8.5 Advisory Committee Meeting

This NDA has not been and is not planned to be discussed at an advisory committee meeting.

8.6 Literature Review

In the Pubmed literature searches by using "aliskiren and HCTZ", there were no additional findings of combined product other than in this NDA.

8.7 Postmarketing Risk Management Plan

The sponsor did not submit a postmarketing risk management plan.

8.8 Other Relevant Materials

All the materials are incorporated in this NDA and have been reviewed.

9 Overall Assessment

9.1 Conclusions

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 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. In the approved NDA 21-985 (aliskiren monotherapy), aliskiren shown reduced efficacy in blacks. In this submission, no meaningful additional BP reduction in the Black patients with the combination therapy compared to the component monotherapies was observed. b(4)

Based on the safety data, the incidence of overall as well as individual AEs were similar in aliskiren/HCTZ combination therapy to each component monotherapy. The incidence of significant AEs identified during aliskiren monotherapy clinical development program including cerebrovascular events, angioedema, and GI events are also similar in the aliskiren/HCTZ combination therapy. There is no clearly dose-dependent or age-, gender-related AEs. No significant new AEs were observed with long-term treatment compared to short-term treatment.

In the changes of laboratory parameters, both aliskiren and HCTZ monotherapies increased the serum level of uric acids. The combination of aliskiren/HCTZ increased serum level of uric acid even further. There was no difference of incidence rates of gout and kidney stone in short-term studies. In the long-term open label study, however, the incidence rate of gout was 0.5% (4 cases) in the combination therapy and 0.1% (1 case) in the aliskiren monotherapy. Difference for the incidence of kidney stone was not observed in this long-term open label study. Overall, AE profile is considered to be acceptable for antihypertensive therapy.

9.2 Recommendation on Regulatory Action

From clinical perspective, the combination of aliskiren/HCTZ should be approved for the treatment of hypertension. This combination generally produced clinically and statistically significant reductions in both diastolic and systolic blood pressure compared to placebo and each respective monotherapy. Its adverse event profile is similar to each component therapy.

Based on the analysis of provided data sets, the recommended dosage strengths of aliskiren/HCTZ should be 150/12.5 mg, 150/25 mg, 300/12.5 mg, and 300/25 mg once-a-day.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

The combination of aliskiren/HCTZ does not have any unusual risks for which a postmarketing risk management plan would be useful. The adverse events caused by this combination are similar to those seen with each component of the monotherapies.

9.3.2 Required Phase 4 Commitments

No Phase 4 commitments are required at this time.

9.3.3 Other Phase 4 Requests

In the approved NDA 21-985 (aliskiren monotherapy), aliskiren shown reduced efficacy in blacks. b(4)

9.4 Labeling Review

The labeling review will be discussed in the upcoming labeling meetings.

9.5 Comments to Applicant

b(4)

10 Appendices

10.1 Review of Individual Study Reports

10.1.1 Study 0014: Effect of the combination of Aliskiren and Hydrochlorothiazide on daytime systolic blood pressure measured by 24-Hour Ambulatory Blood Pressure Monitoring Following Once-a-Day Administration of 150mg of Aliskiren alone and in combination with 25 mg Hydrochlorothiazide in Patients with Mild to Moderate Hypertension

10.1.1.1 Protocol, Amendment and Post Hoc Changes

The initial study protocol is dated July 23, 2001. The protocol was amended 4 times:
Amendment (August 28, 2001): Following internal site availability, investigator responsibilities were shifted from [redacted] to [redacted]; defined ECG as 12 lead; urine sticks test changed and will not include ketones, hemoglobin, urobilinogen and red cells; PK analysis not to be performed on hydrochlorothiazide because the assay of trough levels was not of value in this limited population; b(4)

Amendment two (October 4, 2001): On visit 4, Sitting (5 mins) and standing (2 mins) systolic and diastolic blood pressure and heart rate, pre dose and three hours post dose was amended to Sitting (5 mins) and standing (2 mins) systolic and diastolic blood pressure and heart rate, pre dose. A three hours post dose measurement might be done should the investigator feel it is warranted.

Amendment three (November 2001): Daytime ABPM required a minimum of 14 readings and night time ABPM required a minimum of 8 readings.

Amendment four (December 14, 2001): One to two additional blood samples for the determination of aliskiren and Plasma Renin Activity (PRA) were drawn on Visit 3 or 4. These samples were collected 3-5 hours and 6-8 hours after the morning administration of aliskiren.

10.1.1.2 Sites and Investigators

One study cite: [redacted] b(4)
Ireland

10.1.1.3. Study dates

The first subject was enrolled on October 15, 2001 and the last subject was enrolled on February 7, 2002.

10.1.1.4. Study design

This was a phase II, open-label, randomized design. Twenty three male or female patients from 18-70 years of age were recruited. The study consisted of the following: A screening phase followed by a 7 to 10-day baseline washout of RAS active drugs, i.e. ACE and Ang II antagonists. All subjects received aliskiren 150mg once daily for three weeks. For non-responders, this was followed by the combination of aliskiren 150mg with HCTZ 25 mg for another three weeks; responders remained on aliskiren 150mg once daily for the remaining three weeks. Responders were defined as patients whose systolic blood pressure was < 135/85 mmHg at the end of the first three week monotherapy with aliskiren 150 mg. Ambulatory Blood Pressure Measurements (ABPM) was performed after an initial washout (baseline), at the end of the 1st 3 weeks of treatment and after the second 3 weeks of treatment. Safety and tolerability were evaluated after each treatment cycle before proceeding further.

10.1.1.5. Study objectives

The Primary Objective is to determine the effects of the combination of hydrochlorothiazide (HCTZ) and aliskiren on daytime ambulatory systolic blood pressure upon once-a-day administration of aliskiren 150mg alone for three weeks followed by the combination of aliskiren 150mg with HCTZ 25 mg for another three weeks in non-responders. Responders remained on aliskiren150mg once daily for the remaining three weeks.

The Secondary Objectives are to determine: 1) the tolerability and safety of aliskiren given in combination with HCTZ in patients with mild to moderate hypertension; 2) the plasma trough levels of aliskiren following combination therapy; and 3) the effects of aliskiren on Plasma Renin Activity at steady-state as measured by PRA trough levels.

10.1.1.6. Inclusion, exclusion criteria and stop rule

Inclusion Criteria: male or female patients from 18-70 years of age without treatment or only on monotherapy for hypertension. Systolic Blood pressure: mild to moderate > 140 and < 180 mmHg.

Exclusion Criteria: blood pressure ≥ 180/110 mmHg after the washout phase; unable to discontinue use of antihypertensive therapy, including diuretics, ACE inhibitors, Ang II antagonists, calcium antagonists or beta-blockers; on multiple antihypertensive therapy prior to washout; pregnant or lactating women, or women of childbearing potential not practicing an adequate method of contraception, such as oral contraception; secondary hypertension; malignant hypertension; history of acute renal failure, or evidence of significant renal impairment, i.e. serum creatinine > 180 μmol/l, or proteinuria > 2+ on urine dipstick; history of unstable angina, acute myocardial infarction, PTCA, CABG or stroke in the last 6 months;

uncontrolled hyper- or hypothyroidism; history of autonomic dysfunction; any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of any drug such as: history of inflammatory bowel syndrome, gastritis, ulcers, gastrointestinal or rectal bleeding, major gastrointestinal tract surgery, pancreatic injury or pancreatitis, liver disease as indicated by an abnormal liver function profile (ASAT and ALAT >3x upper normal limit); type I Diabetes (IDDM); a known hypersensitivity to renin inhibitors, or to HCTZ; participation in any clinical drug investigation within four weeks prior to dosing or longer as required by local regulation; donation or loss of 400 ml or more of blood within three months prior to dosing; contraindications of hydrochlorothiazide (hydrochlorothiazide is contraindicated in patients with severe hepatic impairment, hepatic cirrhosis, severe renal impairment, anuria, pre-existing hypercalcemia and Addison's disease. All patients should be carefully observed for signs of fluid electrolyte imbalance, especially in the presence of vomiting or during parenteral fluid therapy.)

Stop rule: adverse event(s); abnormal laboratory value(s); abnormal test procedure result(s); protocol violation; subject withdrew consent; lost to follow-up; administrative problems; the systolic daytime BP is < 120 mm Hg; the systolic daytime BP > 195 on two consecutive visits; failing to cooperate with the Investigator or staff

10.1.1.7. Treatment

The treatments to be administered were as follows:
Visit 1 – 2: Washout
Visit 2 – 3: aliskiren 150mg once daily for three weeks
Visit 3 – 4: aliskiren 150mg + hydrochlorothiazide 25 mg once daily for three weeks or aliskiren 150mg once daily for three weeks

Figure 3:Study design flow chart in Study 0014

Study Flow Chart

Assessment	Visit 1 Screening	Visit 2 End of Washout-Baseline	Visit 3 End of 3 weeks Treatment	Visit 4 End of 3 weeks Treatment	Visit 5 End of study evaluation
Written informed Consent	X				
aliskiren 150mg		X			
aliskiren 150mg + HCTZ 25 mg (non-responders)			X		
aliskiren 150mg (responders)			X		
Adverse events and SAEs		X	X	X	X
Medical history	X				
Physical Exam	X				X
12 Lead ECG	X	X	X	X	X
Blood pressure and heart rate[2]	X	X	X	X	X
24 hour ABPM		X	X	X	
Routine safety Lab evaluations	X[1]	X	X	X	X
Assay of Plasma renin activity and aliskiren/HCTZ drug levels		X	X	X	

Key
1. Including screening for Hepatitis B surface antigen and Hepatitis C antibody
2. Sitting (5 min) and standing (2 min) systolic and diastolic blood pressure

10.1.1.8 Efficacy and safety endpoints

Efficacy Assessment: Primary efficacy parameter was the change from baseline to the end of a three week period (i.e. from visit 2 to visit 3 and from visit 2 to visit 4) in daytime ambulatory systolic blood pressure (DASBP).

