Table 74: Reviewer's Mean Change from Baseline in DBP by Age in Study 2201

	Age<65	Age≥65
Irbesartan	-8.4	-10.9
Placebo	-6.3	-7.3
150	-9.3	-10.1
300	-11.9	-12.5
600	-11.4	-12.7

Table 75: Reviewer's Mean Change from Baseline in DBP by Gender in Study 2201

	Male	Female
Irbesartan	-9.2	-8.9
Placebo	-4.4	-8.6
150	-9.2	-9.8
300	-10.9	-12.8
600	-10.1	-13.4

COMMENT: In this study there do not appear to be differential effects by age. Females appear to show a greater placebo effect than males.

10.1.3.38 Safety

10.1.3.39 Exposure
Median exposure was the same in all groups, 57 days.

10.1.3.40 Serious Adverse Events

10.1.3.41 Deaths
No deaths occurred.

10.1.3.42 Hospitalizations
No patients in the aliskiren group were hospitalized for AEs, although two each in the placebo and irbesartan groups were hospitalized for AEs.

10.1.3.43 Other serious adverse events
There were no SAEs in the aliskiren groups.

10.1.3.44 Events Leading to Discontinuation
Discontinuations due to AEs were slightly higher with aliskiren (3%) than with placebo or irbesartan (both about 2%). The aliskiren discontinuations included several for GI disturbances

(dyspepsia, nausea, vomiting) and several for neurologic symptoms (somnolence, dizziness, headache, paresthesias) but otherwise showed no patterns.

10.1.3.45 Events of Special Interest

There were no specific reports of angioedema, but there were one case of eyelid edema (right eye) and one case of swelling of the hands and feet in the aliskiren 600 mg group. Both cases resolved without discontinuation of study drug. Note also the peripheral edema AEs tabulated in the next section.

10.1.3.46 Overall Adverse Events

The common adverse events, those with a frequency ≥ 2% in any group, are shown in Table 76.

Table 76: Sponsor's Adverse Events ≥ 2% Frequency in Any Group in Study 2201

	Placebo N=131 n (%)	Aliskiren 150 mg N=127 n (%)	Aliskiren 300 mg N=130 n (%)	Aliskiren 600 mg N=130 n (%)	Aliskiren subtot N=387 n (%)	Irbesartan 150 mg N=134 n (%)
Any adverse events	42 (32.1)	34 (26.8)	47 (36.2)	43 (33.1)	124 (32.0)	49 (36.6)
Headache	7 (5.3)	3 (2.4)	8 (6.2)	6 (4.6)	17 (4.4)	4 (3.0)
Diarrhea	2 (1.5)	2 (1.6)	1 (0.8)	9 (6.9)	12 (3.1)	2 (1.5)
Dizziness	5 (3.8)	2 (1.6)	4 (3.1)	3 (2.3)	9 (2.3)	5 (3.7)
Fatigue	4 (3.1)	1 (0.8)	5 (3.8)	2 (1.5)	8 (2.1)	2 (1.5)
Back pain	0 (0.0)	2 (1.6)	3 (2.3)	2 (1.5)	7 (1.8)	6 (4.5)
Cough	1 (0.8)	2 (1.6)	4 (3.1)	0 (0.0)	6 (1.6)	1 (0.7)
Nasopharyngitis	4 (3.1)	2 (1.6)	0 (0.0)	2 (1.5)	4 (1.0)	1 (0.7)
Edema peripheral	1 (0.8)	0 (0.0)	1 (0.8)	3 (2.3)	4 (1.0)	2 (1.5)
Nausea	2 (1.5)	0 (0.0)	3 (2.3)	1 (0.8)	4 (1.0)	2 (1.5)
Sinus congestion	2 (1.5)	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.3)	3 (2.2)
Depression	3 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

COMMENT: Note that diarrhea and peripheral edema appear to show a dose-related frequency.

10.1.3.47 Laboratory Findings

Other drugs that block or reduce angiotensin, such as ACEIs and ARBs, have recognized renal and hematologic adverse effects. They increase serum potassium, reduce renal function, and reduce hemoglobin slightly. Aliskiren appears to share these properties. I show changes from baseline in selected lab tests (ones that suggest some effects of aliskiren) in Table 77 and the most pertinent shift table changes in Table 78.

Table 77: Reviewer's Percent Mean Change from Baseline in Selected Lab Tests in Study 2201

Group	Hemoglobin	RBC	Potassium	Uric Acid	ALT
0	0.8%	0.4%	0.0%	-0.1%	-5.6%

150	-0.1%	-0.6%	0.2%	1.3%	-3.1%
300	-0.8%	-1.7%	1.9%	2.9%	3.9%
600	-2.0%	-2.9%	0.7%	3.0%	8.5%
Irbesartan	-1.3%	-2.1%	0.2%	-0.8%	1.8%

RBC = red blood cell count; ALT = alanine aminotransferase

Mean changes in creatinine and urea were not differentiated among the groups.

Table 78: Reviewer's Shift Table Changes (Extreme Values) for Selected Lab Tests in Study 2201

Group	Hemoglobin	RBC	Potassium	Uric Acid	ALT
Shift	N→L	N→L	N→H	N→H	N→H
0	0.0%	1.9%	0.8%	1.7%	0.9%
150	0.9%	3.6%	1.7%	5.3%	3.5%
300	0.0%	4.5%	0%	5.7%	4.4%
600	2.5%	8.5%	0.8%	2.6%	5.9%
Irbesartan	3.4%	2.7%	0%	3.4%	1.7%

N→L= normal to low; N→H = normal to high

In addition to these numeric findings, there were two AEs reported of increased creatine kinase, one in an aliskiren 150 mg patient and one in an aliskiren 600 mg patient.

COMMENT: Aliskiren appears to produce a small, dose-related drop in hemoglobin similar to that produced by ACEIs and ARBs. Note that the drops appear to be greater for the RBC count than hemoglobin (suggesting a macrocytic effect). Aliskiren also increases potassium slightly like ACEIs and ARBs. Aliskiren increases serum uric acid and liver function tests. All of these changes are explored in more detail in the Integrated Summary of Safety.

10.1.3.48 Adverse Events in Subgroups

Adverse event rates in subgroups (age, gender, race, etc.) were not analyzed in this study but are analyzed in the Integrated Summary of Safety.

10.1.3.49 Summary

10.1.3.50 Efficacy Summary

Aliskiren appears to show reasonable anti-hypertensive activity with mean placebo-subtracted reductions in blood pressure of -16/-12. The 600 mg dosage is not clearly differentiated from the 300 mg. The trough/peak ratios suggest BID dosing may be preferable. Reductions appear to be less in blacks than whites.

10.1.3.51 Safety Summary

Aliskiren appears to have a reasonable adverse event profile with the most common adverse events different from placebo being diarrhea and peripheral edema. Aliskiren, like other RAAS inhibitors, reduces hemoglobin slightly and increases serum potassium. It also appears to

increase uric acid and ALT. Effects upon renal function are unclear from this study. Whether the uric acid and ALT increases are clinically important is not determinable from this small, short term study.

10.1.3.52 Conclusions

From these study results aliskiren appears to be an effective anti-hypertensive. Its short-term adverse effect profile appears reasonable, but the duration and extent of exposure is too limited in this one study to conclude that the drug is safe.

10.1.4 Study 2203 - A randomized, double-blind, multicenter, multifactorial, placebo-controlled, parallel-group study to confirm the efficacy and safety of aliskiren monotherapy, and evaluate efficacy and safety of combinations of aliskiren and valsartan in hypertensive patients

10.1.4.1 Background

This is a large study using aliskiren in combination with valsartan. Because it includes large placebo and monotherapy arms, it could be supportive of efficacy of monotherapy.

10.1.4.2 Initial Protocol

The original protocol is dated October 6, 2003.

10.1.4.3 Protocol Amendments

There was one amendment dated January 20, 2004, implementing the following changes:

1. The primary objective was changed from comparing the combination and monotherapy to comparing monotherapy to placebo. The number of subjects randomized into the placebo and aliskiren monotherapy groups was increased to provide 90% power to detect a 3.5 mmHg difference between any aliskiren dose group and placebo.

2. Numbers of subjects in the combination groups as well as the active control group (valsartan/HCTZ) were slightly reduced to provide enough information to explore three combinations of aliskiren and valsartan.

3. The study treatment duration was extended from 6 weeks to 8 weeks.

4. The protocol allowed for the inclusion of type 1 and type 2 diabetic patients and patients who were taking insulin who had a baseline HbA1c $\leq$ 8%.

5. hsC-reactive protein was added to the biomarkers of cardiovascular risk measured at baseline and end of study.

6. The [redacted] automated blood pressure device was replaced with the standard calibrated mercury sphygmomanometer for blood pressure assessment.

10.1.4.4 Sites and Investigators

There were 94 centers in Denmark (5), France (11), Germany (41), Poland (8), and the US (29).

10.1.4.5 Study Dates

The first patient enrolled on March 15, 2005, and the last patient completed on October 12, 2004.

10.1.4.6 Study Design

This was an international, multicenter, randomized, double-blind, multiple dosage, placebo and active-controlled, mono- and combination therapy, parallel group study.

10.1.4.7 Objectives

The primary objective of this study (based on amendment 1) was to confirm the blood pressure lowering effects of aliskiren 75 mg, 150 mg and 300 mg given alone versus placebo administered for 8 weeks in patients with mild-to-moderate hypertension. The secondary objectives were to assess the safety and tolerability of the monotherapy and combinations, to compare the antihypertensive effects of the combinations to the monotherapy, and to assess various biomarkers.

10.1.4.8 Number of Subjects, Randomization, and Blinding

The planned number of subjects was 1064. Three times the numbers of patients were to be randomized in the three aliskiren monotherapy and placebo groups than in the seven combination groups. Randomization was by IVRS.—stratification or blocking is not stated. Blinding was accomplished by using identical appearing capsules for all study drugs except that aliskiren 300 mg and matching placebo were provided as tablets. If necessary, unblinding was to be accomplished by IVRS.

10.1.4.9 Inclusion and Exclusion Criteria

The inclusion criteria were the following: age 18 or older; male or post-menopausal, surgically sterile, or using effective contraception female; BP 80-109 at day -7 and 95-109 day 1; DBP difference <11 during last two visits; and written informed consent. The exclusion criteria were previous treatment; BP >179/109; inability to stop antihypertensives; secondary hypertension; grade III-IV hypertensive retinopathy; history of CVA or hypertensive encephalopathy; TIA within 12 months; heart failure; CABG or PTCA within 6 months; MI within 12 months; unstable angina; 2nd or 3rd degree heart block without pacemaker; serious arrhythmias; diabetes with HgbA1c>8%; abnormal serum sodium or potassium or dehydration; condition affecting ADME, including AST/ALT > 2x, creatinine > 1.5x ULN; malignancy within 5 years; any life-threatening disease; drug or alcohol abuse within 12 months; pregnant or nursing; any condition jeopardizing patient or study per investigator; allergies or contraindications to study drugs; SLE; gout; noncompliance; any condition jeopardizing evaluation; and involved in protocol execution.

10.1.4.10 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 to one of groups: aliskiren 75, 150, or 300 mg; valsartan 80, 160, or 320 mg; aliskiren/valsartan 75/80, 140/160, or 300/320 mg; valsartan/HCTZ 160/12.5 mg; or placebo once daily for an 8-week treatment period. Three times as many patients were to be randomized to aliskiren monotherapy and placebo groups than to the other groups. Seated cuff blood pressure was measured at trough at visits at 1, 2, 4, 6, and 8 weeks. Electrolytes and creatinine were measured at week 2, and ECG and routine safety labs were done at screening and end of study. A diagram of the study plan is presented in Figure 24.

Figure 24: Study 2203 Plan

Single-blind run-in			Double-blind treatment					
2 weeks	1 week	1 week, optional	8 weeks					
Visit 1	Visit 2	Optional visit[1] 201	3	4	5	6	7	8
Day -21	Day -7		1	7	14	28	42	56
			↓ Randomization					
			Aliskiren 75 mg o.d.					
			Aliskiren 150 mg o.d.					
			Aliskiren 300 mg o.d.					
			Valsartan 80 mg o.d.					
			Valsartan 160 mg o.d.					
			Valsartan 320 mg o.d.					
			Aliskiren 75 mg/valsartan 80 mg o.d.					
			Aliskiren 150 mg/valsartan 160 mg o.d.					
			Aliskiren 300 mg/valsartan 320 mg o.d. (titrated from aliskiren 150 mg/valsartan 160 mg o.d. on day 7)					
			Valsartan 160 mg/HCTZ 12.5 mg o.d.					
			Placebo o.d.					

10.1.4.11 Treatment

10.1.4.12 Dosage and Administration

All dosing was orally (two capsules and one tablet) in the morning. Aliskiren 75 mg was an overencapsulated tablet and aliskiren 150 mg was an overencapsulated film-coated tablet. These latter formulations are different than the to-be-marketed formulation. Aliskiren 300 mg was the market formulation.

10.1.4.13 Duration and Adjustment of Therapy

Duration of treatment was eight weeks. Patients randomized to aliskiren/valsartan 300/320 were started on 150/160 and then up-titrated to 300/320 at one week.

10.1.4.14 Concomitant Therapy
Other antihypertensives were prohibited.

10.1.4.15 Safety and Efficacy Endpoints
The primary efficacy endpoint was change in trough seated DBP at eight weeks. The protocol lists secondary endpoints of safety and tolerability, change in SBP, safety and tolerability of the combination, BP changes with the combination, and biomarkers. The protocol does not define an approach for preserving alpha for the secondary endpoints except to assert that the BP lowering effects of the combination will also be evaluated at an alpha of 0.05.

