was a 12-week, randomized, double-blind, parallel group study evaluating the efficacy and safety of the combination of aliskiren with HCTZ compared to irbesartan or amlodipine with HCTZ or HCTZ alone in hypertensive patients with BMI ≥30 kg/m^2 not adequately responsive to HCTZ 25 mg monotherapy. After 4-week treatment with HCTZ 25 mg, patients who were not adequately responsive (msDBP ≥90 and <110 mmHg) were randomized to one of the 4 treatment groups: HCTZ 25 mg monotherapy, combination therapies of aliskiren/HCTZ 150/25 mg, irbesartan/HCTZ 150 /25 mg or amlodipine/HCTZ 5/25 mg for the

initial 4 weeks. The doses in the combination groups were force-titrated to aliskiren/HCTZ 300/25 mg, irbesartan/HCTZ 300/25 mg or amlodipine/HCTZ 10/25 mg for another 8 weeks. The total duration of the double-blind treatment was 12 weeks. The primary efficacy variable was change from baseline in msDBP at Week 8 endpoint. Aliskiren/HCTZ 300/25 mg produced a statistically significant reduction in msDBP and msSBP compared to HCTZ 25 mg alone ($p<0.0001$) at the Week 8 endpoint. Similar results were found after both 4 and 12 weeks of treatment. The reductions from baseline to Week 8 in msDBP and msSBP with aliskiren/HCTZ were not statistically different from irbesartan/HCTZ or amlodipine/HCTZ as shown the table 22.

Table 22: Mean change in sitting BP at Week 8 endpoint (ITT population – Study 2309)

Change in msDBP (mmHg) (primary efficacy variable)		
Treatment (mg):	**N**	**LSM change from baseline (SE)**
Aliskiren/HCTZ 300/25	113	-11.91 (0.74)
Irbesartan/HCTZ 300/25	117	-11.33 (0.72)
Amlodipine/HCTZ 10/25	122	-10.30 (0.71)
HCTZ 25	117	-7.89 (0.73)
Pairwise Comparison:		**P-Value**
Ali/HCTZ 300/25 vs. HCTZ 25		<0.0001
Ali/HCTZ 300/25 vs. Irb/HCTZ 300/25		0.5757
Ali/HCTZ 300/25 vs. Amlo/HCTZ 10/25		0.1135
Change in msSBP (mmHg) (key secondary efficacy variable)		
Treatment (mg):	**N**	**LSM change from baseline (SE)**
Aliskiren/HCTZ 300/25	113	-15.79 (1.01)
Irbesartan/HCTZ 300/25	117	-15.44 (1.00)
Amlodipine/HCTZ 10/25	122	-13.55 (0.98)
HCTZ 25	117	-8.62 (1.00)
Pairwise Comparison:		**P-Value**
Ali/HCTZ 300/25 vs. HCTZ 25		<0.0001
Ali/HCTZ 300/25 vs. Irb/HCTZ 300/25		0.8006
Ali/HCTZ 300/25 vs. Amlo/HCTZ 10/25		0.1071

msDBP/msSBP = mean sitting diastolic/systolic BP, SE = standard error, LSM = Least Square Mean,
Ali = aliskiren, Irb = irbesartan, Amlo = amlodipine
P-values and treatment comparisons derived from ANCOVA model with treatment, region, centered baseline

Study 2303 was an 8-week, randomized, double-blind, parallel group, multicenter study to evaluate the safety and efficacy of aliskiren with optional addition of HCTZ compared to lisinopril with optional addition of HCTZ in patients with uncomplicated severe hypertension. Both treatment regimens showed clinically significant reductions in msDBP and msSBP at all time points. The reductions at endpoint were comparable for the two treatment regimens and the proportion of responders was very similar. Data were summarized in the following tables 23 and 24.

Table 23: Changes from baseline in mean sitting diastolic blood pressure (msDBP, mmHg) at double blind visit by randomized treatment group in Study CSPP100A2303 (ITT population)

		Aliskiren regimen		Lisinopril regimen	
Visit	Day	N*	Mean (SD)	N*	Mean (SD)
3	1	124		58	
4	7	124	-10.1 (8.6)	58	-11.0 (8.6)
5	14	123	-13.3 (8.6)	58	-15.0 (10.2)
6	28	118	-16.1 (9.2)	57	-17.7 (9.8)
7	42	115	-19.4 (8.7)	56	-18.5 (9.2)
8	56	113	-19.1 (8.4)	54	-20.0 (8.0)
Endpoint**		124	-18.5 (8.7)	58	-20.1 (7.9)