Ambulatory blood pressure monitoring (ABPM) was performed using an ambulatory blood pressure monitor. The monitor was applied to the non-dominant arm between 0900 hours and noon, and the patient was instructed to carry on life as normal between measurements but to rest the arm at heart level during measurements. Monitors were programmed to measure blood pressure at 30- minute intervals day and night. The monitor was removed the next day, and the data were transferred into a personal computer and loaded into a specialized software package. The initial, daytime and night time systolic, diastolic and mean blood pressures were calculated. Daytime was defined as the hours between 0900 and 2100 hours (excluding the initial period of one hour after applying the device), and night time as the hours between 0100 and 0600 hours. Transition times (2101 to 0059 hours, and 0601 to 0859 hours) were not included in the estimation of day and night mean pressures, as these periods represent times during which bed rest was inconsistent and therefore could not reliably be categorized. Erroneous measurements identified by the editing software were removed from the recording.

Casual Blood Pressure: Blood pressure was measured at each clinic visit on the non-dominant arm (same arm as the ABP measurement). The physician, nurse or technician measured blood pressure in the standing position, after standing quietly for 2 minutes, and in a sitting position, after five minutes of sitting quietly. The diastolic pressure was recorded as phase five of the Korotkov sounds. At least three measurements in each position were obtained per patient at one-minute intervals. The second and third interval measurements were averaged and recorded in the CRF.

PK/PD study: Venous blood samples were drawn via an intravenous catheter for aliskiren trough levels and plasma rennin activity at the following times:
Sample 1: Visit 2 – Baseline; prior to the start of the first cycle of therapy
Sample 2: Visit 3 – End of first cycle of therapy, prior to the start of the ABPM
Sample 3: Visit 4 – End of second cycle of therapy, prior to the start of the ABPM

Safety Assessments: Safety of the study drugs was evaluated by monitoring the patient's vital signs, physical exam, ECG, and by the assessment of routine laboratory safety tests hematology, chemistry and urinalysis.

10.1.1.9. Statistical and Analytical Plans

Parameters and Analysis: The analysis of the primary efficacy parameter was performed on the ITT and PP populations, with the main analysis being on the ITT population. Other analyses were performed on the ITT population only. The analysis of all safety parameters was performed on the Safety population.

The primary efficacy parameter was the change from baseline to the end of a three week period (i.e. from visit 2 to visit 3 and from visit 2 to visit 4) in daytime ambulatory systolic blood pressure (DASBP). Moreover, the change from visit 3 to visit 4 was examined. If a second ABPM was taken at any time period due to technical reasons (i.e. loss of power, clamped tubing, too few measurements) the repeat ABPM replaced the original in the calculations of change over baseline, if it was a valid ABPM. All ABPMs were listed and marked accordingly. The primary comparison was between the monotherapy treatment with aliskiren 150mg once daily and HCTZ 25 mg + aliskiren 150mg once daily. The assumption was that there was a further decrease in DASBP of at least 5 mmHg when adding HCTZ 25 mg to aliskiren 150mg. In order to report descriptively a p-value for the differences between both treatment regimens, an ANCOVA model was used to compare the mean changes from baseline to the end of the three week treatment period. The baseline ABPM was used as a covariate.

The secondary efficacy parameters were defined as the change from baseline to trial treatment end in day-time ambulatory diastolic blood pressure (DADBP); night-time ambulatory systolic blood pressure (NASBP); night-time ambulatory diastolic blood pressure (NADBP); sitting cuff-measurement systolic blood pressure (SiSBP); sitting cuff-measurement diastolic blood pressure (SiDBP); standing cuff-measurement systolic blood pressure (StSBP); standing cuff-measurement diastolic blood pressure (StDBP). All of these parameters were analyzed on the ITT population only and the same models as for the primary efficacy parameter were used. Beside these secondary efficacy parameters, the number and percentage of patients reaching a diastolic blood pressure of 90 mmHg or lower (cuff measurement) were calculated. Likewise the numbers and the percentage of patients having a reduced diastolic blood pressure by a minimum of 10 mmHg (cuff measurement) were calculated.

Determination of Sample Size: This was a pilot phase IIa exploratory study to investigate the safety and tolerability of an orally available renin inhibitor, aliskiren, administered alone or in combination with HCTZ. Descriptive statistics were performed. No formal sample size determination had been performed. Twenty three patients were included into the study.

10.1.1.10. Protocol violation

Only 5 minor protocol violations and one major protocol violation were observed in this study. In subjects nos. 312, 314 and 318 receiving aliskiren throughout the study a mean daytime diastolic blood pressure below 80 mmHg was reported. Subject no. 309 who received aliskiren and hydrochlorothiazide had a history of peptic ulcer and ulcerative colitis while subject no. 329 who received aliskiren and hydrochlorothiazide took 50 mg of the beta-blocking agent atenolol on 18 Nov 2001 between visit 1 and visit 2. A premature withdrawal due to adverse events was reported only in subject no. 328 who suffered from irritable bowel syndrome and a psychiatric disorder after visit 3 which was not related to the study medication. Hence, this patient was excluded from PP analysis set.

10.1.1.11. Demographic and other baseline characteristics

A total of 23 subjects were enrolled in this trial and were eligible for analysis of efficacy and safety. The SAF analysis and the ITT analysis were identical in this study while 22 subjects were included in the PP analysis set. Of the 23 subjects included in the ITT analysis, 18 subjects were male and 5 subjects were female. Of these, 4 male and 2 female subjects received aliskiren throughout the study while 14 males and 3 females received aliskiren and hydrochlorothiazide. All subjects were Caucasians. The following table presents the average age, body height, body weight and body mass index for the study patients.

Table 69: Baseline Characteristics in study 0014

		N	Mean	Std Dev	Min	Median	Max
Age [years]	MALE	18	58.2	8.7	40.0	59.0	70.0
	FEMALE	5	54.4	5.5	49.0	53.0	63.0
	Overall	23	57.4	8.1	40.0	58.0	70.0
Height [cm]	MALE	18	175.1	4.5	163.0	176.8	180.0
	FEMALE	5	160.6	4.5	153.5	162.5	165.0
	Overall	23	171.9	7.5	153.5	175.5	180.0
Weight [kg]	MALE	18	85.2	8.6	70.0	85.5	97.0
	FEMALE	5	70.3	11.1	61.5	64.0	86.0
	Overall	23	82.0	10.9	61.5	85.0	97.0
Body Mass Index [kg/cm2]	MALE	18	27.8	3.0	22.5	27.9	32.1
	FEMALE	5	27.5	6.0	23.3	23.5	36.5
	Overall	23	27.8	3.7	22.5	27.9	36.5

10.1.1.12. Efficacy

Primary efficacy analysis: Primary efficacy parameter was the change from baseline to the end of a three week period (i.e. from visit 2 to visit 3 and from visit 2 to visit 4) in daytime ambulatory systolic blood pressure (DASBP). Mean DASBP decreased from 150.6 ± 8.9 mmHg to 139.1 ± 11.4 mmHg ($p<0.20$) after the first three weeks of aliskiren monotherapy. Addition of HCTZ led to a statistically significant decrease in DASBP to 133.8 ± 7.0 mmHg ($p<0.03$); patients on a further 3 weeks of aliskiren monotherapy showed a trend towards a further decrease in DASBP (from 139.1±11.4 mmHg to 131.8 ± 10.3 mmHg). Patients who underwent 6 weeks treatment with aliskiren showed a statistically significant decrease in DASBP versus baseline, from 150.6 ±8.9 mmHg to 131.8 ±10.3 mmHg ($p<0.01$). At visit 4, the DASBP of all patients was below 150 mmHg. The ANCOVA for the mean change in DASBP from visit 2 to 4 showed a statistically significant decrease in patients treated with aliskiren monotherapy ($p = 0.0119$) as well as in patients on combination therapy with hydrochlorothiazide ($p = 0.0202$). Data were summarized in the following table 70.