10.1.4.16 Statistical Considerations

10.1.4.17 Sample Size Calculations
The sample size calculations (1064 total) use a power of 90% at alpha 0.05 to detect a 3.5 mm Hg difference for the proposed primary analysis assuming a standard deviation of 8 mm Hg and dropout rate of 10%.

10.1.4.18 Analysis Cohorts and Missing Data
The protocol defines the primary analysis cohort as all randomized patients with at least one post-treatment BP measurement. It specifies last observation carried forward (LOCF) for missing data.

10.1.4.19 Pre-specified Analyses
The protocol defines the primary endpoint analysis as a two-way analysis of covariance model with treatment and region (randomization strata) as two factors, and the baseline as a covariate. It specifies Dunnett's procedure to control for multiplicity of the comparisons of the three dose levels to placebo.

10.1.4.20 Results

10.1.4.21 Study Implementation

10.1.4.22 Disposition of Subjects
A total of 1441 patients were enrolled in the single-blind period of the study. Of these, 1123 (78%) patients completed the single-blind period and were randomized to double-blind treatment and 318 (22%) discontinued from the single-blind period. The most common reasons given were: abnormal test procedure results (13%), abnormal laboratory values (3%), withdrew consent (3%), and adverse events (1.5%). The disposition of the randomized patients is shown in Table 79.

COMMENT: The dropout rates and reasons for dropout don't suggest any consistent problems.

Table 79: Sponsor's Disposition of Patients in Study 2203

Disposition	Placebo n (%)	ALI 75 n (%)	ALI 150 n (%)	ALI 300 n (%)	VAL 80 n (%)	VAL 160 n (%)
Randomized:						
Total	177	179	178	175	58	59
Completed	162 (91.5)	158 (88.3)	165 (92.7)	166 (94.9)	54 (93.1)	52 (88.1)
Discontinued	15 (8.5)	21 (11.7)	13 (7.3)	9 (5.1)	4 (6.9)	7 (11.9)
Reason for discontinuation						
Adverse event(s)	6 (3.4)	5 (2.8)	2 (1.1)	3 (1.7)	0 (0.0)	2 (3.4)
Abnormal laboratory value(s)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Unsatisfactory therapeutic effect	5 (2.8)	10 (5.6)	4 (2.2)	4 (2.3)	2 (3.4)	0 (0.0)
Protocol violation	0 (0.0)	2 (1.1)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Patient withdrew consent	2 (1.1)	4 (2.2)	5 (2.8)	1 (0.6)	1 (1.7)	2 (3.4)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (1.7)	2 (3.4)
Administrative problems	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)
Death	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0) [1]

Disposition	VAL 320 n (%)	ALI 75/ VAL 80 n (%)	ALI 150/ VAL 160 n (%)	ALI 300/ VAL 320 n (%)	VAL 160/ HCTZ 12.5 n (%)	Total n (%)
Randomized:						
Total	60	60	60	58	59	1123
Completed	55 (91.7)	55 (91.7)	56 (93.3)	55 (94.8)	56 (94.9)	1034 (92.1)
Discontinued	5 (8.3)	5 (8.3)	4 (6.7)	3 (5.2)	3 (5.1)	89 (7.9)
Reason for discontinuation						
Adverse event(s)	3 (5.0)	0 (0.0)	1 (1.7)	2 (3.4)	0 (0.0)	24 (2.1)
Abnormal laboratory value(s)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Unsatisfactory therapeutic effect	0 (0.0)	2 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	27 (2.4)
Protocol violation	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)	1 (1.7)	5 (0.4)
Patient withdrew consent	2 (3.3)	2 (3.3)	2 (3.3)	0 (0.0)	2 (3.4)	23 (2.0)
Lost to follow-up	0 (0.0)	1 (1.7)	1 (1.7)	0 (0.0)	0 (0.0)	6 (0.5)
Administrative problems	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1) [1]

10.1.4.23 Subject Demographics and Baseline Characteristics

Demographics and other selected baseline characteristics are shown in Table 80.

Table 80: Reviewer's Baseline Characteristics in Study 2203

Aliskiren	Valsartan	Other	Male %	Black %	Other race %	Median age	Age ≥65	Median BMI	Median SBP	Median DBP
		Placebo	55	8	0	55	22	29	152	99
75			55	6	0	57	29	30	153	99
150			57	6	1	56	23	29	153	99
300			57	6	1	58	27	30	152	99

Aliskiren	Valsartan	Other	Male %	Black %	Other race %	Median age	Age ≥65	Median BMI	Median SBP	Median DBP
	80		66	3	2	56.5	33	29	151	99
	160		50	9	2	55	19	30	155	99
	320		52	8	5	57	17	29	152	99
75	80		50	8	3	55.5	23	31	152	99
150	160		58	10	2	61	28	30	155	99
300	320		55	7	0	57.5	26	30	154	99
	160	HCTZ 12.5	61	9	2	58	27	30	153	99

COMMENT: The baseline characteristics appear well-balanced among the groups.

10.1.4.24 Conduct

10.1.4.25 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.

10.1.4.26 Protocol Changes and Violations

There was one protocol amendment prior to study initiation as described in Section 10.1.4.3. About 8% of patients were excluded from the per protocol analysis for protocol violations judged major. The reasons were varied, including blood pressure too low or variable at baseline (5%) and use of other antihypertensives (2%).

10.1.4.27 Dosing

10.1.4.28 Study Drug

Seven patients took study drug with the wrong number. One of these was still the correct drug, while the others were a one-week supply. The study report does not describe any other variations in dosing and it does not report compliance.

10.1.4.29 Concomitant Therapy

Overall, about 23 patients started taking concomitant medications during the double-blind treatment period; rates were similar in all groups. The most common concomitant medication was ibuprofen (3%).

10.1.4.30 Blinding

The blind for one patient in the valsartan 160 mg group was broken prior to 8 weeks.

10.1.4.31 Efficacy

10.1.4.32 Primary Endpoint

The sponsor's analyses of the primary endpoint, change from baseline in DBP, are shown in Table 81.

Table 81: Sponsor's Change from Baseline in DBP at 8 Weeks LOCF in Study 2203

Treatment Group	N	LSM change from baseline (SE)
Placebo	176	-8.6 (0.62)
Aliskiren 75 mg	177	-10.3 (0.62)
Aliskiren 150 mg	177	-10.3 (0.62)
Aliskiren 300 mg	175	-12.3 (0.62)
Valsartan 80 mg	58	-10.5 (1.07)
Valsartan 160 mg	58	-11.0 (1.07)
Valsartan 320 mg	60	-11.3 (1.05)
Aliskiren 75 mg/Valsartan 80 mg	60	-11.8 (1.05)
Aliskiren 150 mg/Valsartan 160 mg	60	-12.1 (1.05)
Aliskiren 300 mg/Valsartan 320 mg	58	-12.9 (1.07)
Valsartan 160 mg/HCTZ 12.5 mg	58	-13.5 (1.07)

Pairwise Comparison	LSM difference in change from baseline (SE)	95% CI for LSM difference	P-Value[1]
Aliskiren 75 mg vs. Placebo	-1.68 (0.86)	(-3.37, 0.02)	0.0524[+]
Aliskiren 150 mg vs. Placebo	-1.69 (0.86)	(-3.39, 0.00)	0.0506[+]
Aliskiren 300 mg vs. Placebo	-3.67 (0.87)	(-5.36,-1.97)	<.0001[+*]
Valsartan 80 mg vs. Placebo	-1.92 (1.23)	(-4.32, 0.49)	0.1188
Valsartan 160 mg vs. Placebo	-2.42 (1.23)	(-4.82,-0.01)	0.0494*
Valsartan 320 mg vs. Placebo	-2.69 (1.21)	(-5.07,-0.31)	0.0267*
Aliskiren 75 mg/Valsartan 80 mg vs. Aliskiren 75 mg	-1.57 (1.21)	(-3.95, 0.80)	0.1944
Aliskiren 75 mg/Valsartan 80 mg vs. Valsartan 80 mg	-1.33 (1.49)	(-4.26, 1.60)	0.3722
Aliskiren 75 mg/Valsartan 80 mg vs. Placebo	-3.25 (1.21)	(-5.63,-0.87)	0.0075*
Aliskiren 150 mg/Valsartan 160 mg vs. Aliskiren 150 mg	-1.79 (1.21)	(-4.17, 0.59)	0.1403
Aliskiren 150 mg/Valsartan 160 mg vs. Valsartan 160 mg	-1.06 (1.49)	(-3.99, 1.87)	0.4766
Aliskiren 150 mg/Valsartan 160 mg vs. Placebo	-3.48 (1.21)	(-5.86,-1.10)	0.0042*
Aliskiren 300 mg/Valsartan 320 mg vs. Aliskiren 300 mg	-0.67 (1.23)	(-3.09, 1.74)	0.5834
Aliskiren 300 mg/Valsartan 320 mg vs. Valsartan 320 mg	-1.65 (1.49)	(-4.58, 1.28)	0.2689
Aliskiren 300 mg/Valsartan 320 mg vs. Placebo	-4.34 (1.23)	(-6.75,-1.93)	0.0004*
Valsartan 160 mg/HCTZ 12.5 mg vs. Placebo	-4.88 (1.23)	(-7.29,-2.47)	<.0001*
Aliskiren 150 mg/Valsartan 160 mg vs. Valsartan 160 mg/HCTZ 12.5 mg	1.40 (1.49)	(-1.52, 4.33)	0.3468
Aliskiren 300 mg/Valsartan 320 mg vs. Valsartan 160 mg/HCTZ 12.5 mg	0.54 (1.51)	(-2.41, 3.50)	0.7182

SE = Standard Error; LSM = Least Squares Mean; CI = Confidence Interval
[+]The overall Dunnett's procedure between aliskiren monotherapy and placebo shows statistical significance between placebo and one aliskiren treatment. The smallest Dunnett's adjusted p-value among these comparisons is <0.0001.

COMMENT: Note the substantial change in the placebo group (-8.6 mm Hg). Of the aliskiren monotherapies only the 300 mg group is clearly distinguished from placebo. None of the aliskiren/valsartan combinations produce significantly greater reductions than the monotherapies.

10.1.4.33 Secondary Endpoints

The change from baseline in SBP is shown in Table 82.

Table 82: Sponsor's Change from Baseline in SBP at 8 Weeks LOCF in Study 2203

Treatment Group	N	LSM change from baseline (SE)
Placebo	176	-10.0 (0.96)
Aliskiren 75 mg	177	-12.1 (0.96)
Aliskiren 150 mg	177	-12.1 (0.95)
Aliskiren 300 mg	175	-15.0 (0.96)
Valsartan 80 mg	58	-11.2 (1.65)
Valsartan 160 mg	58	-15.5 (1.65)
Valsartan 320 mg	60	-16.5 (1.62)
Aliskiren 75 mg/Valsartan 80 mg	60	-14.5 (1.62)
Aliskiren 150 mg/Valsartan 160 mg	60	-16.6 (1.62)
Aliskiren 300 mg/Valsartan 320 mg	58	-18.0 (1.65)
Valsartan 160 mg/HCTZ 12.5 mg	58	-18.9 (1.65)

Pairwise Comparison	LSM difference in change from baseline (SE)	95% CI for LSM difference	P-Value[1]
Aliskiren 75 mg vs. Placebo	-2.17 (1.33)	(-4.78, 0.45)	0.1040[+]
Aliskiren 150 mg vs. Placebo	-2.13 (1.33)	(-4.75, 0.48)	0.1098[+]
Aliskiren 300 mg vs. Placebo	-5.08 (1.34)	(-7.70,-2.46)	0.0001[+*]
Valsartan 80 mg vs. Placebo	-1.27 (1.89)	(-4.98, 2.45)	0.5041
Valsartan 160 mg vs. Placebo	-5.57 (1.90)	(-9.29,-1.85)	0.0034*
Valsartan 320 mg vs. Placebo	-6.54 (1.87)	(-10.21,-2.87)	0.0005*
Aliskiren 75 mg/Valsartan 80 mg vs. Aliskiren 75 mg	-2.33 (1.87)	(-5.99, 1.34)	0.2137
Aliskiren 75 mg/Valsartan 80 mg vs. Valsartan 80 mg	-3.23 (2.30)	(-7.75, 1.29)	0.1617
Aliskiren 75 mg/Valsartan 80 mg vs. Placebo	-4.49 (1.87)	(-8.16,-0.82)	0.0165*
Aliskiren 150 mg/Valsartan 160 mg vs. Aliskiren 150 mg	-4.52 (1.87)	(-8.19,-0.86)	0.0157*
Aliskiren 150 mg/Valsartan 160 mg vs. Valsartan 160 mg	-1.09 (2.30)	(-5.61, 3.43)	0.6373
Aliskiren 150 mg/Valsartan 160 mg vs. Placebo	-6.66 (1.87)	(-10.33,-2.99)	0.0004*
Aliskiren 300 mg/Valsartan 320 mg vs. Aliskiren 300 mg	-2.99 (1.90)	(-6.71, 0.73)	0.1150
Aliskiren 300 mg/Valsartan 320 mg vs. Valsartan 320 mg	-1.53 (2.30)	(-6.05, 2.99)	0.5063
Aliskiren 300 mg/Valsartan 320 mg vs. Placebo	-8.07 (1.90)	(-11.79,-4.36)	<.0001*
Valsartan 160 mg/HCTZ 12.5 mg vs. Placebo	-8.89 (1.89)	(-12.61,-5.17)	<.0001*
Aliskiren 150 mg/Valsartan 160 mg vs. Valsartan 160 mg/HCTZ 12.5 mg	2.23 (2.30)	(-2.29, 6.75)	0.3330
Aliskiren 300 mg/Valsartan 320 mg vs. Valsartan 160 mg/HCTZ 12.5 mg	0.81 (2.32)	(-3.75, 5.37)	0.7261

SE = Standard Error; LSM = Least Squares Mean; CI = Confidence Interval
[+]The overall Dunnett's procedure between aliskiren monotherapy and placebo shows statistical significance between placebo and one aliskiren treatment. The smallest Dunnett's adjusted p-value among these comparisons is 0.0004.