(*) N is the number of patients with values at both baseline and post-baseline visit.
(**) Endpoint is Day 56, or last visit carried forward.
Note: A decrease in the mean change indicates improvement

Table 24: Changes from baseline in mean sitting systolic blood pressure (msSBP, mmHg) at double-blind visit by randomized treatment group in Study 2303 (ITT population)

		Aliskiren regimen		Lisinopril regimen	
Visit	Day	N*	Mean (SD)	N*	Mean (SD)
3	1	124		58	
4	7	124	-8.2 (13.3)	58	-10.9 (13.3)
5	14	123	-12.5 (13.7)	58	-13.4 (15.3)
6	28	118	-15.7 (15.1)	57	-18.7 (15.0)
7	42	115	-20.0 (13.7)	56	-20.2 (14.2)
8	56	113	-21.2 (15.0)	54	-23.0 (14.6)
Endpoint**		124	-20.0 (15.3)	58	-22.3 (14.6)

(*) N is the number of patients with values at both baseline and post-baseline visit.
(**) Endpoint is Day 56, or last visit carried forward.
Note: A decrease in the mean change indicates improvement

A pooled analysis of efficacy data was not performed due to the differences in study design, patient, characteristics and length of treatment.

6.1.5 Clinical Microbiology

Clinical microbiology is not applicable for this oral formulation.

6.1.6 Efficacy Conclusions

Based on the pivotal study, the combination of aliskiren/HCTZ generally produced clinically and statistically significant reductions in both diastolic and systolic blood pressure compared to placebo and each respective monotherapy in the studied dose ranges of aliskiren doses of 150 mg or 300 mg in combination with HCTZ 12.5 mg or 25 mg. The antihypertensive effect of aliskiren/HCTZ was largely manifested within 1 week after initiating therapy. The maximum antihypertensive effect was generally attained after 4 weeks of therapy. In addition, when administered in combination with HCTZ, aliskiren is able to prevent the PRA increase caused by

HCTZ treatment. In the other support clinical trials, an aliskiren based regimen (with optional addition of HCTZ) produced clinically significant reductions in both diastolic and systolic blood pressure in patients with severe hypertension.

In the subgroup analysis, the combination of aliskiren/HCTZ was effective regardless of gender, age, and disease factor of obesity. Regarding the race/ethnicity, however, due to the paucity of non-Caucasian patients in the studies, the subgroup analysis for race/ethnicity (Caucasian, Black, Asian, Native American, Pacific Islander, and Other) was not performed. From the sponsor provided data with black patients (table 18), significantly additional BP reduction in the Black patients with the combination therapy compared to the component monotherapies was not clear.

b(4)

7 Integrated Review of Safety

7.1 Methods and Findings

The data sources for supporting the safety claims of this combination product in the original submission were from the three short-term controlled trials (1 placebo-controlled: Study 2204, 2 active-controlled: Studies 2203, 2309), 1 long-term active-controlled trial (study 2306), and 1 uncontrolled, long-term study and its extension in the target populations (Study 2202 and 2202E1). Studies were summarized in the following tables 25, and 26. In addition, a short-term placebo controlled study (study 2331) was provided later as a 120-day safety update.

Table 25:Summary of short term placebo controlled and active controlled studies

Study no.	Study objective, population	Total number of randomized/ treated patients	Treatment duration	Treatments and daily doses (mg)
Placebo-controlled studies				
CSPP100A 2204	Efficacy/safety in hypertensive patients	2776/2762	8 weeks	Aliskiren 75, 150, or 300 HCTZ 6.25, 12.5 mg, or 25 Aliskiren 75 with HCTZ 6.25, 12.5, or 25 Aliskiren 150 with HCTZ 6.25, 12.5, or 25 Aliskiren 300 with HCTZ 12.5 or 25 Placebo
Active-controlled studies				
CSPP100A 2309	Efficacy/safety in obese hypertensive patients	493*/493	12 weeks	Aliskiren 150 or 300 with HCTZ 25 Irbesartan 150 or 300 with HCTZ 25 Amlodipine 5 or 10 with HCTZ 25 HCTZ 25
CSPP100A 2303	Safety/efficacy in uncomplicated severe hypertensive patients	183/183	8 weeks	Aliskiren 150 titrated to 300 with optional addition of HCTZ 25 Lisinopril 20 titrated to 40 with optional addition of HCTZ 25