Table 70: Course of day-time ambulatory systolic blood pressure (from visit 2 to visit 4) in study 0014

		N	Mean	Std Dev	Min	Median	Max
Visit 2	Overall	23	150.6	8.9	140.0	148.0	171.0
Visit 3	Overall	23	139.1	11.4	107.0	137.0	164.0
Visit 4	Treatment						
	aliskiren	6	131.8	10.3	113.0	134.0	143.0
	aliskiren & hydrochlorothiazide	16	133.8	7.0	122.0	133.5	147.0

Secondary efficacy analysis: Mean DADBP decreased from 90.7 ± 8.2 mmHg to 84.3 ± 9.2 mmHg with aliskiren 150mg after three weeks monotherapy (p=0.58). Addition of HCTZ did not result in a statistically significant change in DADBP (83.3 ± 4.7 mmHg), whereas patients who remained on aliskiren monotherapy showed a further decrease in mean DADBP to 74.5 ± 10.3 mmHg . The ANCOVA for the mean change in DADBP from visit 2 to 4 showed a statistically significant decrease for the combination treatment (p = 0.0028). Data were summarized in the following table 71.

Table 71: Course of daytime ambulatory diastolic blood pressure (from visit 2 to visit 4) in study 0014

		N	Mean	Std Dev	Min	Median	Max
Visit 2	Overall	23	90.7	8.2	78.0	90.0	107.0
Visit 3	Overall	23	84.3	9.2	55.0	88.0	96.0
Visit 4	Treatment						
	aliskiren	6	74.5	10.3	59.0	72.5	87.0
	aliskiren & hydrochlorothiazide	16	83.3	4.7	77.0	83.5	93.0

NASBP decreased significantly, from 132.1 ±+ 12.4 mmHg to 116.7 ±+ 7.9 mmHg in the combination arm (p = 0.007) at the end of the study. The ANCOVA for the mean change in NASBP from visit 2 to 4 showed a statistically significant decrease for the combination treatment (p = 0.0070); the difference in NASBP between visits 3 and 4 did also show statistical significance for the combination treatment arm (p = 0.0003). The ANCOVA for the mean change in NADBP from visit 2 to 4 did not show a statistically significant decrease for either treatment. The combination arm, however, showed a statistically significant decrease in NADBP between visits 3 and 4 (p = 0.0254). Data were summarized in the following table 72.

Table 72: Course of night-time ambulatory blood pressure (from visit 2 to visit 4) in study 0014

Mean Night-Time SBP		N	Mean	Std Dev	Min	Median	Max
Visit 2	Overall	19	132.1	12.4	106.0	131.0	160.0
Visit 3	Overall	16	120.8	13.0	101.0	118.0	143.0
Visit 4	Treatment Group						
	aliskiren	4	108.8	12.0	95.0	108.5	123.0
	aliskiren & hydrochlorothiazide	13	116.7	7.9	105.0	117.0	132.0
Mean Night-Time DBP		**N**	**Mean**	**Std Dev**	**Min**	**Median**	**Max**
Visit 2	Overall	19	76.7	7.9	59.0	77.0	90.0
Visit 3	Overall	16	72.5	8.1	56.0	72.0	85.0
Visit 4	Treatment Group						
	aliskiren	4	56.5	8.1	46.0	57.5	65.0
	aliskiren & hydrochlorothiazide	13	70.7	6.8	60.0	70.0	81.0

For cuff blood pressure measurement, sitting systolic blood pressure decreased from 148.4 ± 12.5 mmHg to 139.7 ± 12.4 mmHg after the first three weeks on aliskiren monotherapy. The addition of HCTZ resulted in a further decrease to 130.9 ± 12.0 mmHg. Patients who continued on aliskiren monotherapy also showed a further decrease, to 133.0 ± 10.9 mmHg. Sitting diastolic blood pressure decreased from 88.6 ± 7.5 mmHg to 86.7 ± 9.1 mmHg after the first three weeks on aliskiren monotherapy. The addition of HCTZ resulted in a further decrease to 80.5 ± 9.2 mmHg. Patients who continued on aliskiren monotherapy also showed a further decrease, to 76.8 ± 12.3 mmHg. 16 subjects did reach a sitting diastolic blood pressure of 90 mmHg or lower during treatment with aliskiren at visit 3, all except one subject receiving aliskiren at visit 4 and all except two subjects at visit 5 (one subject in each treatment group). Exactly 50.0% of the patients in both treatment groups showed a decrease in sitting diastolic blood pressure of at least 10 mmHg at visit 4. Data were summarized in the following table 73.

Table 73: Cuff blood pressure measurement in study 0014

(mean +/- SD)	SiSBP (mmHg)	SiDBP (mmHg)	StSBP (mmHg)	StDBP (mmHg)
Baseline (V2)	148.4±12.5 (n=23)	88.6±7.5 (n=23)	150.8±12.5 (n=23)	90.8±7.2 (n=23)
Overall (V3)	139.7±12.4 (n=23)	86.7±9.1 (n=23)	139.6±13.2 (n=23)	87.1±9.2 (n=23)
aliskiren 150mg (V4)	133.0±10.9 (n=6)	76.8±12.3 (n=6)	134.0±9.2 (n=6)	81.5±9.7 (n=6)
aliskiren 150mg + HCTZ 25mg (V4)	130.9±12.0 (n=16)	80.5±9.2 (n=16)	131.4±11.6 (n=16)	82.7±10.8 (n=16)

Drug Dose, Concentration, and relationships to Response: Both PRA and aliskiren were measured in 23 patients from the ITT population. Patients were excluded from this analysis if they received aliskiren on the day of sampling and hence measurements were not at trough, or if either a PRA or aliskiren sample was missing. All samples were generally taken 24 hours after the last treatment dose; 25.81 ± 1.97 hours across all patients at visit 3 and 25.80 ± 1.42 hours across all patients at visit 4, respectively. Baseline PRA levels were similar across patients with a median of 0.72 ng/ml/hr, ranging from 0.13 to 5.0 ng/ml/hr across all patients. The two treatment groups, patients only treated with aliskiren and patients receiving aliskiren + hydrochlorthiazide, were similar at baseline with medians 0.81 and 0.70 ng/ml/hr, respectively. There was a clear decrease in PRA following aliskiren treatment. PRA was inhibited by up to 95% of baseline activity during the first three weeks with aliskiren monotherapy at visit 3 (average decrease in

PRA of 68.2±19.0 %, see table below). The PRA remained depressed after the second 3 weeks of aliskiren monotherapy. In the group treated with aliskiren + hydrochlorothiazide, PRA increased due to hydrochlorothiazide treatment. In 10 patients at visit 4 PRA was equal to or higher than baseline levels and in 5 other patients PRA remained inhibited. This is reflected in the average PRA activity of 0.56±0.45 ng/ml/hr, but the average inhibition of only 14.3% with a large SD of 74.2%. Data were summarized in the following tables 74 and 75.

Table 74: Plasma Renin Activity Following 150 mg of aliskiren- (ITT Population) in study 0014

Visit	Treatment		
	aliskiren throughout the Study N=6	aliskiren + hydrochlorothiazide N=17	All Subjects N=23
	PRA (ng/ml/hr) (mean ± standard deviation)		
Baseline	1.38 ± 1.33	1.06 ±1.15	1.14 ± 1.17
End of First Cycle of aliskiren Treatment (Visit 3)	0.33 ± 0.28	0.28 ± 0.22	0.29 ± 0.23
Percentage Change %	68.2 ± 18.8	64.1 ± 25.5	65.2 ± 23.6

Table 75: Plasma Renin Activity following 150 mg of aliskiren or 150 mg aliskiren + 25 mg hydrochlorothiazide - (ITT Population) in study 0014

Visit	Treatment	
	aliskiren throughout the Study N=6	aliskiren + hydrochlorothiazide N=15
	PRA (ng/ml/hr) (mean ± standard deviation)	
Baseline	1.38 ± 1.33	1.06 ±1.15
End of Second Cycle of aliskiren treatment or aliskiren + hydrochlorothiazide (Visit 4)	0.55 ± 0.41	0.56 ± 0.45
Percentage Change %	44.8 ± 35.7*	14.3 ± 74.2

The average trough plasma concentrations of aliskiren following three weeks of treatment and following combination with hydrochlorothiazide are shown in the following table 76 below. Plasma levels of aliskiren remained constant throughout the study and did not change after three or six weeks of treatment. The addition of hydrochlorothiazide did not significantly affect the trough concentrations of aliskiren.

Table 76: Plasma concentrations of aliskiren following 150 mg of aliskiren- (ITT Population) in study 0014

Visit	Treatment		
	aliskiren throughout the Study	aliskiren + hydrochlorothiazide	All Subjects
	aliskiren (ng/ml) (mean ± standard deviation)		
Baseline	0	0	0
End of First Cycle of aliskiren Treatment (Visit 3)	12.6 ± 8.1 (N=6)	15.8 ± 11.7 (N=17)	15.0 ± 10.8 (N=23)
End of Second Cycle of aliskiren Treatment or aliskiren + hydrochlorothiazide (Visit 4)	10.7 ± 6.7 (N=6)	13.1 ± 8.3 (N=14)	NA

10.1.1.13. Extent of exposure and summary of adverse events

Extent of exposure: The mean duration of treatment with aliskiren was (arithmetic mean ± standard deviation) 47.3 ± 5.0 days (44.8 ± 3.6 days in subjects who received aliskiren throughout the study versus 48.3 ± 5.2 days in subjects who received aliskiren and hydrochlorothiazide). With regard to the mean time intervals between each visits, both treatment groups were similar.