COMMENT: As for DBP, there is a large placebo effect (-10 mm Hg) and only the aliskiren 300 mg monotherapy is distinguished from placebo. The aliskiren 150/valsartan 160 is distinguished from aliskiren 150 but not from valsartan 160.

10.1.4.34 Subgroup Analyses

10.1.4.35 Country

The placebo effect was lowest in the US (although still substantial) as shown in Table 83.

Table 83: Reviewer's BP Changes from Baseline for Placebo by Country in Study 2203

	N	SBP	DBP
Denmark	21	-9.2	-7.2
France	27	-11.3	-10.0
Germany	63	-9.3	-8.9
Poland	23	-10.2	-11.7
USA	42	-6.7	-5.6

The BP changes from baseline in the US are shown in Table 84.

Table 84: Reviewer's BP Changes from Baseline by Group in US in Study 2203

Group	Raw		Placebo-subtracted	
	SBP	DBP	SBP	DBP
Placebo	-6.7	-5.6		
Aliskiren 75 mg	-7.8	-5.8	-1.0	-0.2
Aliskiren 150 mg	-9.7	-7.6	-2.9	-2.0
Aliskiren 300 mg	-8.5	-7.3	-1.8	-1.7
Valsartan 80 mg	-5.6	-5.4	1.1	0.2
Valsartan 160 mg	-9.7	-6.4	-2.9	-0.8
Valsartan 320 mg	-11.1	-9.4	-4.4	-3.8
Aliskiren 75 mg / Valsartan 80 mg	-8.3	-6.2	-1.6	-0.6
Aliskiren 150 mg / Valsartan 160 mg	-16.0	-10.0	-9.3	-4.5
Aliskiren 300 mg / Valsartan 320 mg	-20.6	-16.1	-13.8	-10.5
Valsartan 160 mg / HCTZ 12.5 mg	-14.5	-11.6	-7.7	-6.0

COMMENT: The US results do not differentiate aliskiren 150 and 300 mg, although this failure may be due to small numbers of patients. The US results suggest that the aliskiren/valsartan combinations may be more effective than the overall study results indicate.

10.1.4.36 Race

The BP changes from baseline by group for whites and blacks are shown in Table 85.

Table 85: Reviewer's BP Changes from Baseline by Group for Whites and Blacks in Study 2203

Group	SBP	DBP

	White	Black	White	Black
Placebo	-8.8	-11.8	-8.6	-7.0
Aliskiren 75 mg	-11.7	-7.1	-10.5	-4.2
Aliskiren 150 mg	-12.3	-5.8	-10.5	-5.0
Aliskiren 300 mg	-15.2	-2.7	-12.7	-3.4
Valsartan 80 mg	-10.6	-7.0	-10.5	-5.3
Valsartan 160 mg	-15.7	-12.0	-11.1	-8.3
Valsartan 320 mg	-16.2	-11.0	-11.3	-5.3
Aliskiren 75 mg / Valsartan 80 mg	-13.6	-15.1	-12.1	-6.9
Aliskiren 150 mg / Valsartan 160 mg	-16.6	-10.2	-12.7	-5.4
Aliskiren 300 mg / Valsartan 320 mg	-18.2	-10.5	-13.3	-7.0
Valsartan 160 mg / HCTZ 12.5 mg	-18.7	-16.3	-13.6	-11.2

COMMENT: BP reductions appear to be less in blacks than whites for aliskiren, valsartan, and their combinations.

10.1.4.37 Age and Gender

Although not shown with data in this review, there do not appear to be any consistent variations in BP changes by age or gender as shown in the NDA submission tables and as confirmed by the reviewer.

10.1.4.38 Safety

10.1.4.39 Exposure

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

10.1.4.40 Serious Adverse Events

10.1.4.41 Deaths

No deaths occurred in the aliskiren groups, but one patient died in each of the placebo and valsartan 160 mg groups.

10.1.4.42 Hospitalizations

Two patients in aliskiren groups were hospitalized due to AEs:

In the aliskiren 75 mg group, a 64 year-old Caucasian male, was diagnosed with coronary artery disease and was admitted to the hospital on study day 4. The last dose of study drug was taken on day 2 and the patient was discontinued from the study on day 3 due to this adverse event. The patient underwent quadruple bypass surgery two weeks after discontinuing the study and recovered without sequelae.

In the aliskiren 75 mg/valsartan 80 mg group, a 49 year-old Caucasian male, was hospitalized for dyspnea and chest pressure 3 days after successfully completing the study. Myocardial infarction was ruled out and a diagnosis of functional disorder was made.

10.1.4.43 Other serious adverse events

One patient in the aliskiren 300 mg group became pregnant, discontinued, and delivered normally as described in Section 10.1.4.45.

10.1.4.44 Events Leading to Discontinuation

Few patients discontinued due to AEs, with the greatest number of discontinuations in the placebo group (6). There were no obvious patterns to discontinuations in the aliskiren groups.

One patient in the aliskiren 150 mg group, a 32-year-old black male, discontinued due to an elevated creatine kinase on day 46. The patient had an adverse event of elevated creatine kinase reported as starting on study day 2. Another patient in the aliskiren 300 mg group also had an AE of creatine kinase increased.

COMMENT: I scrutinize AEs of CK elevation in the ISS.

10.1.4.45 Events of Special Interest

In the aliskiren 300 mg group, a 31-year-old black female had a positive pregnancy test result 42 days after starting study drug. The patient discontinued study drug, with an expected delivery date of — On — ne patient gave birth by normal vaginal delivery to a male, weight 3.8 kg and height 54 cm, with no abnormalities associated.

One patient (83-15) in the valsartan 160 mg group presented with moderate facial edema diagnosed as angioedema. Drug was discontinued and the edema resolved. This patient had a history of a similar episode with an ACE inhibitor. One patient (71-34) in the aliskiren 150 mg group also had facial edema starting with treatment and resolving 8 days prior to discontinuing treatment. One patient (517-17) in the aliskiren 300 mg / valsartan 320 mg group had ankle and periorbital edema 5 days after starting treatment and 3 days prior to discontinuing.

COMMENT: In addition to the valsartan case labeled as angioedema, the two aliskiren cases also appear to be angioedema, particularly the one in the combination group. I scrutinize angioedema in the ISS.

10.1.4.46 Overall Adverse Events

Overall rates of AEs were similar in most groups (about 31%), although the valsartan/HCTZ group had the lowest rate (22%) and the aliskiren 75 mg group the highest (35%). The common adverse events, those with a frequency $\geq 2\%$ in any group, are shown in Table 86.

Table 86: Sponsor's Adverse Events ≥ 2% Frequency in Any Group in Study 2203

Preferred term	Placebo N=177 n (%)	ALI 75 N=179 n (%)	ALI 150 N=178 n (%)	ALI 300 N=175 n (%)	VAL 80 N=58 n (%)	VAL 160 N=59 n (%)
Headache	15(8.5)	15(8.4)	9(5.1)	7(4.0)	3(5.2)	4(6.8)
Diarrhea	3(1.7)	2(1.1)	1(0.6)	5(2.9)	1(1.7)	0(0.0)
Fatigue	4(2.3)	7(3.9)	4(2.2)	4(2.3)	0(0.0)	3(5.1)
Back pain	2(1.1)	2(1.1)	4(2.2)	3(1.7)	1(1.7)	0(0.0)
Dizziness	2(1.1)	4(2.2)	4(2.2)	3(1.7)	0(0.0)	1(1.7)
Vertigo	0(0.0)	2(1.1)	0(0.0)	3(1.7)	0(0.0)	1(1.7)
Nausea	1(0.6)	4(2.2)	0(0.0)	2(1.1)	0(0.0)	3(5.1)
Urinary tract infection	3(1.7)	1(0.6)	2(1.1)	2(1.1)	1(1.7)	1(1.7)
Cough	2(1.1)	2(1.1)	5(2.8)	1(0.6)	0(0.0)	0(0.0)
Edema peripheral	2(1.1)	1(0.6)	2(1.1)	1(0.6)	1(1.7)	0(0.0)
Bronchitis	0(0.0)	2(1.1)	1(0.6)	0(0.0)	2(3.4)	0(0.0)
Dyspnoea	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(1.7)
Myalgia	0(0.0)	1(0.6)	0(0.0)	0(0.0)	0(0.0)	1(1.7)
Nasopharyngitis	5(2.8)	1(0.6)	1(0.6)	0(0.0)	1(1.7)	0(0.0)

Preferred term	VAL 320 N=60 n (%)	ALI 75/ VAL 80 N=60 n (%)	ALI 150/ VAL 160 N=60 n (%)	ALI 300/ VAL 320 N=58 n (%)	VAL 160/ HCTZ 12.5 N=59 n (%)	Total N=1123 n (%)
Headache	2(3.3)	3(5.0)	4(6.7)	2(3.4)	0(0.0)	64(5.7)
Diarrhea	1(1.7)	1(1.7)	3(5.0)	1(1.7)	0(0.0)	18(1.6)
Fatigue	1(1.7)	1(1.7)	4(6.7)	3(5.2)	0(0.0)	31(2.8)
Back pain	3(5.0)	2(3.3)	1(1.7)	1(1.7)	1(1.7)	20(1.8)
Dizziness	1(1.7)	1(1.7)	0(0.0)	1(1.7)	0(0.0)	17(1.5)
Vertigo	0(0.0)	1(1.7)	0(0.0)	2(3.4)	0(0.0)	9(0.8)
Nausea	0(0.0)	0(0.0)	1(1.7)	1(1.7)	0(0.0)	12(1.1)
Urinary tract infection	1(1.7)	0(0.0)	1(1.7)	2(3.4)	0(0.0)	14(1.2)
Cough	1(1.7)	1(1.7)	0(0.0)	1(1.7)	0(0.0)	13(1.2)
Edema peripheral	2(3.3)	0(0.0)	0(0.0)	1(1.7)	0(0.0)	10(0.9)
Bronchitis	1(1.7)	1(1.7)	0(0.0)	0(0.0)	0(0.0)	7(0.6)
Dyspnoea	0(0.0)	2(3.3)	0(0.0)	1(1.7)	0(0.0)	4(0.4)
Myalgia	0(0.0)	0(0.0)	2(3.3)	0(0.0)	1(1.7)	5(0.4)
Nasopharyngitis	1(1.7)	2(3.3)	1(1.7)	1(1.7)	0(0.0)	13(1.2)

COMMENT: The one common AE that appears dose-related is diarrhea with aliskiren. (The rate in the aliskiren 300 mg/valsartan 320 mg group is an exception.)

10.1.4.47 Laboratory Findings

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.

Table 87: Reviewer's Change from Baseline in Selected Lab Values in Study 2203

Group	Hgb	RBC	Potassium	Urea	Uric Acid	ALT
Placebo	1.2%	0.6%	-0.5%	-0.1%	0.7%	-1.8%
Aliskiren 75	-0.2%	-0.6%	0.0%	0.6%	2.0%	3.1%
Aliskiren 150	0.4%	0.0%	1.6%	0.3%	4.1%	3.3%
Aliskiren 300	-0.3%	-0.8%	0.9%	3.8%	4.3%	7.5%
Valsartan 80	-0.3%	-0.8%	-0.5%	2.7%	4.3%	5.2%
Valsartan 160	-0.6%	-1.7%	1.9%	1.2%	3.8%	2.7%
Valsartan 320	-1.2%	-1.5%	0.0%	7.8%	4.5%	3.6%
Aliskiren 75/valsartan 80	-0.3%	-0.6%	0.7%	1.5%	3.6%	5.3%
Aliskiren 150/valsartan 160	-1.5%	-1.3%	0.5%	2.1%	2.8%	-4.0%
Aliskiren 300/valsartan 320	-2.0%	-2.6%	3.2%	1.7%	2.5%	-3.0%
Valsartan 160/HCTZ 12.5	-1.6%	-2.7%	0.0%	19.0%	9.3%	2.5%

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

Table 88: Reviewer's Shift Table Changes (Extreme Values) for Selected Lab Tests in Study 2203

Group	Hgb	RBC	Potassium	Urea	Uric Acid	ALT
	N→L	N→L	N→H	N→H	N→H	N→H
Placebo	5.4%	7.1%	0.0%	4.9%	9%	8.0%
Aliskiren 75	3.8%	4.9%	0.0%	4.5%	10%	10.3%
Aliskiren 150	1.9%	10.1%	0.0%	8.2%	18%	11.5%
Aliskiren 300	4.1%	8.9%	0.6%	6.0%	20%	12.0%
Valsartan 80	4.1%	3.9%	0.0%	5.9%	17%	10.0%
Valsartan 160	2.1%	11.4%	0.0%	4.2%	13%	8.9%
Valsartan 320	8.0%	8.2%	0.0%	5.4%	26%	7.5%
Aliskiren 75/valsartan 80	8.3%	8.9%	0.0%	13.5%	15%	7.8%
Aliskiren 150/valsartan 160	8.2%	11.1%	1.9%	14.5%	21%	4.4%
Aliskiren 300/valsartan 320	16.4%	18.4%	1.8%	10.2%	13%	8.9%
Valsartan 160/HCTZ 12.5	5.8%	13.2%	0.0%	17.0%	21%	10.4%

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

Note also the AEs of creatine kinase increased described in Section 10.1.4.44.