Table 26: Summary of studies providing long-term safety data

Study no.	Study objective, population	Total number of randomized/ treated patients	Treatment duration	Treatment and daily doses (mg)
Open-label, long-term trials				
CSPP100A 2302	Long-term efficacy/safety in hypertensive patients	1951/1955	52 weeks; last 4 weeks comprised blinded withdrawal period	Aliskiren 150 or 300 mg with optional addition of HCTZ 12.5 or 25
CSPP100A 2302E1	Long-term safety in hypertensive patients	NA/198	4-month extension to 12-month core study	Aliskiren 300 mg with HCTZ 25
Double-blind, long-term trials				
CSPP100A 2306	Efficacy/safety in essential hypertension patients	842/841	26 weeks + 4 weeks withdrawal	Aliskiren 150 or 300 with optional addition of HCTZ 12.5 or 25 Ramipril 5 or 10 with optional addition of HCTZ 12.5 or 25

7.1.1 Deaths

Overall, 12 deaths occurred during or after completed studies which contained the treatment of aliskiren in combination with HCTZ (Table 27). Two patients are known to have taken aliskiren/HCTZ at any time, five patients were treated with aliskiren monotherapy, one patient was treated with HCTZ monotherapy, and one patient was treated with valsartan/HCTZ. The remaining cases involved patients treated with active comparators or placebo/no treatment. Most deaths were related to cardiovascular or cerebrovascular events, as would be expected in an older hypertensive population. The causes of death were similar in all groups, and the rate was not higher in patients treated with aliskiren/HCTZ compared with component monotherapies, active comparators, or placebo.

1. Patient 1 died in Study 2204. This 74 year old male Caucasian patient was diagnosed with hypertension one year prior to entering the study. The patient had no other relevant medical history and was not on any concomitant medications at the time of the adverse event. Baseline ECG was normal. He was in the aliskiren/HCTZ 150/25 mg group. [redacted] of the double-blind study period, the patient died due to a traffic accident. According to the investigator, the patient did not have a recent history of syncope, hypotension or other cardiac conditions. The autopsy result indicated thoracic trauma. b(6)

2. Patient 2 died in Study 2302. This 74 year old Caucasian male patient was diagnosed with hypertension 15 years prior to entering the study. There was no other significant medical history recorded for this patient. The patient was not on any concomitant medications during the study. He was randomized into the open label phase of the study, and began study medication (Aliskiren 150 mg) on 5 October 2004. On [redacted] the patient experienced an abdominal aortic aneurysm rupture and was subsequently admitted to the hospital. The study medication was stopped. On [redacted] the patient died. b(6)

3. Patient 3 died in Study 2302. This 61 year old female Caucasian patient was diagnosed with hypertension 5 years prior to entering the study. The patient's other significant medical history included vertigo, menopause and intermittent pain in the left side of the abdomen since 2003. The concomitant medication taken during the study included pantaprazole and penicillin. This patient was randomized into the open label phase of the study, and began study medication (Aliskiren 150 mg) on 30 August 2004. She was subsequently up titrated to aliskiren 300 mg on 25 October 2004. On [redacted] the patient was found dead in her bed and "arrived dead at hospital". No autopsy was performed. There were no notable laboratory abnormalities detected. b(6)

4. Patient 4 died in Study 2302. This 79 year old female Caucasian patient was diagnosed with hypertension 2 years prior to entering the study. The patient's other significant medical history included an appendectomy, mastectomy (right), gonarthrosis, hyperlipidemia, acute cystitis and varicose veins. Concomitant medications taken during the study included cotrim forte, diclofenac and troxerutan. This patient was randomized into the open label phase of the study, and began study medication (Aliskiren 300 mg) on 25 June 2004. [redacted], the patient experienced an acute myocardial infarction, and subsequently died. b(6)

5. Patient 5 died in Study 2302. This 77 year old male patient was diagnosed with hypertension 27 years prior to entering the study. There was no other significant medical history recorded for this patient. Concomitant medications taken during the study included mannitol, dexamethasone, ranitidine and nimodipine. The patient was randomized into the open label phase of the study, and began study medication (Aliskiren 150 mg) on 01 September 2004. He was subsequently up titrated to Aliskiren 300 mg on 01 December 2004. [redacted] the patient presented with dizziness, headache, confusion and hypertension. He was subsequently admitted to the stroke trauma unit, where he was diagnosed with a cerebrovascular accident. The study drug was permanently discontinued. [redacted] a computerized tomography scan showed an intracerebral hemorrhage in the posterior fossa and hydrocephalus. On [redacted] the patient died. b(6)