Brief Summary of Adverse Events: 11 adverse events were observed in 5 subjects receiving combination treatment with aliskiren and hydrochlorothiazide; in 3 of these subjects (nos. 321, 329 and 335) 5 adverse events occurred during monotherapy with aliskiren. No adverse event was mentioned more than once. 9 adverse events were assessed as unrelated to the trial medication while 2 adverse events were judged as unlikely related. 3 adverse events were of mild intensity while 8 adverse events were of moderate intensity. All adverse events in this study were resolved. In 2 subjects (nos. 321 and 328) serious adverse events were reported. All serious adverse events were of moderate intensity and unrelated to the study medication. No deaths were reported. A premature withdrawal due to adverse events was reported only in subject no. 328 who suffered from irritable bowel syndrome and a psychiatric disorder after visit 3. These adverse events were unrelated to the study medication and were also reported as completely recovered, but the treatment with aliskiren and hydrochlorothiazide was stopped on 24 Dec 2001. Data were displayed in the following table 77.

Table 77: Display of Adverse Events by Subject in study 0014

Pat.	Treatment Group	Report Date	Onset Date	Resolve Date	Preferred Term	Intensity	Causality	Time from Last Intake	Unit
309	aliskiren & HCTZ	23NOV01	21NOV01	23NOV01	ABDOMINAL PAIN UPPER	MILD	UNLIKELY	5.0	HOURS
		23NOV01	21NOV01	23NOV01	DYSPNOEA NOS	MILD	UNLIKELY	5.0	HOURS
321	aliskiren & HCTZ	09NOV01	[redacted]		HEAD INJURY**	MODERATE	UNRELATED	*	
		13NOV01	[redacted]		PNEUMOTHORAX NOS**	MODERATE	UNRELATED	*	
		13NOV01	09NOV01	11DEC01	SUBCUTANEOUS EMPHYSEMA**	MODERATE	UNRELATED	*	
328	aliskiren & HCTZ	19DEC01	19DEC01	15JAN02	PARAESTHESIA	MODERATE	UNRELATED	6.0	HOURS
		25DEC01	25DEC01	15JAN02	DIVERTICULITIS NOS	MODERATE	UNRELATED	2.0	DAYS
		25DEC01	25DEC01	15JAN02	MENTAL DISORDER NOS	MODERATE	UNRELATED	2.0	DAYS
		9DEC01	19DEC01	15JAN02	DYSURIA	MODERATE	UNRELATED	6.0	HOURS
329	aliskiren & HCTZ	19NOV01	18NOV01	19NOV01	SPONDYLITIS NOS**	MODERATE	UNRELATED	*	
335	aliskiren & HCTZ	19DEC01	18DEC01	24DEC01	UPPER RESPIRATORY**	MILD	UNRELATED	2.0	HOURS

*not applicable **during treatment phase with aliskiren

b(6)

10.1.1.14. Narratives of Deaths, Other Serious Adverse Events and Certain Other

No deaths were reported. Significant Adverse Events: Subject no. 321 (aliskiren/hydrochlorothiazide) is a 66-year old man. He had his first visit on 05 Nov 2001. At the time, he discontinued Centyl K® (bendrofluazide). On [redacted] he fell off a scaffolding (scaffolding broke), and landed on concrete blocks. He experienced loss of consciousness for a few minutes and was admitted for observation. A laceration to right side of head was observed. X-ray reports were normal. Prophylactic subcutaneous heparin and analgesics were given. This event should not be unrelated to the study drug.

b(6)

Subject no. 328 (aliskiren/hydrochlorothiazide) is a 55-year old man. He attended casualty on 20 Dec 01 because of pins and needles in the left leg and arm and dysuria. Intensity of symptoms

was moderate. The relationship to the study medication was judged as unrelated. The patient was treated with paracetamol 100mg and sent home. Later on the same day, the patient was seen again by the research physician. Blood pressure was 154/92mmHg. He was admitted with symptoms of loose bowel movements, altered distal sensation, and frequent micturition. The investigator suspected the symptoms to be of psychiatric origin. Hence, the patient was withdrawn from study on 24 Dec 2001. The patient was discharged from hospital on [redacted] b(6) with pending appointment at psychiatrist's. As discharge therapy the patient received Zimovane® 15 mg po, Risperidone® 0.5 mg bd, Cozaar® 50 mg od po, Fybogel® TBD po, Spasmonol® BD po, and Zoton® 15 mg OD po. On 15 Jan 2002 the events were reported as resolved. These events should be unrelated to the study drug.

10.1.1.15. Clinically relevant laboratory changes

No changes in laboratory values were considered to be clinically relevant. No clinically relevant changes were reported for urine examination. Data were summarized in the following table 78.

Table 78: Changes of clinically relevant laboratory parameters in study 0014

		NO		YES		Overall	
		N	%	N	%	N	%
ALT (SGPT)	aliskiren throughout the Study	5	83.3	1	16.7	6	100.0
	aliskiren & hydrochlorothiazide	14	82.4	3	17.6	17	100.0
	All	19	82.6	4	17.4	23	100.0
BILIRUBIN	aliskiren throughout the Study	5	83.3	1	16.7	6	100.0
	aliskiren & hydrochlorothiazide	13	76.5	4	23.5	17	100.0
	All	18	78.3	5	21.7	23	100.0
CREATINE KINASE	aliskiren throughout the Study	5	83.3	1	16.7	6	100.0
	aliskiren & hydrochlorothiazide	11	64.7	6	35.3	17	100.0
	All	16	69.6	7	30.4	23	100.0
CREATININE	aliskiren throughout the Study	6	100.0			6	100.0
	aliskiren & hydrochlorothiazide	16	94.1	1	5.9	17	100.0
	All	22	95.7	1	4.3	23	100.0
EOSINOPHIL	aliskiren throughout the Study	6	100.0			6	100.0
	aliskiren & hydrochlorothiazide	15	88.2	2	11.8	17	100.0
	All	21	91.3	2	8.7	23	100.0
GGT	aliskiren throughout the Study	4	66.7	2	33.3	6	100.0
	aliskiren & hydrochlorothiazide	14	82.4	3	17.6	17	100.0
	All	18	78.3	5	21.7	23	100.0
LACTATE DEHYDROGENASE	aliskiren throughout the Study	6	100.0			6	100.0
	aliskiren & hydrochlorothiazide	16	94.1	1	5.9	17	100.0
	All	22	95.7	1	4.3	23	100.0
NEUTROPHIL	aliskiren throughout the Study	5	83.3	1	16.7	6	100.0
	aliskiren & hydrochlorothiazide	16	94.1	1	5.9	17	100.0
	All	21	91.3	2	8.7	23	100.0
URIC ACID	aliskiren throughout the Study	6	100.0			6	100.0
	aliskiren & hydrochlorothiazide	16	94.1	1	5.9	17	100.0
	All	22	95.7	1	4.3	23	100.0

10.1.1.16. Vital Signs, Physical Findings, and Other Observations Related to Safety

There were no abnormal findings of vital signs, physical examination and 12 lead ECG.

10.1.1.17. Summary

This study was designed to investigate the effect of the combination of aliskiren and hydrochlorothiazide on DASBP following once-a-day administration of 150mg of aliskiren alone and in combination with 25 mg HCTZ in patients with mild to moderate hypertension. The study results demonstrate that aliskiren 150mg, with or without HCTZ, significantly decreases DASBP as well as other BP measurement ($p = 0.0119$ for aliskiren monotherapy and $p = 0.0202$ for the combination arm). A statistically significant decrease in DADBP could also be shown for the combination arm from visit 2 to 4, in NADBP from visit 3 to 4 as well as NASBP from visit 2 to 4 and 3 to 4. 11 adverse events were observed in 5 subjects receiving combination treatment with aliskiren and HCTZ; in 3 of them 5 AEs happened during the first monotherapy treatment with aliskiren. 5 adverse events in 2 subjects (nos. 321 and 328) were reported as serious. All serious adverse events were of moderate intensity and unrelated to the study medication. No deaths were reported. All adverse events, whether serious or not, were resolved. A premature withdrawal due to adverse events was reported only in one subject. There were no clinically significant vital signs, physical examination, laboratory or ECG changes, except for one single patient on combination treatment whose ALAT and ASAT increased three times above the upper limit of normal at visit 3 and returned to normal at visit 4. There is no comparison of efficacy between the aliskiren monotherapy and the combination of aliskiren with HCTZ.

10.1.1.18 Conclusion

This study indicate that both aliskiren monotherapy and the combination of aliskiren and HCTZ are effective and safe for the treatments of essential mild and moderate hypertension in short term (6 weeks). However, there is no comparison of efficacy between the aliskiren monotherapy and the combination of aliskiren with HCTZ.