COMMENT: As noted in other studies, aliskiren appears to decrease hemoglobin and RBC counts slightly, increase potassium and uric acid, and increase ALT.

10.1.4.48 Adverse Events in Subgroups

Adverse event rates in subgroups (age, gender, race, etc.) were not analyzed in this study but are analyzed in the Integrated Summary of Safety.

10.1.4.49 Summary

10.1.4.50 Efficacy Summary

This study again shows an antihypertensive effect from aliskiren, although only for the highest dosage. The effects of the combinations with valsartan do not clearly exceed those of the monotherapies. The lack of success in this study appears to be related to the large placebo effect, particularly outside the US.

10.1.4.51 Safety Summary

In addition to showing the typical effects of a RAAS inhibitor upon lab values, this study also raises safety issues for aliskiren regarding angioedema and creatinine kinase increases. The results also suggest a slight effect of aliskiren upon liver enzymes.

10.1.4.52 Conclusions

This study is weakly supportive of approval.

10.1.5 Study 2308 - An eight-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter study comparing aliskiren 150 mg, 300 mg, and 600 mg to placebo in patients with essential hypertension

10.1.5.1 Background

This appears to be a classic, placebo-controlled dose-ranging trial to support a hypertension indication.

10.1.5.2 Initial Protocol

The initial protocol is dated 05-Aug-2004.

10.1.5.3 Protocol Amendments

One amendment, dated 07-Jan-2005, eliminated two biomarkers (angiotensin II and pro-renin) and clarified some inclusion criteria.

10.1.5.4 Sites and Investigators

There were 68 centers: 37 in the US, 4 in Canada, 3 in Guatemala, 15 in the Netherlands, and 10 in Korea.

10.1.5.5 Study Dates

The first patient was enrolled November 10, 2004, and the last patient completed on June 30, 2005.

10.1.5.6 Study Design

This was an eight-week, international, multicenter, randomized, double-blind, multiple dosage, placebo-controlled, parallel group study.

10.1.5.7 Objectives

The primary objective of this study was to evaluate the diastolic blood pressure lowering effects of aliskiren 150, 300, and 600 mg compared to placebo in patients with essential hypertension. Secondary objectives included evaluating dose response, responders, safety and tolerability, rebound, effects on plasma renin, and trough-to-peak effects and 24-hour control by ABPM.

10.1.5.8 Number of Subjects, Randomization, and Blinding

The planned number of subjects was 612. The protocol and report do not describe clearly what investigators had to do for randomization, although they do describe how randomization lists were produced. Blinding was by double dummy with placebo matched to the different aliskiren 150 and 300 mg tablets. Unblinding was possible by scratch-off of a code break card at the site.

10.1.5.9 Inclusion and Exclusion Criteria

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

The exclusion criteria were the following: prior aliskiren use; BP ≥ 180/110; 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 > 3x ULN or serum creatinine > 1.7 for women or 2.0 mg/dL for men; malignancy within 5 years; alcohol or drug abuse within 12 months; pregnant or nursing; any condition increasing risk per investigator; noncompliance; any condition jeopardizing evaluation; investigational drug within 1 month; directly involved in protocol.

10.1.5.10 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 four treatment groups: aliskiren 150, 300, or 600 mg or placebo once daily for an 8-week treatment period. The effect of drug withdrawal was evaluated at the end of the double blind treatment period by recording blood pressure and adverse events four days and again at two weeks after the last dose of study medication (non-blinded withdrawal). The primary endpoint was seated trough cuff DBP. ABPM was also done in a subset of patients prior to randomization and at 8 weeks. Safety monitoring was by AE recording, routine safety labs, vitals signs, physical exams, and ECGs. A diagram of the study plan is presented in Figure 25.

Figure 25: Study 2308 Plan

Phase	Pre-Randomization			Study Drug Treatment					Follow up	
Period	Screening / Washout	Single-blind Run-in		Double-blind treatment					Drug Withdrawal	
Duration	2 weeks	2 weeks	2 weeks optional	8 weeks					2 weeks	
Visit	1	2	Optional Visit 201[1]	3[2]	4	5	6	7[3]	8[4]	9
Day	-28 to -14 or * -42 to -28	-14 to -1 or *-28 to -14	* -14 to -1	1	14	28	42	56	60	70
				Randomization Visit 3						
Treatment		Placebo		Aliskiren 150 mg o.d. Aliskiren 300 mg o.d. Aliskiren 600 mg o.d. Placebo o.d.					Study drug stopped at/after Visit 7	

10.1.5.11 Treatment

10.1.5.12 Dosage and Administration
All dosing was orally (three tablets) taken with water in the morning.

10.1.5.13 Duration and Adjustment of Therapy
Duration of treatment was eight weeks followed by a two-week withdrawal. No adjustments were done.

10.1.5.14 Concomitant Therapy
Other antihypertensives were prohibited.

10.1.5.15 Safety and Efficacy Endpoints
The primary endpoint was change in trough seated cuff DBP at eight weeks. The protocol defined change in SBP, peak-to-trough ratios, and percent responders as secondary endpoints but there does not appear to be a defined statistical analysis plan preserving alpha for the evaluation of secondary endpoints. The protocol did not define specific safety endpoints.

10.1.5.16 Statistical Considerations

10.1.5.17 Sample Size Calculations
A sample size of 552 patients was estimated based on these assumptions: 90% power, 3.5 mm Hg difference of at least one aliskiren group from placebo, 8 mm Hg standard deviation, dropout rate of 10%, and Dunnett's procedure to adjust for the multiple comparisons.

10.1.5.18 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.

10.1.5.19 Pre-specified Analyses

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.

10.1.5.20 Results

10.1.5.21 Study Implementation

There were no problems reported with study implementation.

10.1.5.22 Disposition of Subjects

A total of 833 patients were enrolled in the single-blind period of the study. Of these, 671 (81%) patients completed the single-blind period and were randomized to double-blind treatment. Of the 672 patients randomized, 608 (91%) completed the double-blind treatment phase and entered the withdrawal period. The disposition of the randomized patients is shown in Table 89.

Table 89: Sponsor's Disposition of Patients in Study 2308

Disposition	Placebo n (%)	Aliskiren 150 mg od n (%)	Aliskiren 300 mg od n (%)	Aliskiren 600 mg od n (%)	Total n (%)
Enrolled					833
Randomized	165	172	169 [4]	166	672
Completed double-blind period[1]	135 (81.8)	162 (94.2)	159 (94.1)	152 (91.6)	608 (90.5)
Discontinued during double-blind period	30 (18.2)	10 (5.8)	9 (5.3)	14 (8.4)	63 (9.4)
Reason for discontinuation during the double-blind period:					
Adverse event(s)	5 (3.0)	1 (0.6)	3 (1.8)	2 (1.2)	11 (1.6)
Lost to follow-up	2 (1.2)	3 (1.7)	1 (0.6)	1 (0.6)	7 (1.0)
Patient withdrew consent	6 (3.6)	3 (1.7)	4 (2.4)	7 (4.2)	20 (3.0)
Unsatisfactory therapeutic effect	17 (10.3) [3]	3 (1.7)	1 (0.6)	4 (2.4)	25 (3.7)
Entered withdrawal period	135	162	159	152	608
Completed withdrawal period[2]	134 (99.3)	158 (97.5)	159 (100.0)	151 (99.3)	602 (99.0)
Discontinued during withdrawal period	1 (0.7)	4 (2.5)	0 (0.0)	1 (0.7)	6 (1.0)
Reason for discontinuation during the withdrawal period:					
Unsatisfactory therapeutic effect	1 (0.6)	2 (1.2)	0 (0.0)	1 (0.6)	4 (0.6)
Patient withdrew consent	0 (0.0)	2 (1.2)	0 (0.0)	0 (0.0)	2 (0.3)

COMMENT: The dropout rates are acceptable. The higher dropout in the placebo group is accounted for mainly by the unsatisfactory therapeutic effect.

10.1.5.23 Subject Demographics and Baseline Characteristics

Demographics and other selected baseline characteristics are shown in Table 90.

Table 90: Reviewer's Baseline Characteristics in Study 2308

	Placebo	Aliskiren			Total
		150	300	600	
Male	63	62	63	58	62
Black	15	13	11	10	12
Asian	18	18	17	19	18
Other race	8	8	9	8	8
Mean age	53	52	54	53	53
Age ≥65	12	11	14	16	13
Mean BMI	30	29	29	30	29
Median SBP	150	151	153	151	151
Median DBP	98	99	99	99	99

COMMENT: The baseline characteristics appear well-balanced among the groups.

10.1.5.24 Conduct

10.1.5.25 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. An occasional query was handled by paper documents.

10.1.5.26 Protocol Changes and Violations

There was one amendment as described in Section 10.1.5.3. Also, evaluating SBP changes was added to the analysis plan although analyzing SBP was not stated in the protocol. About 7% of patients were excluded from the per-protocol analysis for protocol violations judged major. The reasons were varied, including blood pressure too low or variable at baseline (2%) and use of other antihypertensives (2%).

10.1.5.27 Dosing

10.1.5.28 Study Drug

One patient received double-blind medication (aliskiren 300 mg) during the single-blind run-in period. One patient in the 600 mg group was dispensed the wrong drug during the double-blind period for about 2 weeks—this patient took the correct medication for most of the double-blind period.

10.1.5.29 Concomitant Therapy

Overall, 69% of patients took concomitant medication during the double-blind treatment period;

rates were similar among the treatment groups. The most frequently used medications overall were paracetamol (11%) and ibuprofen (8%). About 2% took an ARB and rare patients took other antihypertensives.

10.1.5.30 Blinding

Premature breaking of the blind is not mentioned.

10.1.5.31 Efficacy

10.1.5.32 Primary Endpoint

The sponsor's analyses of the primary endpoint, change from baseline in DBP, are shown in Table 91 and the change in DBP by visit in Figure 26.

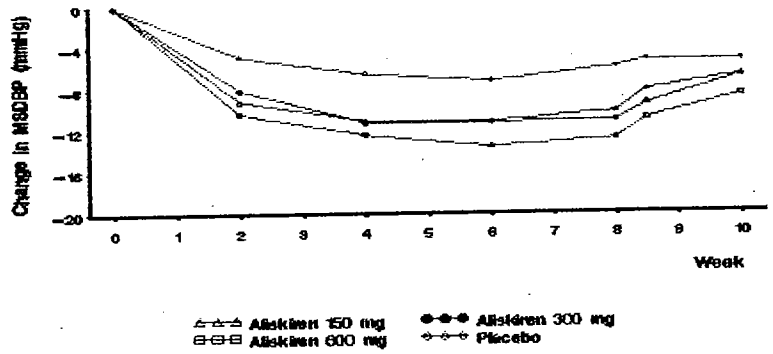
Table 91: Sponsor's Change from Baseline in DBP at 8 Weeks LOCF in Study 2308

Treatment Group	N	LSM change from Baseline(SE)
Placebo	163	-4.92 (0.64)
Aliskiren 150 mg od	167	-10.33 (0.63)
Aliskiren 300 mg od	166	-11.10 (0.64)
Aliskiren 600 mg od	166	-12.52 (0.64)

Pairwise Comparison	LSM difference in change from Baseline (SE)	95% CI for LSM	p-value
Aliskiren 150 mg vs. Placebo	-5.40 (0.87)	(-7.11, -3.70)	< .0001*
Aliskiren 300 mg vs. Placebo	-6.18 (0.87)	(-7.88, -4.47)	< .0001*
Aliskiren 600 mg vs. Placebo	-7.60 (0.87)	(-9.30, -5.89)	< .0001*

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

Figure 26: Sponsor's Change from Baseline in DBP by Visit in Study 2308



COMMENT: The changes in DBP show reasonable efficacy for aliskiren (placebo-corrected reductions of -5.4 to -7.6 mm Hg) but only a modest dose-response from 150 to 600 mg. There appears to be slight further reductions in BP after four weeks.

10.1.5.33 Secondary Endpoints

The change from baseline in SBP is shown in Table 92 and the change in DBP by hour from the

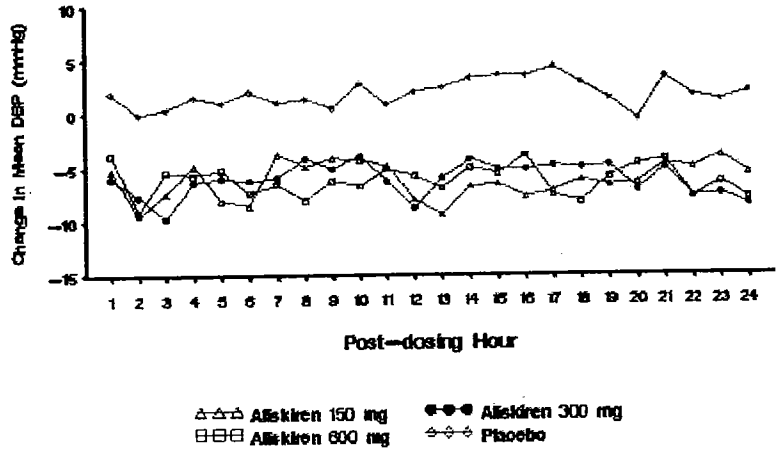
ABPM sample is shown in Figure 27.