6. Patient 6 died in Study 2302. This 57 year old male Caucasian patient had a significant medical history of hypertension (unknown duration), tobacco abuse, coronary artery disease, peripheral vascular disease and erectile dysfunction. Concomitant medications taken during the study included rosuvastin calcium, acetylsalicylic acid and sildenafil citrate. The patient was randomized into the open label phase of the study and began medication (Aliskiren 300mg) on 08 September 2004. HCTZ 12.5 mg was added from 02 December 2004 to 05 January 2005. Starting on 06 January 2005, HCTZ 25 mg was added to Aliskiren 300mg until 12 July 2005. On [redacted] of the open label study period, the patient died at his home. An autopsy showed hypertensive atherosclerotic cardiovascular disease. b(6)

7. Patient 7 died in Study 2306. This is a 57 year-old Caucasian male with a significant medical history including ischemic heart disease with coronary bypass surgery in 1981 and a smoking history of 34 years, collapsed and was unable to breathe on Day 18 of the placebo-controlled treatment withdrawal period and Day 198 of the double-blind treatment phase. The patient had completed the active-controlled treatment period with aliskiren 300 mg/day and had been

re-randomized to placebo. The investigator was subsequently informed that the cause of death was either a massive pulmonary embolism or myocardial infarction.

8. Patient 8 died in Study 2306. This is a 53- year-old Caucasian male in the ramipril regimen with a 21- year history of essential hypertension and relevant medical history and risk factors including dyslipidemia and a smoking history of 30 years, experienced a stroke and was hospitalized on Day 186 of the double-blind active-control period. Study drug treatment with ramipril 10 mg + hydrochlorothiazide 25 mg/day was subsequently discontinued due to this event. Other symptoms included breathlessness and paresis and paresthesia of the left arm. An x- ray performed at hospitalization revealed pneumonia and infiltration of lungs. Computed tomography of the cerebrum showed a small infarction in right hemisphere. Three days later the patient experienced abdominal pain and nausea and was transferred to intensive care due to suspected septicemia. An exploratory laparotomy was performed, which revealed mesenteric thrombosis with massive necrosis of the small intestine and colon. The patient died 3 days later due to mesenteric thrombosis.

9. Patient 9 died in Study 2306 due to the traffic accident in the washout phase (detailed information was not provided).

10. Patient 10 was on aliskiren 300 mg group in Study 2204 and died of colon cancer (detailed information was not provided).

11. Patient 11 was on HCTZ 25 mg group in Study 2204 and died of rectal cancer (detailed information was not provided).

12. Patient 12 was died on current going study (Study 2331, HCTZ only or combination with aliskiren, valsartan or both) due to sudden death (detailed information was not provided).

SAEs are summarized by primary system organ class for the placebo-controlled and all-controlled studies in the following tables 28 and 29, respectively.

Table 28: Number (%) of patients with serious adverse events in placebo controlled studies by primary system organ class (Study 2204, safety population)

Primary system organ class	Placebo N=193 n (%)	Ali 75 mg N=184 n (%)	Ali 150 mg N=185 n (%)	Ali 300 mg N=181 n (%)	Mono Ali N=550 n (%)	HCTZ 6.25 mg N=194 n (%)	HCTZ 12.5 mg N=188 n (%)	HCTZ 25 mg N=173 n (%)	Mono HCTZ N=555 n (%)
-Any organ class	0 (0.0)	1 (0.5)	1 (0.5)	1 (0.6)	3 (0.5)	1 (0.5)	3 (1.6)	2 (1.2)	6 (1.1)
Blood and lymphatic system disorders	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 (0.2)
Cardiac disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Eye disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
General disorders and administration site Conditions	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Infections and infestations	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 (0.2)
Injury, poisoning and procedural Complications	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.2)
Metabolism and nutrition disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Musculoskeletal and connective tissue Disorders	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 (0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	0 (0.0)	2 (0.4)
Nervous system disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pregnancy, puerperium and perinatal Conditions	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.2)
Psychiatric disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Renal and urinary disorders	0 (0.0)	1 (0.5)	1 (0.5)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal Disorders	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 (0.2)
Social circumstances	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vascular disorders	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 (0.2)