10.1.2. Study 2204: An 8-week, double-blind, multicenter, randomized, multifactorial, placebo-controlled, parallel-group study to evaluate the efficacy and safety of aliskiren administered alone and in combination with hydrochlorothiazide in patients with essential hypertension

10.1.2.1. Protocol, Amendment and Post Hoc Changes

This is the pivotal study for approval of the aliskiren/HCTZ combination. The initial protocol is dated March 18, 2004. The protocol was amended twice: (1) Amendment 1, dated July 21, 2004, modified the statistical analysis plan to use the AVE test by Hung to assess the overall effect of combinations versus their respective monotherapies if a critical negative interaction was observed in the overall contribution of the two monotherapy contributions. (2) Amendment 2, dated November 10, 2004, dropped measuring angiotensin II levels because of difficulties in specimen handling, added an initial IVRS contact to visit 1 (or visit 2 if subject was treatment-naïve), dropped the requirement for drug accountability at visits 5-7 (since study drug was

neither returned nor dispensed at the visits), and removed allergy to angiotensin receptor blockers from exclusion criteria since there was minimal risk of hypersensitivity reactions. In Norway the IRBs also requested to add an amendment dated July 7, 2004 including patients with essential hypertension who were previously untreated (for at least 3 months prior to visit 1).

10.1.2.2. Sites and Investigators

This study was performed at 213 sites in 19 countries: Argentina (9), Brazil (6), Canada (12), Colombia (2), Finland (11), France (16), Germany (29), Guatemala (4), Italy (23), Netherlands (12), Norway (5), Peru (8), Poland (3), Russia (11), Slovakia (5), Spain (11), Sweden (6), Taiwan (6), and United States (34).

10.1.2.3. Study Dates

The first patient was enrolled on August 27, 2004, and the last patient completed on June 27, 2005.

10.1.2.4. Study Design

This was an eight-week, international, multicenter, randomized, double-blind, placebo controlled, double dummy, two drug factorial, parallel group study.

10.1.2.5. Objectives

The primary objectives of this study were to confirm the efficacy of aliskiren monotherapy and to demonstrate the efficacy of the combination of aliskiren and HCTZ. Secondary objectives included effects upon SBP, dose-response, safety and tolerability, and effects upon plasma renin and renin activity.

10.1.2.6. Number of Subjects, Randomization, and Blinding

The planned number of subjects was 2685. Randomization was by IVRS. Blinding was maintained by using a double dummy approach with matching placebos.

10.1.2.7. Inclusion and Exclusion Criteria

The inclusion criteria were the following: 18 or older; females post-menopausal, sterile, or using adequate contraception; essential hypertension with DBP 90-109 mmHg at visit 2 to 95-109 mmHg at visit 3; DBP difference ≤10 mmHg; written informed consent.

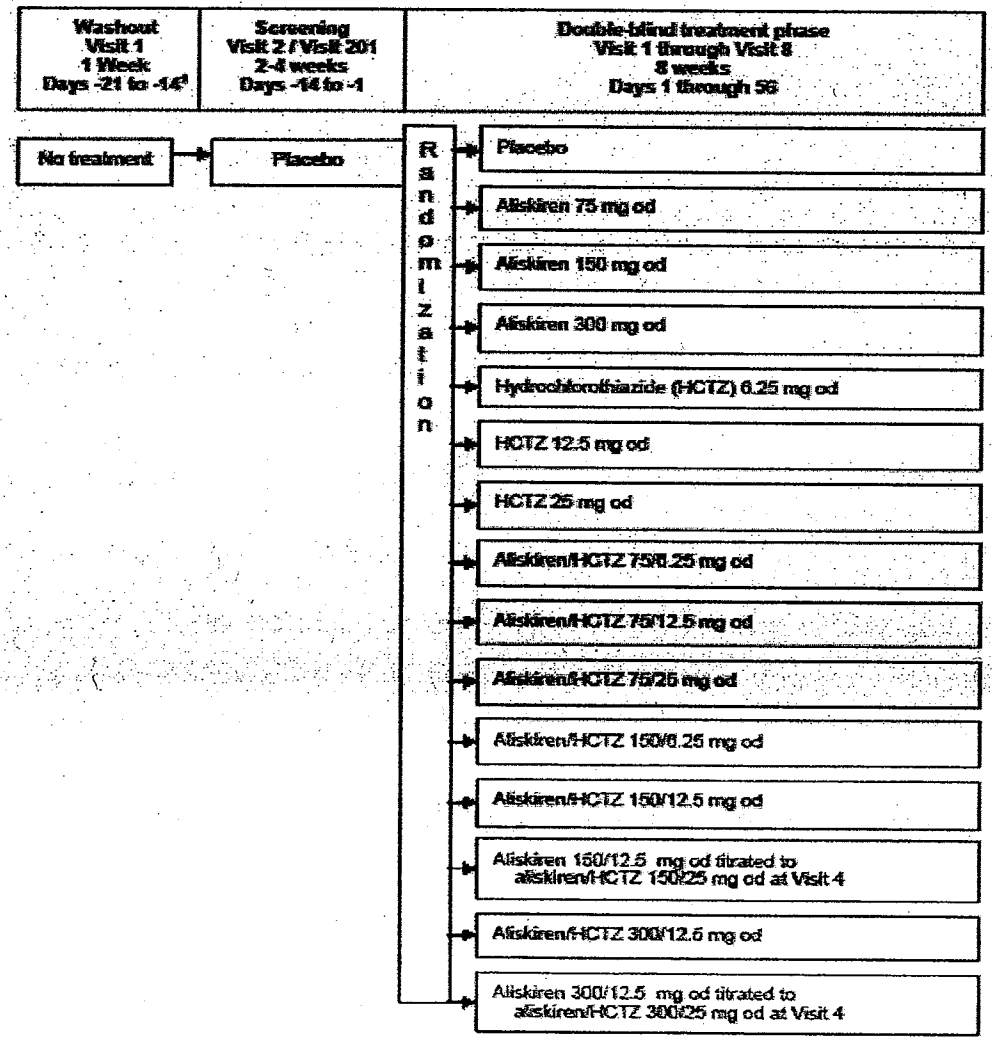
The exclusion criteria were the following: prior aliskiren use; BP ≥180/110 mmHg; secondary hypertension; grade III-IV retinopathy; history of hypertensive encephalopathy or stroke; TIA within 12 months; heart failure class II-IV; MI, CABG, or PTCA within 6 months; angina; > 1° heart block without pacemaker; arrhythmias; valvular heart disease; diabetes with HgbA1c> 9%; low serum sodium, dehydration, or potassium <3.5 or ≥5.5; any condition affecting ADME, including ALT/AST > 2x ULN or serum creatinine > 1.5x ULN; malignancy within 5 years;

alcohol or drug abuse within 12 months; pregnant or nursing; any condition increasing risk per investigator; allergy to ARB, thiazides, or sulfonamides; gout; noncompliance; any condition jeopardizing evaluation; investigational drug within 1 month; directly involved in protocol.

10.1.2.8 Study Plan and Monitoring

Patients who met the study inclusion/exclusion criteria at the end of the single-blind, placebo, run-in period were randomized equally to one of 15 treatment groups: placebo; aliskiren 75, 150, or 300 mg; HCTZ 6.25, 12.5, or 25 mg; or the combinations except for 300/6.25. Patients assigned to 300/25 were started on 300/12.5 and then escalated to 300/25 at one week. The blinded treatment period was eight weeks, with a primary endpoint of seated trough cuff DBP at the end. Safety monitoring was by AE recording, routine safety labs, vitals signs, physical exams, and ECGs. A diagram of the study plan is presented in the following Figure 4.

Figure 4: Study 2204 Plan



10.1.2.9. Treatment

Dosage and Administration: Aliskiren 75 and 150 mg and HCTZ were formulated as over encapsulated film-coated tablets; aliskiren 300 mg was formulated as a film-coated tablet. Matching placebos for all formulations were provided. All patients were to take two capsules and one tablet at about 8:00 am each morning.

Duration and Adjustment of Therapy: Duration of treatment was eight weeks. Patients assigned to 300/25 were started on 300/12.5 and then escalated to 300/25 at one week. No other adjustments were done.

Concomitant Therapy: Other antihypertensives were prohibited.

10.1.2.10. Safety and Efficacy Endpoints

The primary endpoint was change in trough seated cuff DBP at eight weeks.

10.1.2.11 Statistical Considerations

Sample Size Calculations: A sample size of 2415 completed patients (161 per arm) was targeted. Assuming a dropout rate of 10%, a randomized sample size of 2685 patients was calculated based on a 3.3 mm Hg difference, a standard deviation of 8 mm Hg, and 90% power at the two-sided 0.05 significance level using Dunnett's multiple comparison procedure.

Analysis Cohorts and Missing Data: The primary analysis was to use the "ITT" population (all randomized patients with at least one post-baseline efficacy measurement.) LOCF was to be used for missing data.

Pre-specified Analyses: Both the monotherapy and combination therapy efficacy hypotheses were to be tested at two sided alpha 0.05 without adjustment for multiplicity. For monotherapy the primary analysis model proposed was a two-way ANCOVA with treatment and region as factors and baseline as a covariate. Dunnett's procedure was to be used to adjust for the multiple comparisons between each aliskiren dose and placebo. For combination therapy the primary analysis model proposed was a two-way analysis of covariance model with 4-level aliskiren and 4-level HCTZ treatments as two factors, the baseline as a covariate, and the aliskiren-by-HCTZ interaction terms included in the model.