Table 92: Sponsor's Change from Baseline in SBP at 8 Weeks LOCF in Study 2308

Treatment Group	N	LSM change from Baseline(SE)	
Placebo	163	-3.77 (1.02)	
Aliskiren 150 mg od	167	-13.04 (1.01)	
Aliskiren 300 mg od	166	-14.67 (1.02)	
Aliskiren 600 mg od	166	-15.83 (1.02)	
Pairwise Comparison	**LSM difference in change from Baseline (SE)**	**95% CI for LSM difference**	**p-value**
Aliskiren 150 mg vs. Placebo	-9.27 (1.39)	(-11.99, -6.55)	<.0001*
Aliskiren 300 mg vs. Placebo	-10.90 (1.39)	(-13.62, -8.17)	<.0001*
Aliskiren 600 mg vs. Placebo	-12.06 (1.39)	(-14.78, -9.34)	<.0001*

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

Figure 27: Sponsor's Change from Baseline in DBP by Post-dosing Hour in Study 2308



The mean change in 24-hour ambulatory BP was actually greater in the aliskiren 150 mg group (-9.6/-6.6) than in the 300 mg group (-8.8/-6.0) and almost equaled that in the 300 mg group (-9.9/-7.4). I examined the ABPM data and found it somewhat erratic: about 22% of the values were labeled as bad. I generated both mean and median BP and BP change from baseline for each group. Because the medians in the placebo group tracked better, I generated the following graphs of medians by group.

Figure 28: Reviewer's Median Ambulatory DBP by Hour at Baseline and 8 Weeks in Study 2308

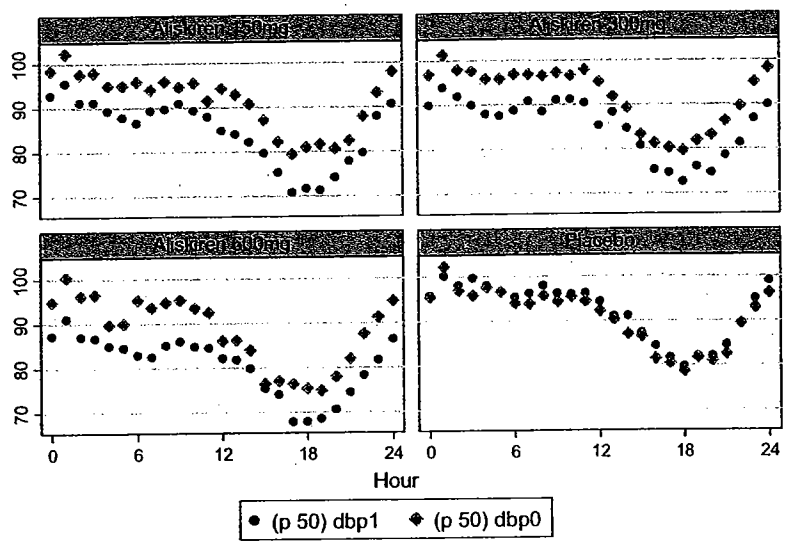


Figure 29: Reviewer's Median Change from Baseline in Ambulatory DBP by Hour in Study 2308

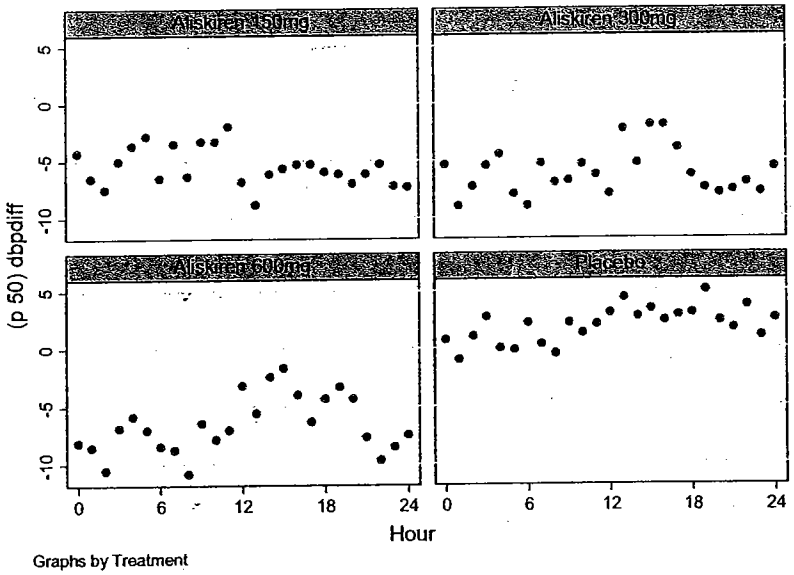


Figure 30: Reviewer's Median Ambulatory SBP by Hour at Baseline and 8 Weeks in Study 2308

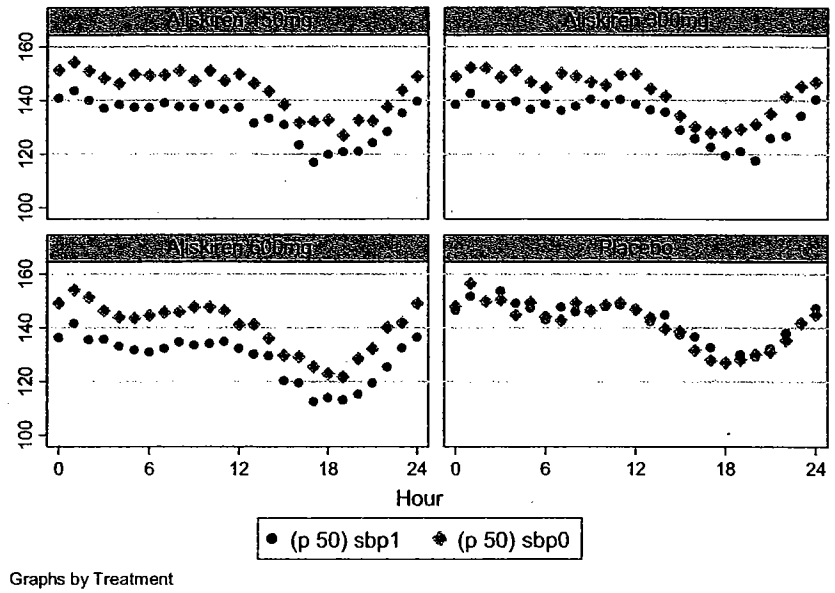
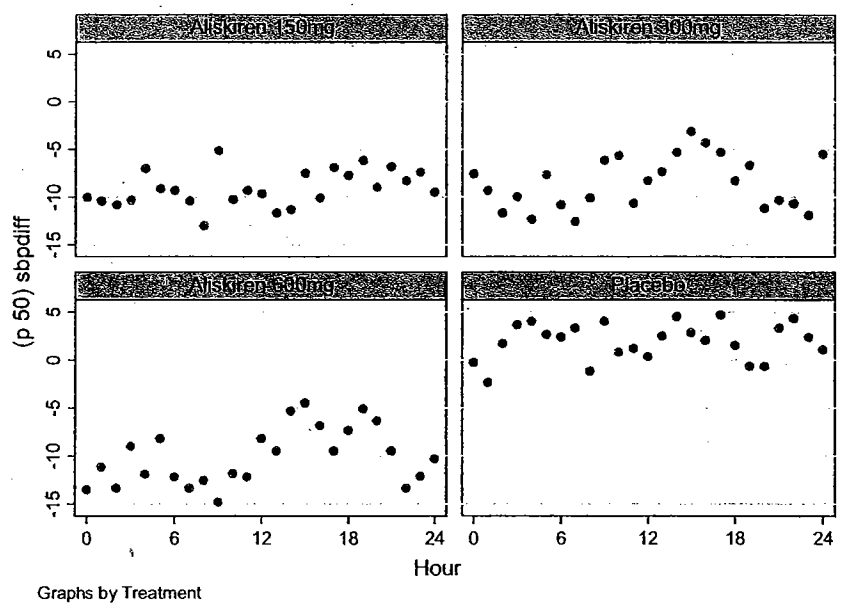


Figure 31: Reviewer's Median Change from Baseline in Ambulatory SBP by Hour in Study 2308



COMMENT: The placebo-corrected changes from baseline in SBP are reasonable (-9.3 to -12.1

mm Hg) with a relatively flat dose-response as for DBP. The ABPM data are confusing and show better nighttime control with aliskiren 150 mg than daytime and better than aliskiren 300 mg. Aliskiren 600 mg appears to show better reductions during the daytime and poor control of DBP at night. The summation of the three dosages might be that there are reductions throughout the 24-hour interdosing interval, but this finding needs to be confirmed with less erratic data.

The mean study day for the week 8 efficacy visit was about day 55, and the mean study days for the subsequent withdrawal period visits were days 61 and 71. Hence the first visit following discontinuation was usually too late to catch an early rebound effect. The visit timings were adequate to document the effects of withdrawing aliskiren upon blood pressure. The mean change in SBP during the withdrawal period is shown in Figure 32 and the mean change in DBP in Figure 33.

Figure 32: Reviewer's Mean Change in SBP During the Withdrawal Period in Study 2308

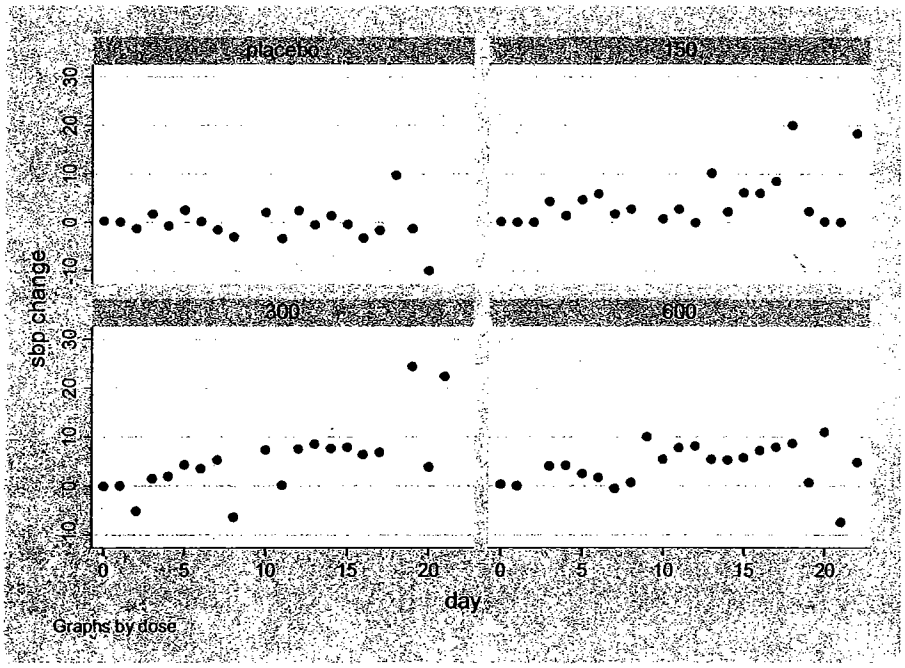
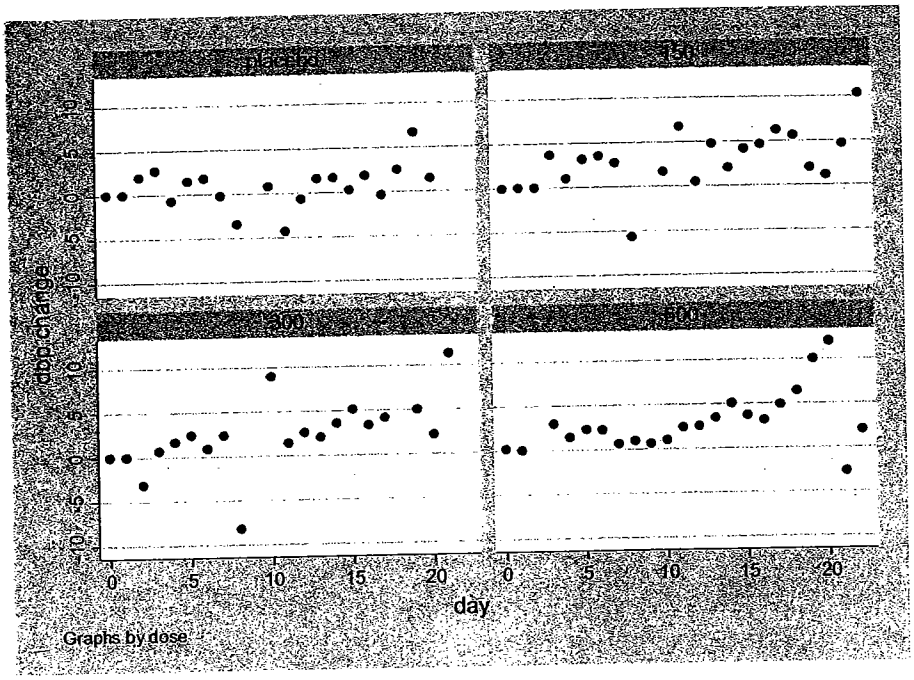


Figure 33: Reviewer's Mean Changes in SBP during the Withdrawal Period in Study 2308



COMMENT: The withdrawal period results do not show any evidence of an immediate rebound. The mean increases in BP in the aliskiren groups appear gradual over 20 days with the increases more pronounced at the higher dosages.