Primary system organ class	Ali/HCTZ 75/6.25 mg N=188 n (%)	Ali/HCTZ 75/12.5 mg N=190 n (%)	Ali/HCTZ 75/25 mg N=186 n (%)	Ali/HCTZ 150/6.25 mg N=174 n (%)	Ali/HCTZ 150/12.5 mg N=184 n (%)	Ali/HCTZ 150/25 mg N=188 n (%)	Ali/HCTZ 300/12.5 mg N=181 n (%)	Ali/HCTZ 300/25 mg N=173 n (%)	Ali/HCTZ N=1464 n (%)
-Any organ class	0 (0.0)	5 (2.6)	4 (2.2)	2 (1.1)	3 (1.6)	2 (1.1)	2 (1.1)	1 (0.6)	19 (1.3)
Blood and lymphatic system disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac disorders	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	2 (0.1)
Eye disorders	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 (0.1)
Gastrointestinal disorders	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
General disorders and administration site Conditions	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 (0.1)
Infections and infestations	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 (0.1)
Injury, poisoning and procedural Complications	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 (0.1)
Metabolism and nutrition disorders	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 (0.1)
Musculoskeletal and connective tissue Disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	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 (0.1)
Nervous system disorders	0 (0.0)	2(1.1)	1(0.5)	0(0.0)	1(0.5)	0(0.0)	0(0.0)	0(0.0)	4(0.3)
Pregnancy, puerperium and perinatal Conditions	0 (0.0)	0(0.0)	1(0.5)	0(0.0)	1(0.5)	0(0.0)	0(0.0)	0(0.0)	2(0.1)
Psychiatric disorders	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(0.1)
Renal and urinary disorders	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(0.1)
Respiratory, thoracic and mediastinal Disorders	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(0.1)
Social circumstances	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(0.1)
Vascular disorders	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(0.1)

Table 29: Number (%) of patients with serious adverse events in short term controlled studies by primary system organ class (safety population)

Primary system organ class	Placebo N=193 n (%)	Mono Ali N=675 n (%)	Mono HCTZ N=678 n (%)	Ali/HCTZ 75/6.25 mg N=188 n (%)	Ali/HCTZ 75/12.5 mg N=190 n (%)	Ali/HCTZ 75/25 mg N=186 n (%)	Ali/HCTZ 150/6.25 mg N=174 n (%)	Ali/HCTZ 150/12.5 mg N=184 n (%)
-Any organ class	0 (0.0)	3 (0.4)	10 (1.5)	0 (0.0)	5 (2.6)	4 (2.2)	2 (1.1)	3 (1.6)
Blood and lymphatic system disorders	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Eye disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.6)	0 (0.0)
General disorders and administration site conditions	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
Infections and infestations	0 (0.0)	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Injury, poisoning and procedural complications	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Metabolism and nutrition disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Musculoskeletal and connective tissue disorders	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0.0)	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nervous system disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.1)	1 (0.5)	0 (0.0)	1 (0.5)
Pregnancy, puerperium and perinatal conditions	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.5)
Psychiatric disorders	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Renal and urinary disorders	0 (0.0)	2 (0.3)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Social circumstances	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Vascular disorders	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)

Primary system organ class	Ali/HCTZ 150/25 mg N=311 n (%)	Ali/HCTZ 300/12.5 mg N=181 n (%)	Ali/HCTZ 300/25 mg N=354 n (%)	Ali/HCTZ N=1654 n (%)	Amlodipine/ HCTZ N=127 n (%)	Irbesartan/ HCTZ N=120 n (%)	Lisinopril N=58 n (%)	Lisinopril/ HCTZ N=26 n (%)
-Any organ class	2 (0.6)	2 (1.1)	3 (0.8)	21 (1.3)	4 (3.1)	3 (2.5)	1 (1.7)	1 (3.8)
Blood and lymphatic system disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac disorders	0 (0.0)	0 (0.0)	2 (0.6)	3 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)
Eye disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)
General disorders and administration site conditions	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Infections and infestations	0 (0.0)	0 (0.0)	1 (0.3)	2 (0.1)	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)
Injury, poisoning and procedural complications	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)
Metabolism and nutrition disorders	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Musculoskeletal and connective tissue disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nervous system disorders	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.2)	2 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
Pregnancy, puerperium and perinatal conditions	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Psychiatric disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Renal and urinary disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.1)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Social circumstances	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vascular disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Summaries of the SAEs in the long-term open-label and the long-term double-blind studies presented by system organ class and preferred term are summarized in the following tables 30 and 31, respectively. Results were consistent with the data from the short-term studies given the relative lengths of treatment exposure in the one-year and 6-month trials and the 8-week and 12-week trials, respectively.