10.1.2.12 Study Implementation

Disposition of Subjects: A total of 3190 patients enrolled in the single-blind, placebo run-in period of the study and 2763 (87%) patients completed. The most common reason for discontinuation from this period was abnormal test procedure results (7.1%), which included those patients who failed to meet the blood pressure criteria for randomization. Randomization numbers were assigned to 2776 single-blind patients: 2762 of the 2763 patients who completed the single-blind period and 14 patients randomized in error. All 2776 patients were included in the randomized population; however, the 14 patients with erroneous randomization numbers

were not treated and did not provide any post baseline double-blind study data; and therefore, were not included in the other analyses populations.

Of the 2776 randomized patients, 2558 (92%) completed the double-blind treatment period. The proportions of study discontinuations for the treatment groups ranged from 4.0% (300/25) to 11.3% (placebo). The discontinuation rate was highest in the placebo group, most often due to unsatisfactory therapeutic effect and adverse events (AEs). The disposition of the randomized patients is shown in table 79.

Table 79:Disposition of Patients in Study 2204

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

Combination therapy - n (%)	ALI75 / HCTZ6.25	ALI75 / HCTZ12.5	ALI75 / HCTZ25	ALI150 / HCTZ6.25	ALI150 / HCTZ12.5	ALI150 / HCTZ25	ALI300 / HCTZ12.5	ALI300 / HCTZ25	Total
Randomized*	185	193	185	175	186	188	184	173	2776
Completed†	179 (95.2)	175 (90.7)	173 (93.0)	157 (89.2)	177 (95.2)	170 (90.4)	170 (93.9)	166 (96.0)	2558 (92.1)
Discontinued†	9 (4.8)	15 (7.8)	13 (7.0)	17 (9.7)	7 (3.8)	18 (9.6)	11 (6.1)	7 (4.0)	204 (7.3)
Adverse event(s)	3 (1.6)	7 (3.6)	4 (2.2)	7 (4.0)	4 (2.2)	6 (3.2)	3 (1.7)	5 (2.9)	63 (2.3)
Abnormal lab value(s)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	4 (0.1)
Abnormal test/procedure result(s)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.1)
Unsatisfactory therapeutic effect	2 (1.1)	4 (2.1)	4 (2.2)	5 (2.8)	0 (0.0)	1 (0.5)	2 (1.1)	2 (1.2)	56 (2.0)
Cond. no longer requires therapy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.0)
Protocol violation	1 (0.5)	0 (0.0)	3 (1.6)	0 (0.0)	1 (0.5)	1 (0.5)	1 (0.6)	0 (0.0)	13 (0.5)
Subject withdrew consent	2 (1.1)	3 (1.6)	1 (0.5)	2 (1.1)	2 (1.1)	4 (2.1)	2 (1.1)	0 (0.0)	42 (1.5)
Lost to follow-up	1 (0.5)	1 (0.5)	0 (0.0)	2 (1.1)	0 (0.0)	3 (1.6)	2 (1.1)	0 (0.0)	16 (0.6)
Administrative problems	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	5 (0.2)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.0)

10.1.2.14 Subject Demographics and Baseline Characteristics

Overall Baseline Comparisons: The demographics and other selected baseline characteristics are shown in Table 80. The baseline characteristics appear balanced among groups.

Table 80: Baseline characteristics in study 2204

Aliskiren	HCTZ	Male %	White %	Black %	Hispanic %	Mean age	Age ≥65	Mean BMI	Median SBP	Median DBP
Placebo		56	84	4	28	54	20	30	151	99
75		56	83	5	26	55	25	30	153	99
150		61	85	6	30	54	19	29	152	98
300		54	85	4	30	54	21	30	153	99
	6.25	56	83	7	28	55	28	30	153	99
	12.5	55	85	5	27	55	27	29	153	99
	25	52	88	5	26	55	21	29	156	99
75	6.25	57	88	3	25	55	19	29	153	99
75	12.5	52	86	6	23	54	14	30	155	99
75	25	54	89	3	29	55	21	30	153	98
150	6.25	55	85	5	31	54	16	30	152	98
150	12.5	53	85	5	28	55	20	29	155	98
150	25	55	87	3	27	54	20	29	153	98
300	12.5	49	85	6	28	56	27	30	153	99
300	25	57	86	4	28	55	20	30	155	99

10.1.2.15. Monitoring

Investigator staff entered data into an electronic CRF system. Sponsor staff reviewed the data and generated queries that were tracked in an electronic data query system at the sites.

10.1.2.16. Protocol Changes and Violations

The following are some significant protocol violations: 1)Fourteen patients received randomization numbers in error, were not treated with double blind study medication, and did not provide any post-baseline study data. These patients are included in the randomized population (n=2776); however, they are not included in the other analysis populations; 2) One patient successfully completed the single blind phase and was dispensed double blind study medication without randomization and medication assignment by IVRS. The patient was treated for up to 6 days prior to discontinuation (protocol violator), and there were no reported AEs. Post-baseline laboratory tests were not performed; 3) One patient received an additional week of aliskiren/HCTZ 150/12.5 mg prior to titrating to their assigned aliskiren/HCTZ 150/25 mg due to a technical difficulty with IVRS that resulted in Week 3 treatment being dispensed at Week 4; and 4) Two patients received placebo instead of their assigned study medication (aliskiren 75 mg; aliskiren/HCTZ 75/25 mg) for 9 and 10 days, respectively, were subsequently discontinued due to protocol violation, and excluded from the per protocol population.

Protocol deviations that did not require exclusion from analysis populations each occurred at similar rates across treatment groups. The most frequently occurring deviation was DBP $\geq$110 mm Hg or SBP$\geq$180 mm Hg after visit 3 (overall 2.2 and 1.4%, respectively). Other minor deviations each occurred in less than 1% of the total patients.

10.1.2.17. Dosing

Study Drug: Dosing variations occurred as described in protocol violation.

Concomitant Therapy: The more commonly used concomitant medications were similar in type and proportion to those observed during the pre-randomization period, and included HMG CoA reductase inhibitors (e.g. statins, 14%); anilides (e.g. paracetamol, 12%); salicylic acid and derivatives (11%); and nonsteroidal anti-inflammatory topical preparations (10%). Other antihypertensives were taken by 1.1% of the study population.

Blinding: No patients were unblinded during the study.

10.1.2.18. Efficacy

Primary Endpoint: Changes from baseline in DBP are shown in Table 81. For DBP in this study all dosages of aliskiren show antihypertensive efficacy and most dosages combined with HCTZ show added efficacy. The results are sufficiently robust to be convincing. However, that the effect size is small for aliskiren 75 and 150 mg and they are not differentiated. The dosages of HCTZ alone are also not differentiated. There is also a substantial placebo effect (nearly 7 mm Hg.)

Table 81: Change from Baseline in DBP at 8 Weeks LOCF in Study 2204

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

Pairwise Comparison		LSM difference Change from Baseline (SE)	95% CI	Nominal p-value
Aliskiren 75 mg	vs. placebo	-1.75 (0.83)	(-3.37, -0.13)	0.0344*
Aliskiren 150 mg	vs. placebo	-2.01 (0.83)	(-3.63, -0.39)	0.0152*
Aliskiren 300 mg	vs. placebo	-3.33 (0.83)	(-4.95, -1.70)	< 0.0001*
Aliskiren 75 mg/HCTZ 6.25 mg	vs. aliskiren 75 mg	-2.08 (0.83)	(-3.71, -0.45)	0.0126*
	vs. HCTZ 6.25 mg	-1.69 (0.82)	(-3.30, -0.08)	0.0394*
	vs. placebo	-3.83 (0.82)	(-5.44, -2.22)	< 0.0001*
Aliskiren 75 mg/HCTZ 12.5 mg	vs. aliskiren 75 mg	-2.46 (0.83)	(-4.09, -0.83)	0.0031*
	vs. HCTZ 12.5 mg	-1.03 (0.83)	(-2.65, 0.59)	0.2124
	vs. placebo	-4.21 (0.82)	(-5.82, -2.60)	< 0.0001*
Aliskiren 75 mg/HCTZ 25 mg	vs. aliskiren 75 mg	-2.77 (0.83)	(-4.41, -1.14)	0.0009*
	vs. HCTZ 25 mg	-2.09 (0.85)	(-3.75, -0.43)	0.0136*
	vs. placebo	-4.52 (0.82)	(-6.14, -2.91)	< 0.0001*
Aliskiren 150 mg/HCTZ 6.25 mg	vs. aliskiren 150 mg	-1.41 (0.85)	(-3.08, 0.25)	0.0962
	vs. HCTZ 6.25 mg	-1.29 (0.84)	(-2.93, 0.36)	0.1249
	vs. placebo	-3.42 (0.84)	(-5.07, -1.78)	< 0.0001*
Aliskiren 150 mg/HCTZ 12.5 mg	vs. aliskiren 150 mg	-2.96 (0.84)	(-4.60, -1.32)	0.0004*
	vs. HCTZ 12.5 mg	1.79 (0.83)	(-3.42, -0.16)	0.0314*
	vs. placebo	-4.97 (0.83)	(-6.59, -3.35)	< 0.0001*
Aliskiren 150 mg/HCTZ 25 mg	vs. aliskiren 150 mg	-3.70 (0.83)	(-5.33, -2.07)	< 0.0001*
	vs. HCTZ 25 mg	-3.28 (0.85)	(-4.94, -1.62)	0.0001*
	vs. placebo	-5.71 (0.82)	(-7.33, -4.10)	< 0.0001*
Aliskiren 300 mg/HCTZ 12.5 mg	vs. aliskiren 300 mg	-3.61 (0.84)	(-5.26, -1.95)	< 0.0001*
	vs. HCTZ 12.5 mg	-3.76 (0.84)	(-5.39, -2.12)	< 0.0001*
	vs. placebo	-6.93 (0.83)	(-8.56, -5.31)	< 0.0001*
Aliskiren 300 mg/HCTZ 25 mg	vs. aliskiren 300 mg	-4.00 (0.85)	(-5.68, -2.33)	< 0.0001*
	vs. HCTZ 25 mg	-4.90 (0.86)	(-6.59, -3.21)	< 0.0001*
	vs. placebo	-7.33 (0.84)	(-8.98, -5.68)	< 0.0001*

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

Secondary endpoints: Changes from baseline in SBP are shown in Table 82. For SBP in this study the one aliskiren dosage not showing convincing efficacy is aliskiren 75 mg. The placebo-corrected decreases are reasonable (-5 to -14) for all other dosages and combinations. Aliskiren 150 mg is differentiated from aliskiren 75 mg, as are HCTZ 12.5 and 25 from 6.25. There is also a substantial placebo effect (-7.5 mm Hg) as there was for DBP.