10.1.5.34 Subgroup Analyses

10.1.5.35 Country

The mean change from baseline in DBP by country and treatment group is shown in Table 93.

Table 93: Reviewer's Change from Baseline in DBP by Country in Study 2308

Country	Placebo	Aliskiren		
		150	300	600
Canada	-8.4	-14.0	-14.0	-13.9
Guatemala	-4.4	-8.0	-7.5	-11.7
Korea	-5.7	-9.7	-12.4	-14.5
Netherlands	-4.2	-10.5	-11.1	-13.2
US	-4.1	-9.9	-10.2	-10.8

COMMENT: The results by country are reasonably consistent, although Canada shows more of a placebo effect and Guatemala, Korea, and the Netherlands may show more of a dose response, at least at the highest dose.

10.1.5.36 Race

Change from baseline in DBP by race and treatment group are shown in Table 94.

Table 94: Reviewer's Change from Baseline in DBP by Race in Study 2308

Race	Placebo	Aliskiren		
		150	300	600
White	-5.3	-11.5	-11.1	-12.4
Black	-3.0	-5.4	-8.5	-8.2
Asian	-5.1	-10.0	-12.7	-14.5
native American	-4.4	-9.4	-11.7	-8.8
Pacific islander		-12.0		-12.7
Other	-3.5	-7.7	-9.5	-14.4

COMMENT: Blacks appear to show a reduced effect from aliskiren. Asians and other (Hispanic) may show a better dose-response for the range 150 to 600 mg.

10.1.5.37 Age and Gender

Change from baseline in DBP by age < or ≥ 65 and treatment group are shown in Table 95 and by gender in Table 96.

Table 95: Reviewer's Change from Baseline in DBP by Age in Study 2308

Age	Placebo	Aliskiren		
		150	300	600
<65	-4.6	-9.6	-11.1	-12.6
≥65	-6.4	-15.6	-10.4	-11.4

Table 96: Reviewer's Change from Baseline in DBP by Gender in Study 2308

Gender	Placebo	Aliskiren		
		150	300	600
Male	-4.6	-9.6	-10.5	-11.9
Female	-5.0	-11.2	-11.9	-13.0

COMMENT: Women may show a slighter greater effect with aliskiren. One could speculate that this is related to lower body weight. However, the flat dose-response would argue against that.

10.1.5.38 Safety

10.1.5.39 Exposure

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

10.1.5.40 Serious Adverse Events

10.1.5.41 Deaths
No patients died.

10.1.5.42 Hospitalizations

- A 64 year-old white female in the aliskiren 150 mg group was hospitalized for unstable angina and uncontrolled BP on day 27. This patient discontinued aliskiren and was discharged after three days.
- In the aliskiren 300 mg group one patient was hospitalized with acute appendicitis.
- Another patient in the aliskiren 300 mg group was hospitalized with depression on day 51. The latter patient had a prior history of depression and completed the study.
- A 31 year-old black female in the aliskiren 600 mg group was hospitalized for severe pain ("bodily injury") after being robbed and assaulted on day 35. This patient was lost to follow-up.
- A 48 year-old white male in the aliskiren 150 mg group suffered a venous occlusion and thrombosis of the right eye on day 8 of the withdrawal period. This latter patient, while appearing to have some response to aliskiren at the week 2 visit (baseline 157/104 to 136/91 at week 2), was uncontrolled at week 8 (155/102) and worse (161/108 sitting, 169/115 standing) at day 5 of the withdrawal.

COMMENT: While not alarming from these study results, the possibility of increased rates of thrombotic events such as MIs are scrutinized in the ISS.

10.1.5.43 Other serious adverse events
There were no other SAEs in addition to those leading to hospitalization discussed above.

10.1.5.44 Events Leading to Discontinuation
One patient in the aliskiren 150 mg group discontinued for a sense of oppression, three patients in the aliskiren 300 mg group discontinued for AEs (dizziness, mood altered, and rash), and two patients in the aliskiren 600 mg group discontinued for AEs (diarrhea; flatulence and constipation).

10.1.5.45 Events of Special Interest
One patient in the aliskiren 300 mg group reported "OEDEMA HANDS AND FEETS" on day 53.

COMMENT: This case may represent angioedema.

10.1.5.46 Overall Adverse Events

Overall more patients (52%) in the aliskiren 600 mg group reported AEs than in the placebo (43%) or 150 mg (40%) or 300 mg (47%) groups. The difference results from a higher rate of gastrointestinal disorders (predominantly diarrhea) in the 600 mg group (21%) compared to 7-8% in the other groups. The common adverse events, those with a frequency ≥ 2% in any group, are shown in Table 97.

Table 97: Sponsor's Adverse Events ≥ 2% Frequency in Any Group in Study 2308

Preferred term	Placebo N=165 n (%)	Aliskiren 150 mg od N=172 n (%)	Aliskiren 300 mg od N=169 n (%)	Aliskiren 600 mg od N=166 n (%)
Headache	16 (9.7)	12 (7.0)	13 (7.7)	9 (5.4)
Nasopharyngitis	10 (6.1)	5 (2.9)	6 (3.6)	3 (1.8)
Upper respiratory tract infection	7 (4.2)	4 (2.3)	4 (2.4)	5 (3.0)
Back pain	4 (2.4)	2 (1.2)	0 (0.0)	1 (0.6)
Diarrhoea	2 (1.2)	2 (1.2)	3 (1.8)	19 (11.4)
Dizziness	7 (4.2)	2 (1.2)	9 (5.3)	5 (3.0)
Nausea	4 (2.4)	2 (1.2)	3 (1.8)	0 (0.0)
Epistaxis	1 (0.6)	1 (0.6)	0 (0.0)	4 (2.4)
Constipation	1 (0.6)	0 (0.0)	0 (0.0)	6 (3.6)
Fatigue	1 (0.6)	0 (0.0)	2 (1.2)	5 (3.0)

COMMENT: The increased rate of diarrhea at the 600 mg dose is seen clearly in this study, although more patients also complain of constipation at this dosage. Also note more fatigue and epistaxis with the 600 mg dose.

10.1.5.47 Laboratory Findings

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.

Table 98: Reviewer's Change from Baseline in Selected Lab Values in Study 2308

Group	Hgb	RBC	Potassium	Creatinine	Urea	Uric Acid	ALT
Placebo	0.4%	0.4%	-1.0%	0.7%	0.0%	-0.4%	3.5%
Aliskiren 150	-0.7%	-0.2%	0.7%	2.7%	6.5%	2.9%	0.7%
Aliskiren 300	-1.3%	-0.8%	1.4%	2.9%	4.2%	2.1%	1.5%
Aliskiren 600	-1.4%	-0.8%	1.7%	1.6%	3.9%	-0.3%	6.1%

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

Table 99: Reviewer's Shift Table Changes (Extreme Values) for Selected Lab Tests in Study 2308

Group	Hgb	RBC	Potassium	Creatinine	Urea	Uric Acid	ALT
	N→L	N→L	N→H	N→H	N→H	N→H	N→H
Placebo	0.7%	6.3%	1.4%	2.7%	1.3%	0.7%	4.4%

Aliskiren 150	2.6%	1.3%	0.0%	6.5%	1.9%	5.6%	4.3%
Aliskiren 300	1.3%	3.8%	1.3%	5.6%	0.0%	1.3%	3.3%
Aliskiren 600	1.3%	2.0%	0.7%	6.3%	0.6%	0.7%	7.6%

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

COMMENT: This study shows some minor variations in the lab value changes shown in other studies: There is not a dose-response for the reduction in hemoglobin and the greater reduction in RBCs is also not clearly shown. Urea doesn't show clear changes and uric acid doesn't show a clear dose response. There does appear to be a small increase in creatinine with aliskiren, although it too is not dose related. The lack of dose response does appear to be consistent with the effects upon BP. Note that the placebo group appears to show somewhat unusual responses, e.g., 6.3% shift from normal to high in RBCs and 4.4% in potassium.

10.1.5.48 Adverse Events in Subgroups

Adverse event rates in subgroups (age, gender, race, etc.) were not analyzed in this study but are analyzed in the Integrated Summary of Safety.

10.1.5.49 Summary

10.1.5.50 Efficacy Summary

In this study aliskiren produced reasonable placebo-corrected reductions in DBP (-5.4 to -7.7 mm Hg) and SBP (-9.3 to -12.1 mm Hg) for the dose range 150 to 600 mg QD. The dose-response was relatively flat. The withdrawal did not show evidence of rebound effects, although the BP measurements were not consistently early enough to rule out an early rebound. The ABPM data suggest reasonable control over the 24-hour interdosing interval. Blacks appear to show a reduced effect.

10.1.5.51 Safety Summary

The increased rate of diarrhea at the 600 mg dose is seen clearly in this study (about 11% reported AEs.) The AEs are similar to those shown in other studies, although the lab value changes do not appear as pronounced and thrombotic events and mood changes will have to be scrutinized in the ISS.

10.1.5.52 Conclusions

This study supports the efficacy of aliskiren in the treatment of hypertension with acceptable toxicity. However, any conclusions regarding safety are dependent upon the complete evaluation in the ISS.

10.1.6 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

10.1.6.1 Background

This factorial study with hydrochlorothiazide (HCTZ) is intended to be the pivotal study for approval of the aliskiren/HCTZ combination as well as confirming the efficacy of aliskiren monotherapy.

10.1.6.2 Initial Protocol

The initial protocol is dated 18-Mar-2004.

10.1.6.3 Protocol Amendments

The protocol was amended twice: (1) Amendment 1, dated 21-Jul-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 10-Nov-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 added an amendment dated 07-Jul-2004 including patients with essential hypertension who were previously untreated (for at least 3 months prior to visit 1).

10.1.6.4 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).

10.1.6.5 Study Dates

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

10.1.6.6 Study Design

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

10.1.6.7 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.

10.1.6.8 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.

10.1.6.9 Inclusion and Exclusion Criteria

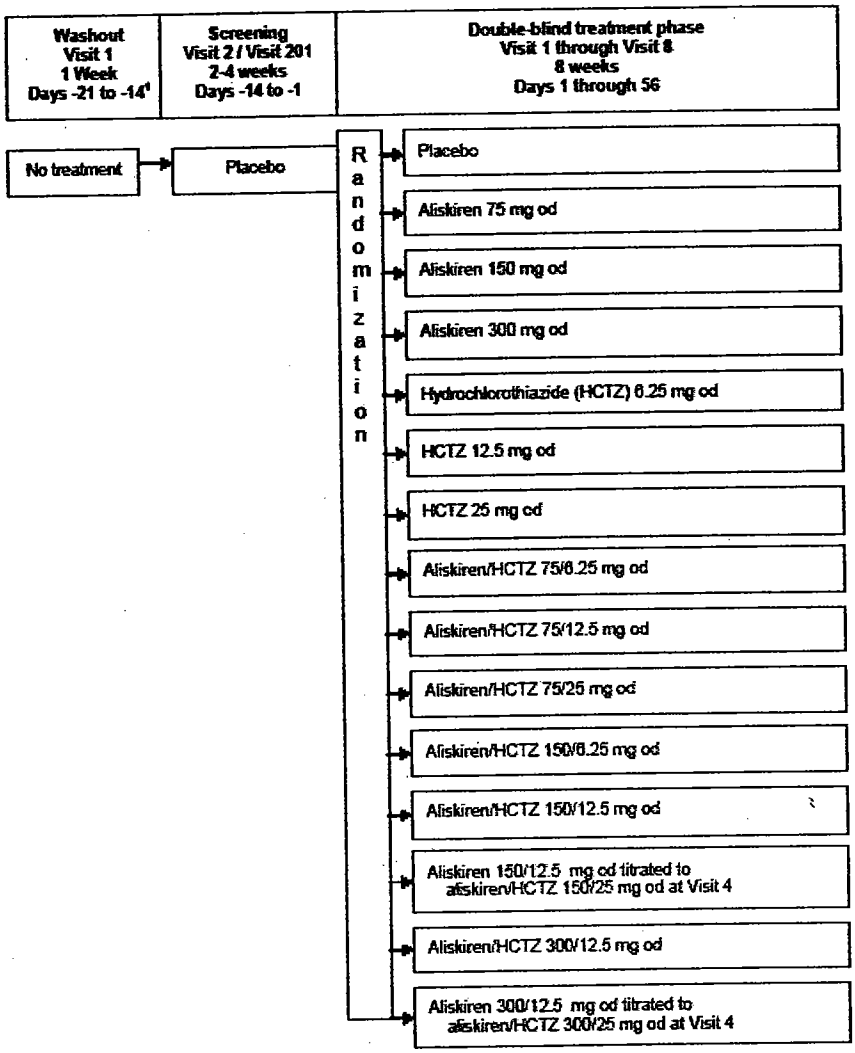
The inclusion criteria were the following: 18 or older; females post-menopausal, sterile, or using adequate contraception; essential hypertension with DBP 90-109 visit 2 to 95-109 at visit 3; DBP difference ≤10; written informed consent.

The exclusion criteria were the following: prior aliskiren use; BP ≥ 180/110; 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.

10.1.6.10 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 Figure 34.

Figure 34: Study 2204 Plan



10.1.6.11 Treatment

10.1.6.12 Dosage and Administration

Aliskiren 75 and 150 mg and HCTZ were formulated as overencapsulated 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.

10.1.6.13 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.

10.1.6.14 Concomitant Therapy
Other antihypertensives were prohibited.

10.1.6.15 Safety and Efficacy Endpoints
The primary endpoint was change in trough seated cuff DBP at eight weeks.

10.1.6.16 Statistical Considerations

10.1.6.17 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.

10.1.6.18 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.

10.1.6.19 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.

COMMENT: The lack of adjustment for the two hypotheses (monotherapy efficacy and combination therapy efficacy) is problematic. The results will need to be robust enough to support statistical significance with a conservative adjustment for multiplicity, e.g., Bonferroni.

10.1.6.20 Results

10.1.6.21 Study Implementation

10.1.6.22 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 (section 7.2). 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 Figure 35.

Figure 35: Sponsor's 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*	188	193	186	176	186	168	181	173	2776
Completed†	179 (95.2)	175 (90.7)	173 (93.0)	157 (89.2)	177 (95.2)	170 (90.4)	170 (93.9)	165 (95.0)	2558 (92.1)
Discontinued‡	9 (4.8)	15 (7.8)	13 (7.0)	17 (9.7)	7 (3.8)	16 (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)	5 (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)

COMMENT: The dropout rates are acceptable.

10.1.6.23 Subject Demographics and Baseline Characteristics

10.1.6.24 Overall Baseline Comparisons

Demographics and other selected baseline characteristics are shown in Table 100.

Table 100: Reviewer's 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

COMMENT: The baseline characteristics appear reasonably balanced among the groups.

10.1.6.25 Conduct

10.1.6.26 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.

10.1.6.27 Protocol Changes and Violations

There were two amendments as described in Section 10.1.6.3. The following are some significant protocol violations:

- 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.

- 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.

- 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.

- 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.

10.1.6.28 Dosing

10.1.6.29 Study Drug
Dosing variations occurred as described in Section 10.1.6.27.

10.1.6.30 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 non-steroidal anti-inflammatory topical preparations (10%). Other antihypertensives were taken by 1.1% of the study population.

10.1.6.31 Blinding
No patients were unblinded during the study.

10.1.6.32 Efficacy

10.1.6.33 Primary Endpoint
The sponsor's analyses of the primary endpoint, change from baseline in DBP, are shown in Table 101.

Table 101: Sponsor's 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

COMMENT: 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 despite the lack of a pre-specified approach for handling the multiplicity of the two

sets of hypotheses (i.e., aliskiren doses vs. placebo and aliskiren/HCTZ combination vs. components). Note, 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. Note the substantial placebo effect (nearly 7 mm Hg.) See also the results for SBP in the next section.

10.1.6.34 Secondary Endpoints

The sponsor's analyses of change from baseline in SBP are shown in Table 102.

COMMENT: 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.

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Table 102: Sponsor's 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

10.1.6.35 Subgroup Analyses

10.1.6.36 Country

The changes from baseline in DBP at eight weeks LOCF by region are shown in Table 103.

Table 103: Reviewer's 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

COMMENT: 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.

10.1.6.37 Race

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

10.1.6.38 Age and Gender

The placebo-corrected changes from baseline in DBP at eight weeks LOCF by gender are shown in Table 104.

Table 104: Reviewer's 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

COMMENT: 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. Although I don't show the data here, I did not find any differential effects by age.

10.1.6.39 Safety

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

10.1.6.41 Serious Adverse Events

10.1.6.42 Deaths
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.

10.1.6.43 Hospitalizations
The following hospitalizations were reported:

- A 61-year-old white male in the 75/25 group experienced dysarthria on day 2 and problems with moving his right hand on day 3. An MRI on day 7 showed a cerebral infarction. His BP at randomization was 165/97.

- A 44-year-old white male in the 75 mg group experienced renal colic on day 19. A renal sonogram revealed dilation of the left urinary tract. He was treated with analgesics with resolution in about a week. A month later he developed renal colic and fever. He was hospitalized and discharged after three days. The study medication was not discontinued.

- An 80-year-old white male with a history of prostate cancer in the 150 mg group developed hematuria and urinary retention on day 19. He was hospitalized and treated by urinary catheterization to unblock a clot. Study medication was not discontinued.

- A 69-year-old white male in the 300 mg group developed rectal bleeding on day 46. A colonoscopy showed a stenosing tumor confirmed by biopsy to be a mucous adenocarcinoma. Study medication was not discontinued.

- A 42-year-old black female in the 300 mg group developed chest pain and headache on December 12, 2004, day 25 of the single-blind study period. On December 16, 2004, she was given one dose of blinded study medication. Cardiac ischemia was diagnosed based on ST depression in V3-5 not present on the baseline ECG. Study drug was discontinued. Subsequently she was hospitalized for unstable angina on ——→ A stress test on December 29 was interpreted as negative. ECGs were interpreted as showed a left precordial repolarization abnormality. On January 10 her intermittent pain was reproduced by palpation of the anterior thorax.

- A 59-year-old female in the 75/12.5 group experienced feeling different, unmotivated crying, and difficulties with movement of her right hand on day 13. She was taken to the ER where she was noted to have difficulties in writing her own name, dysarthria, and the mood disorder. A CAT scan was normal. Her BP was 166/104 and study medication was discontinued and ramipril and HCTZ started. She gradually improved but was still noted to have unmotivated crying and dysarthria on day 17. She returned to work on day 28 but had memory problems with usual passwords and phone numbers. A MRI scan on day 44 showed a superior paramedian left pontine lesion considered ischemic, myelinolysis, or vasculitis.

- A 46-year-old male in the 75/12.5 group experienced phlebitis and severe pain in the right calf on day 23. Deep vein thrombosis was confirmed by echo. Study medication was discontinued.

- A 57-year-old white male in the 75/12.5 group experienced syncope requiring hospitalization on day 60. BP at the time of the event is unknown, but BP two weeks earlier was 137/87 and the next day 149/98. ECG and CAT scan were reported as normal. No diagnosis was made. Study medication was not interrupted.

- A 51-year-old white, diabetic male in the 75/12.5 group experienced dizziness and double vision on day 26. Neuro-ophthalmologic exam was normal except the patient experienced diplopia when looking to the right and left. CAT scan was normal. BP "before the event was 169/97 sitting, 165/101 standing. The hospitalization was only for evaluation and the patient was discharged the same day. Study medication was continued. No further follow-up is provided.

- A 56-year-old white male in the 75/12.5 group post abdominal hernia repair a year earlier experienced vomiting on day 10. He was hospitalized and treated with IV fluids. Small intestinal obstruction was diagnosed by CAT scan. He was discharged after two days. Study medication was not interrupted and he completed the study.

- A 57-year-old white male in the 75/12.5 group with a history of syncope in 2002 experienced vomiting and syncope on day 40. His BP that day was 125/80 and 149/93 the next day (orthostatic readings are not reported.) He was discharged after two days with a diagnosis of dehydration and vasovagal episode. Study medication was interrupted for one day and he completed the study.

- A 45-year-old white male in the 75/25 group treated with atorvastatin and having a history of elevated CK (screening 4407, baseline 444) had several episodes of nocturnal chest pressure in the weeks prior to randomization. On day 17 he was hospitalized with an inferior MI. Angiography showed occlusion of the first and second marginal branches and ischemic cardiomyopathy with ejection fraction 0.37. Study medication was discontinued.

- A 34-year-old white male experienced renal colic on day 38. Study drug was temporarily interrupted and he completed the study successfully.

- A 54-year-old white male in the 150/6.25 group experienced abdominal pain and rectal bleeding on day 24. Videocolonoscopy showed diffuse inflammatory colitis. He withdrew from the study on day 34 and a biopsy showed idiopathic ulcerative colitis on day 40.

- A 49-year-old black male in the 300/25 group developed angina on day 62. A cath showed blockage of the LAD and he underwent PTCA with stenting. Study drug was discontinued.

- A 56-year-old white female in the 150/6.25 group was hospitalized with pneumonia on day 15. Study drug was not interrupted and she completed the study.

- A 60-year-old white male in the 150/12.5 group was hospitalized with chest pain on day 41. He was diagnosed with hiatus hernia and study drug was discontinued.

- A 65-year-old white male smoker in the 150/25 group had two lung tumors on chest x-ray six months prior to randomization, but the patient was not aware of the tumors. On day 6 he felt, hurt his chest, and had another chest x-ray revealing the two tumors. He completed the study and then had an operation for the tumors.

- A 56-year-old white male in the 300/12.5 group had an elevated fast blood sugar at screening (6.3 mmol/L) that increased at randomization and further increased at day 51 (16 mmol/L). He was diagnosed as diabetes type 2 and completed the study.

- A 66-year-old white female in the 300/12.5 group had sudden breathlessness on day 22 and was hospitalized with suspected pulmonary embolism. Scans were negative and no diagnosis was made. Study medication was not interrupted and she completed the study.

- A 61-year-old white male diabetic in the 75 group developed dyspnea and edema of the lower limb to the knee, hands and face (eyelid but no lip or tongue) on day 22. He also had purplish-blue lesions with angiomatous aspect on the upper part of his trunk. He had slightly increased IgA and slight proteinuria (0.26g/24h). He completed the study with continuation of the edema and also developed anorexia, weight loss, tachycardia (100-115), and elevated CRP. He has been diagnosed as scleroedema.

- A 67-year-old white male in the 150/6.25 group completed the study and was allowed to continue in the follow-up period despite uncontrolled BP (180/105). On day 19 of the follow-up he suddenly experienced a partial deficit of the right side "with elocution disorders". BP was 170/90 and a scan was negative in the ER and a later scan showed left temporal and right parietal hypodensity. He was diagnosed as an ischemic stroke with partial resolution.

- A 57-year-old female in the 150/6.25 group completed the study and had a mammogram the same day showing a breast tumor. The tumor was confirmed as malignant by biopsy.

- A 43-year-old black female in the 150/6.25 group was hospitalized for a thyroidectomy for an asymptomatic nodule displacing the trachea 18 days after completing the study. No pathology is reported.

In addition to events during active treatment, a 67-year-old white male in the 150/6.25 group suffered a stroke 19 days after discontinuing the study. His BP was poorly controlled throughout the study (164-185/101-114).

COMMENT: These events again raise suspicions about increased thrombotic events with aliskiren. Renal stones and colitis are also examined in the Integrated Summary of Safety.

10.1.6.44 Other serious adverse events

A 40-year-old white female in the 75/25 group had a negative pregnancy screen but on day 1 had a positive pregnancy test and an ultrasound showing a 5-week pregnancy. She underwent an abortion and completed the study successfully. A 29-year-old black female in the 150/12.5 group had negative screening and baseline pregnancy tests. On day 28 she had a positive pregnancy test and discontinued study medication. She had a c-section at about 26 weeks delivering a "normal female neonate." One patient in the HCTZ 12.5 group also became pregnant.

10.1.6.45 Events Leading to Discontinuation

The rates of events leading to discontinuation are show in Table 105.

Table 105: Sponsor's 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-year-old 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.

COMMENT: Cough, rash, and GI complaints are scrutinized in the Integrated Summary of Safety.

10.1.6.46 Events of Special Interest

There were no cases of angioedema reported in this study.

10.1.6.47 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%). There was a trend toward higher rates of AEs with increasing dose,

particularly in the combinations with HCTZ. The overall rates of AEs by group and the most frequent AEs (≥ 2% in any group) are shown in Table 106.

Table 106: Sponsor's 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 = 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
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)

10.1.6.48 Laboratory Findings

Changes from baseline in mean values for selected lab tests (those which aliskiren appears to affect) are shown in Table 107 and shift tables for the selected lab tests are shown in.

Table 107: Reviewer's 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 108: Reviewer's 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

COMMENT: The mean changes are more consistent for HCTZ (decrease in potassium, increases in creatinine, urea, uric acid, and ALT) than for 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.

10.1.6.49 Adverse Events in Subgroups
Adverse event rates in subgroups (age, gender, race, etc.) were not analyzed in this study but are analyzed in the ISS.

10.1.6.50 Summary

10.1.6.51 Efficacy Summary
In this study aliskiren again shows antihypertensive efficacy, although a dose-response in the range 75-300 mg is not clearly demonstrated. Aliskiren also appear to be additive with HCTZ. The latter effects will be examined more closely when the NDA for the aliskiren/HCTZ combination is submitted.

10.1.6.52 Safety Summary
The adverse events in this study are similar to those reported in the aliskiren monotherapy trials, with the addition of cough and rash as events to be scrutinized in the overall safety database. The event rates appear to be slightly higher with the higher combination dosages, although no specific events are obviously responsible. The changes in lab values suggest that aliskiren and HCTZ may be additive with regard to increases in creatinine, urea, and uric acid, and perhaps decreases in hemoglobin.

10.1.6.53 Conclusions
Aliskiren has antihypertensive efficacy. While in this study its toxicity appears acceptable, the safety evaluation depends upon the evaluation of the entire safety database in the Integrated Summary of Safety.

10.1.7 Study 2305 - A six-week, randomized, double-blind, parallel-group, multicenter study to evaluate the safety and efficacy of the combination of aliskiren 150 mg and amlodipine 5 mg compared to amlodipine 5 mg and 10 mg in hypertensive patients not adequately responsive to amlodipine 5 mg

10.1.7.1 Background
The rationale of this study is to evaluate the antihypertensive effects of aliskiren combined with amlodipine 5 mg.