Table 82: Change from Baseline in SBP at 8 Weeks LOCF in Study 2204

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

Pairwise Comparison		LSM difference		
		Change from Baseline (SE)	95% CI	Nominal p-value
Aliskiren 75 mg	vs. placebo	-1.89 (1.31)	(-4.46, 0.69)	0.1512
Aliskiren 150 mg	vs. placebo	-4.76 (1.31)	(-7.34, -2.18)	0.0003*
Aliskiren 300 mg	vs. placebo	-8.25 (1.32)	(-10.84, -5.67)	< 0.0001*
Aliskiren 75 mg/HCTZ 6.25 mg	vs. aliskiren 75 mg	-4.93 (1.32)	(-7.52, -2.33)	0.0002*
	vs. HCTZ 6.25 mg	-3.34 (1.30)	(-5.90, -0.79)	0.0103*
	vs. placebo	-6.81 (1.31)	(-9.38, -4.25)	< 0.0001*
Aliskiren 75 mg/HCTZ 12.5 mg	vs. aliskiren 75 mg	-6.27 (1.32)	(-8.86, -3.69)	< 0.0001*
	vs. HCTZ 12.5 mg	-1.71 (1.31)	(-4.28, 0.85)	0.1905
	vs. placebo	-8.16 (1.30)	(-10.71, -5.60)	< 0.0001*
Aliskiren 75 mg/HCTZ 25 mg	vs. aliskiren 75 mg	-7.95 (1.32)	(-10.55, -5.36)	< 0.0001*
	vs. HCTZ 25 mg	-3.02 (1.34)	(-5.66, -0.39)	0.0246*
	vs. placebo	-9.84 (1.31)	(-12.40, -7.27)	< 0.0001*
Aliskiren 150 mg/HCTZ 6.25 mg	vs. aliskiren 150 mg	-3.07 (1.35)	(-5.71, -0.42)	0.0230*
	vs. HCTZ 6.25 mg	-4.36 (1.33)	(-6.97, -1.75)	0.0011*
	vs. placebo	-7.83 (1.33)	(-10.44, -5.21)	< 0.0001*
Aliskiren 150 mg/HCTZ 12.5 mg	vs. aliskiren 150 mg	-5.37 (1.33)	(-7.97, -2.77)	< 0.0001*
	vs. HCTZ 12.5 mg	-3.69 (1.32)	(-6.27, -1.10)	0.0052*
	vs. placebo	-10.13 (1.31)	(-12.70, -7.56)	< 0.0001*
Aliskiren 150 mg/HCTZ 25 mg	vs. aliskiren 150 mg	-7.23 (1.32)	(-9.82, -4.64)	< 0.0001*
	vs. HCTZ 25 mg	-5.17 (1.34)	(-7.81, -2.54)	0.0001*
	vs. placebo	-11.99 (1.31)	(-14.55, -9.43)	< 0.0001*
Aliskiren 300 mg/HCTZ 12.5 mg	vs. aliskiren 300 mg	-4.08 (1.34)	(-6.71, -1.45)	0.0024*
	vs. HCTZ 12.5 mg	-5.89 (1.33)	(-8.49, -3.29)	< 0.0001*
	vs. placebo	-12.33 (1.32)	(-14.92, -9.75)	< 0.0001*
Aliskiren 300 mg/HCTZ 25 mg	vs. aliskiren 300 mg	-5.48 (1.35)	(-8.14, -2.83)	< 0.0001*
	vs. HCTZ 25 mg	-6.92 (1.37)	(-9.60, -4.24)	< 0.0001*
	vs. placebo	-13.74 (1.33)	(-16.35, -11.1)	< 0.0001*

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

10.1.2.19. Subgroup analysis

Country: Other than the varying placebo effect by region and the greater variability in all results due to the smaller sample sizes by region, the results by region do not suggest any clear variation

in effect by region or substantial differences from the overall effect. Data were summarized in the following table 83.

Table 83: Change from Baseline in DBP by Region in Study 2204

Aliskiren	HCTZ	E. Europe/Asia	S. America	US	Canada	W. Europe	All
Placebo		-9.2	-5.7	-5.0	-4.1	-7.6	-7.0
75		-10.0	-10.4	-6.8	-3.5	-9.2	-8.8
150		-11.0	-8.3	-6.9	-5.0	-9.8	-9.1
300		-13.3	-11.7	-10.0	-9.3	-9.6	-10.4
	6.25	-13.8	-11.1	-8.8	-3.4	-8.3	-9.2
	12.5	-10.9	-11.8	-10.0	-7.8	-9.9	-10.2
	25	-9.9	-9.3	-7.1	-10.4	-10.0	-9.4
75	6.25	-10.8	-8.4	-7.9	-9.7	-12.1	-10.8
75	12.5	-12.3	-10.3	-10.7	-8.4	-11.5	-11.2
75	25	-15.4	-11.1	-8.5	-6.2	-12.1	-11.6
150	6.25	-15.5	-12.9	-9.8	-5.8	-9.4	-10.5
150	12.5	-10.8	-13.9	-11.4	-8.7	-12.3	-12.0
150	25	-14.6	-12.7	-13.0	-9.6	-12.6	-12.8
300	12.5	-12.3	-14.7	-14.8	-10.2	-14.2	-14.0
300	25	-16.9	-17.7	-10.8	-10.8	-14.3	-14.3

Race: Because the subjects were predominantly white (86%), the representation of other races is too small to generate reliable estimates of effects by race.

Age and Gender: Women showed a slightly larger placebo effect than men. After performing a gender-specific placebo correction, the BP reductions in women are slightly but not consistently greater than those in men. Data were summarized in the following table 84. There is no significant age-related effect.

Table 84: Placebo-corrected Change from Baseline in DBP by Gender in Study 2204

Aliskiren	HCTZ	Male	Female	Both
Placebo		0.0	0.0	0.0
75		-1.8	-1.8	-1.8
150		-2.0	-2.5	-2.1
300		-2.8	-4.1	-3.4
	6.25	-2.4	-1.9	-2.2
	12.5	-2.7	-3.7	-3.2

Aliskiren	HCTZ	Male	Female	Both
	25	-2.2	-2.6	-2.4
75	6.25	-3.3	-4.7	-3.8
75	12.5	-4.3	-3.9	-4.2
75	25	-4.5	-4.6	-4.6
150	6.25	-2.4	-4.8	-3.5
150	12.5	-4.9	-5.0	-5.0
150	25	-5.9	-5.6	-5.8
300	12.5	-7.0	-6.7	-7.0
300	25	-6.9	-7.9	-7.3

Exposure: Median exposure was the same in all groups, 56 days.

Serious Adverse Events: There was one death in the 150/25 group due to thoracic trauma from a traffic accident. The investigator reported this death as unrelated to study medication. There 21 serious adverse events (see section 7.1.2 for detailed case report)

Events Leading to Discontinuation: The rates of events leading to discontinuation are show in Table 85.

Table 85: Rates of Deaths, SAEs, and Discontinuations in Study 2204

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

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

Reasons for discontinuation were varied, with headache being the most frequent across all groups. Some interesting reasons for discontinuation, in addition to those covered as SAEs above, were the following:

- Three patients, a 37-year-old male in the 75/25 group, a 54-year-old female in the 300 group, and a 61-year-old female in the 300/25 group, withdrew because of cough.
- Four patients, a 57-year-old white male in the 75/6.25 group, a 62-year-old white female and a 41-year-old white male in the 150/6.25 group, and a 46-year-old white female in the 150/12.5 group, withdrew because of rash.
- Eight patients, a 55-year-old white male in the 75 group, a 54-year-old white male (ulcerative colitis, see SAE above) and a 48-year-old white male (abdominal pain, diarrhea) in the 150/6.25 group, a 47-year-old white female (burning, vomiting) and a 60- year-old white male (abdominal pain) in the 150/12.5 group, a 52-year-old white female (stomach pain) and a 41-year-old white female (nausea) in the 150/25 group, a 52-yearold black male (nausea) in the 300/25 group, withdrew because of GI complaints. One patient in each of the placebo, and HCTZ 6.25, 12.5, and 25 groups withdrew because of GI complaints.

Events of Special Interest: There were no cases of angioedema reported in this study.

Overall Adverse Events: Rates of patients with any adverse event ranged from 35% to 45% by group, averaging about 40%. The placebo group had one of the higher rates (44%), notably because of a high rate of headaches (13%). No significant dose-related AEs were observed. The overall rates of AEs by group and the most frequent AEs (≥ 2% in any group) are shown in Table 86.

Table 86: Adverse Events ≥ 2% in Any Group in Study 2204

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

Combination therapy - n (%)	ALI75 / HCTZ6.25 N = 188	ALI75 / HCTZ12.5 N = 198	ALI75 / HCTZ25 N = 186	ALI150 / HCTZ6.25 N = 174	ALI150 / HCTZ12.5 N = 184	ALI150 / HCTZ25 N = 188	ALI300 / HCTZ12.5 N = 181	ALI300 / HCTZ25 N = 173	Total N =2762
Any Adverse Events	65 (34.6)	75 (39.5)	77 (41.4)	66 (37.9)	72 (39.1)	83 (44.1)	82 (45.3)	71 (41.0)	1111 (40.2)
Headache	11 (5.9)	14 (7.4)	11 (5.9)	8 (4.6)	15 (8.2)	9 (4.8)	16 (8.8)	14 (8.1)	199 (7.2)
Nasopharyngitis	9 (4.8)	6 (3.2)	10 (5.4)	5 (2.9)	3 (1.6)	7 (3.7)	7 (3.9)	9 (5.2)	104 (3.8)
Influenza	5 (2.7)	5 (2.6)	4 (2.2)	3 (1.7)	1 (0.5)	6 (3.2)	2 (1.1)	7 (4.0)	53 (1.9)
Vertigo	2 (1.1)	2 (1.1)	1 (0.5)	0 (0.0)	1 (0.5)	3 (1.6)	3 (1.7)	5 (2.9)	27 (1.0)
Diarrhea	0 (0.0)	2 (1.1)	3 (1.6)	3 (1.7)	1 (0.5)	6 (3.2)	6 (3.3)	3 (1.7)	46 (1.7)
Dizziness	2 (1.1)	5 (2.6)	5 (2.7)	2 (1.1)	6 (3.3)	3 (1.6)	9 (5.0)	3 (1.7)	55 (2.0)
Edema peripheral	1 (0.5)	3 (1.6)	0 (0.0)	0 (0.0)	2 (1.1)	1 (0.5)	3 (1.7)	3 (1.7)	29 (1.0)
Abdominal pain upper	1 (0.5)	1 (0.5)	1 (0.5)	0 (0.0)	3 (1.6)	4 (2.1)	1 (0.6)	2 (1.2)	27 (1.0)
Arthralgia	2 (1.1)	2 (1.1)	6 (3.2)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.6)	2 (1.2)	22 (0.8)
Asthenia	1 (0.5)	2 (1.1)	5 (2.7)	2 (1.1)	2 (1.1)	3 (1.6)	2 (1.1)	2 (1.2)	32 (1.2)
Back pain	2 (1.1)	7 (3.7)	1 (0.5)	1 (0.6)	2 (1.1)	3 (1.6)	3 (1.7)	2 (1.2)	40 (1.4)
Muscle spasms	3 (1.6)	1 (0.5)	3 (1.6)	1 (0.6)	1 (0.5)	0 (0.0)	0 (0.0)	2 (1.2)	27 (1.0)
Rhinitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	2 (1.1)	2 (1.1)	2 (1.2)	17 (0.6)
Upper respiratory tract infection	2 (1.1)	0 (0.0)	2 (1.1)	3 (1.7)	3 (1.6)	2 (1.1)	2 (1.1)	2 (1.2)	29 (1.0)
Cough	3 (1.6)	3 (1.6)	2 (1.1)	2 (1.1)	2 (1.1)	4 (2.1)	2 (1.1)	1 (0.6)	28 (1.0)
Flatulence	1 (0.5)	0 (0.0)	4 (2.2)	1 (0.6)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.6)	15 (0.5)
Nausea	2 (1.1)	5 (2.6)	0 (0.0)	1 (0.6)	2 (1.1)	4 (2.1)	2 (1.1)	1 (0.6)	32 (1.2)
Palpitations	1 (0.5)	2 (1.1)	1 (0.5)	1 (0.6)	2 (1.1)	5 (2.7)	2 (1.1)	1 (0.6)	26 (0.9)
Bronchitis	1 (0.5)	2 (1.1)	0 (0.0)	4 (2.3)	2 (1.1)	1 (0.5)	1 (0.6)	0 (0.0)	23 (0.8)
Constipation	3 (1.6)	2 (1.1)	2 (1.1)	0 (0.0)	1 (0.5)	2 (1.1)	2 (1.1)	0 (0.0)	25 (0.9)
Urinary tract inf.	1 (0.5)	0 (0.0)	0 (0.0)	2 (1.1)	3 (1.6)	0 (0.0)	5 (2.8)	0 (0.0)	24 (0.9)
Vomiting	0 (0.0)	1 (0.5)	2 (1.1)	0 (0.0)	3 (1.6)	2 (1.1)	0 (0.0)	0 (0.0)	16 (0.6)

10.1.2.21 Laboratory Findings

The mean changes are consistent with the effects of HCTZ (decrease in potassium, increases in creatinine, urea, uric acid, and ALT) and aliskiren. The mean increases in creatinine, urea, and uric acid appear to be additive for HCTZ and aliskiren. These latter mean increases are confirmed by the shifts from normal to high for these lab values. The shifts also suggest that both HCTZ and aliskiren may produce a slight decrease in hemoglobin and RBC count. Changes from baseline in mean values for selected lab tests (those which aliskiren appears to affect) are shown in table 87 and shift tables for the selected lab tests are shown in table 88. All of these changes are minor and did not show clinical significance.

Table 87: Change from Baseline in Selected Lab Values in Study 2204

Aliskiren	HCTZ	Hgb	RBC	Potassium	Creatinine	Urea	Uric Acid	ALT
Placebo		0.8%	1.9%	0.7%	0.6%	-0.6%	0.3%	3.9%
75		0.1%	0.6%	2.3%	0.5%	2.2%	0.9%	-2.8%
150		0.0%	0.4%	1.8%	0.3%	1.9%	1.7%	5.4%
300		-0.4%	-0.2%	1.8%	0.9%	5.8%	0.0%	2.3%
	6.25	0.6%	0.8%	-0.7%	2.6%	5.0%	4.2%	-1.5%
	12.5	0.7%	1.3%	-3.2%	1.9%	7.1%	7.9%	4.8%
	25	0.1%	0.8%	-4.5%	2.4%	8.4%	12.5%	7.9%
75	6.25	-0.3%	0.2%	0.5%	1.4%	7.7%	7.1%	4.5%
75	12.5	-0.3%	0.6%	-2.5%	2.7%	6.7%	10.1%	1.6%
75	25	0.3%	0.2%	-4.4%	2.5%	8.9%	13.6%	-10.2%
150	6.25	-0.5%	0.0%	-1.6%	1.9%	4.0%	6.2%	7.7%
150	12.5	-0.5%	0.0%	-3.2%	2.5%	8.3%	9.5%	6.0%
150	25	-0.3%	0.0%	-3.7%	4.5%	12.1%	14.7%	2.4%
300	12.5	-0.4%	0.0%	-0.2%	3.0%	9.0%	10.5%	6.1%
300	25	-0.3%	0.2%	-2.5%	6.0%	13.2%	15.8%	4.1%

Hgb = hemoglobin; RBC = red blood cell count; ALT = alanine aminotransferase

Table 88: Shift Table Changes (Extreme Values) for Selected Lab Tests in Study 2204

Aliskiren	HCTZ	Hgb	RBC	Potassium	Creatinine	Urea	Uric Acid	ALT
		N→L	N→L	N→H	N→H	N→H	N→H	N→H
Placebo		2%	2%	1%	8%	3%	9%	6%
75		4%	7%	1%	9%	3%	11%	8%
150		3%	7%	2%	5%	5%	13%	12%
300		4%	8%	3%	9%	6%	10%	3%
	6.25	2%	7%	2%	8%	7%	17%	12%
	12.5	3%	1%	0%	10%	8%	22%	7%
	25	4%	5%	1%	9%	6%	33%	11%
75	6.25	4%	6%	1%	12%	8%	20%	10%
75	12.5	3%	3%	0%	13%	6%	26%	8%
75	25	4%	4%	0%	11%	9%	31%	10%
150	6.25	3%	7%	0%	8%	8%	17%	14%
150	12.5	7%	10%	0%	5%	4%	26%	10%
150	25	5%	5%	1%	14%	7%	37%	11%
300	12.5	3%	10%	1%	13%	12%	26%	7%
300	25	5%	9%	0%	25%	9%	42%	12%

N→L= normal to low; N→H = normal to high
Hgb = hemoglobin; RBC = red blood cell count; ALT = alanine aminotransferase