10.1.7.2 Design and Conduct
This was a six week, international, multicenter, randomized, double-blind, double-dummy, active-controlled, parallel group study. Eligible hypertensive adults (untreated DBP 95-109 or

treated <110) entered a 2-4 week washout period. Patients with DBP 95-109 entered a four-week, single-blind amlodipine 5 mg treatment period. Patients with DBP 90-109 at the end of the single-blind amlodipine treatment period were randomized equally to double-blind amlodipine 5 mg, amlodipine 10 mg, or aliskiren 150 mg/amlodipine 5 mg, all once daily for six weeks. The primary endpoint was trough seated cuff DBP LOCF at the end of the six week double-blind treatment period. The primary comparison was to be the combination vs. amlodipine 5 mg. The primary analysis was to be an ANCOVA with treatment and region as factors and baseline as a covariate. The planned sample size was 504 for 90% power of detecting a 3 mm Hg difference with a 10% dropout rate and SD of 8 mm Hg.
In the end 71 centers in eight countries (12 centers in Denmark, 13 in Germany, 1 in Greece, 8 in Korea, 1 in Malaysia, 5 in Slovakia, 5 in South Africa, and 36 in the US) treated 545 (vs. 762 enrolled) patients from February 9, 2005, to October 24, 2005. The mean age was 53, 54% were male, 69% were white, 18% were black, 11% were Asian, and 45% had a BMI $\geq$ 30 kg/m^2. Baseline characteristics were well balanced among the groups.

10.1.7.3 Efficacy Summary

The sponsor's analyses for the primary endpoint, change from baseline in DBP, are shown in Table 109 and the corresponding analyses for SBP are shown in Table 110.

Table 109: Sponsor's Change from Baseline in DBP in Study 2305

Treatment Group	N	LSM change from Baseline (SE)	
Aliskiren 150 mg + Amlodipine 5 mg	187	-8.46	(0.60)
Amlodipine 5 mg	177	-4.84	(0.62)
Amlodipine 10 mg	177	-8.04	(0.62)

Pairwise Comparison	LSM difference in change from Baseline (SE)		95% CI for LSM difference	p-Value
Aliskiren 150 mg + Amlodipine 5 mg vs. Amlodipine 5 mg	-3.62	(0.83)	(-5.25, -1.99)	<.0001*
Aliskiren 150 mg + Amlodipine 5 mg vs. Amlodipine 10 mg	-0.42	(0.83)	(-2.05, 1.21)	0.6167

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

Table 110: Sponsor's Change from Baseline in SBP in Study 2305

Treatment Group	N	LSM change from Baseline (SE)	
Aliskiren 150 mg + Amlodipine 5 mg	187	-10.98	(0.88)
Amlodipine 5 mg	177	-4.96	(0.90)
Amlodipine 10 mg	177	-9.63	(0.90)

Pairwise Comparison	LSM difference in change from Baseline (SE)		95% CI for LSM difference	p-Value
Aliskiren 150 mg + Amlodipine 5 mg vs. Amlodipine 5 mg	-6.02	(1.21)	(-8.40, -3.64)	<.0001*
Aliskiren 150 mg + Amlodipine 5 mg vs. Amlodipine 10 mg	-1.35	(1.21)	(-3.73, 1.03)	0.2666

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

COMMENT: Aliskiren 150 mg appears to add to amlodipine 5 mg but it is not clear whether the effect of aliskiren 150/amlodipine 5 mg is greater than that of amlodipine 10 mg.

10.1.7.4 Safety Summary

Overall rates of patients with AEs were similar in the three groups (aliskiren/amlodipine 32%, amlodipine 5 mg 29%, and amlodipine 10 mg 31%). The most frequent events were headache, edema, and dizziness, with edema more common with amlodipine 10 mg (11% vs 3.4% with amlodipine 5 mg and 2.1% with the combination).

There were no deaths. SAEs (<1%) and discontinuations (<3%) were rare and similar between the amlodipine 10 mg and combination group and numerically less frequent with amlodipine 5 mg. The only AE leading to discontinuation in more than one patient was edema (in three amlodipine 10 mg patients).

COMMENT: The combination appears to be slightly better tolerated than amlodipine 10 mg monotherapy.

10.1.7.5 Conclusions

Aliskiren 150 mg appears to add to amlodipine 5 mg but it is not clear whether the effect of aliskiren 150/amlodipine 5 mg is greater than that of amlodipine 10 mg. The maximum proposed dose of aliskiren, 300 mg, was not studied. This study does not demonstrate whether aliskiren adds to a maximum dose of a calcium channel blocker, e.g., amlodipine 10 mg. The combination aliskiren 150/amlodipine 5 mg appears to be slightly better tolerated than amlodipine 10 mg monotherapy.

10.1.8 Study 2307 - An eight-week, randomized, double-blind, parallel group, multicenter, dose escalation study to evaluate the efficacy and safety of aliskiren administered alone and in combination with ramipril in patients with hypertension and diabetes mellitus

10.1.8.1 Background

Because hypertension is common in diabetics and ACE inhibitors have been shown to slow the rate of progression of diabetic nephropathy (although ramipril does not have this indication), the sponsor conducted this trial to show the relative antihypertensive effects of aliskiren, ramipril, and their combination.

10.1.8.2 Design and Conduct

This was an eight week, international, multicenter, randomized, double-blind, double-dummy, active-controlled, parallel group study. Patients had to have diabetes (type 1 or 2) and essential hypertension of ≤180/95-109. Following screening and a one-week washout and 2-4 week single-blind placebo run-in, eligible patients were randomized equally to starting double-blind aliskiren 150 mg, ramipril 5 mg, or the combination once daily. After four weeks the dosages

were doubled. The primary endpoint was trough seated cuff DBP at eight weeks LOCF, while a subset also underwent ABPM. The protocol describes two primary endpoints, the combination vs. the monotherapies and aliskiren vs. ramipril, each evaluated at alpha 0.05. For the combination vs. the monotherapies the combination was to be superior to each of the monotherapies at alpha 0.05. For aliskiren vs. ramipril, non-inferiority was to be assessed first with a margin of 2 mm Hg for DBP (4 mm Hg for SBP) and then superiority. The analyses were to be ANCOVAs with treatment and region as factors and baseline as a covariate. The planned sample size was 846 for 90% power of detecting a 2.5 mm Hg difference.

In the end 125 centers in 13 countries in six regions (6 centers in Taiwan and Malaysia, 18 in the US and Canada, 37 in Germany, 22 in France and the Netherlands, 25 in Italy, Turkey and Spain, and 17 in Denmark, Norway, and Sweden) treated 837 patients from November 29, 2004, through August 30, 2005. The mean age was 60, 59% were male, and 91% were white. The treatment groups were comparable for baseline characteristics except that the ramipril group had fewer obese (BMI $\geq$ 30 kg/m^2) patients than the other two groups (45% vs. about 55%).

10.1.8.3 Efficacy Summary

The sponsor's analyses for the primary endpoint, change from baseline in DBP, are shown in Table 111,the corresponding analyses for SBP are shown in Table 112, and the changes in mean 24-hour DBP from the ABPM substudy are shown in Table 113.

Table 111: Sponsor's Change from Baseline in DBP in Study 2307

Treatment Group		N	LS Mean change from baseline (SE)		
Ramipril 10 mg		275	-10.71 (0.54)		
Aliskiren 300 mg		279	-11.32 (0.54)		
Aliskiren 300 mg/ Ramipril 10 mg		274	-12.78 (0.54)		
Pairwise Comparison (A vs. B)		**LS Mean difference**		**P-Value**	
A	**B**	**A – B (SE)**	**95% CI**	**Superiority of A†**	**Non-inferiority‡**
Aliskiren/ Ramipril	Aliskiren	-1.46 (0.72)	(-2.87, -0.05)	0.0426*	-
Aliskiren/ Ramipril	Ramipril	-2.07 (0.72)	(-3.49, -0.65)	0.0043*	-
Aliskiren	Ramipril	-0.61 (0.72)	(-2.02, 0.80)	0.3968	0.0002*

SE = Standard Error; CI = Confidence Interval
* indicates statistical significance at the specified level.
† P-Values and treatment comparisons were evaluated at the average baseline level, with a significance level of 0.05
‡ The margin for non-inferiority was 2 mmHg. A one-sided significance level of 0.025 was used.

Table 112: Sponsor's Change from Baseline in SBP in Study 2307

Treatment Group		N	LS Mean change from baseline (SE)		
Ramipril 10 mg		275	-11.99 (0.86)		
Aliskiren 300 mg		279	-14.65 (0.86)		
Aliskiren 300 mg/ Ramipril 10 mg		274	-16.62 (0.87)		
Pairwise Comparison (A vs. B)		**LS Mean difference**		**P-Value**	
A	**B**	**A – B (SE)**	**95% CI**	**Superiority of A†**	**Non-inferiority‡**
Aliskiren/ Ramipril	Aliskiren	-1.96 (1.15)	(-4.22, 0.29)	0.0881	-
Aliskiren/ Ramipril	Ramipril	-4.63 (1.15)	(-6.89, -2.36)	<0.0001*	-
Aliskiren	Ramipril	-2.67 (1.15)	(-4.92, -0.41)	0.0207*	<0.0001*

SE = Standard Error; CI = Confidence Interval
* indicates statistical significance at the specified level.
† P-Values and treatment comparisons were evaluated at the average baseline level, with a significance level of 0.05
‡ The margin for non-inferiority was 4 mmHg. A one-sided significance level of 0.025 was used.

Table 113: Sponsor's Change from Baseline in Mean 24-hour DBP in Study 2307

Treatment Group		N	LS Mean change from baseline (SE)	
Ramipril 10 mg		55	-3.16 (0.57)	
Aliskiren 300 mg		57	-4.26 (0.56)	
Aliskiren 300 mg/ Ramipril 10 mg		61	-4.75 (0.54)	
Pairwise Comparison (A vs. B)		**LS Mean difference**		**P-Value**
A	**B**	**A – B (SE)**	**95% CI**	**Superiority of A†**
Aliskiren/ Ramipril	Aliskiren	-0.49 (0.74)	(-1.95, 0.98)	0.5109
Aliskiren/ Ramipril	Ramipril	-1.59 (0.75)	(-3.06, -0.12)	0.0344*
Aliskiren	Ramipril	-1.10 (0.76)	(-2.60, -0.40)	0.1496

SE = Standard Error; CI = Confidence Interval
based on a two-way repeated-measures ANCOVA with treatment, region and post-dosing hours as factors and baseline mean ambulatory DBP as a covariate.

COMMENT: These results suggest a modest additive effect of aliskiren 300 mg to ramipril 10 mg at the 24 hour interdosing interval used in this study. The differences in effects upon 24-hour mean DBP are also modest. However, because ramipril is more effective when given BID and because the maximum label dosage of ramipril is 20 mg, the advantages of these small effects are unclear and whether aliskiren adds to the maximum dosage of an ACE inhibitor is not demonstrated.

10.1.8.4 Safety Summary

Overall rates of patients with AEs were similar in the three groups (aliskiren 32%, ramipril 34%, and aliskiren/ramipril 30%). The most frequent events were headache, cough, nasopharyngitis, and diarrhea. Both cough (5%) and diarrhea (2.5%) were more common in the ramipril group than the aliskiren and combination groups (about 2% and 1% respectively.)

Of SAEs, one patient in the ramipril group died due to acute alcohol toxicity. Rates of withdrawals for AEs were similar in the aliskiren and ramipril groups (about 4%) and lower in the combination group (2.2%). SAE rates were slightly higher in the aliskiren group (2.8%), intermediate in the ramipril group (2.2%), and lowest in the combination group (1.4%). With these low rates the types of events were diverse without clear patterns. However, the following AEs are of interest:

- A 48-year-old white female in the combination group was in a traffic accident 8 days prior to randomization and then developed paresis of the right hand 7 days prior to randomization. She was randomized, the paresis worsened, and she presented with monoplegia of the right limb on day 3. She was discontinued on day 6. An echo showed right internal carotid thrombus.

- A 66-year-old white female in the combination group suffered severe right arm paresis on day 7 and was hospitalized. Study medication was discontinued and metoprolol started and she recovered by day 17. No diagnosis of stroke or TIA was made.

- A 75-year-old male in the combination group suffered a TIA on day 4. Treatment was not discontinued.

- A 66-year-old white female in the aliskiren group suffered an allergic skin reaction of the face on day 17. Study drug was discontinued.

- A 50-year-old Asian male in the aliskiren group developed "subclinical" rhabdomyolysis on day 57 and a 59-year-old Asian male in the ramipril group suffered renal impairment on day 18 and suspected myositis on day 58.

COMMENT: The stroke rate again appears higher with aliskiren, although in this study the events are all in the group receiving aliskiren and ramipril. This study also suggests that angioedema and rhabdomyolysis may occur with aliskiren.

No patients discontinued for lab test abnormalities. For the combination group a higher proportion of patients showed increases from normal at baseline to above normal range at the most extreme value compared to the monotherapies for potassium (8.4% vs. 4.3% patients for aliskiren and 4.4% for ramipril) and for urea (12.5% vs. 7.9% for aliskiren and 7.3% for ramipril).

COMMENT: The effects upon potassium and urea appear to be additive for aliskiren and ramipril.

10.1.8.5 Conclusions

Aliskiren 300 mg and ramipril 10 mg combined have a slightly greater antihypertensive effect than the monotherapies. Their effects upon potassium and urea also appear to be additive, although the overall AE rates appear to be similar. This study does not show that aliskiren adds

to the antihypertensive effect of a maximal dose of an ACE inhibitor.

10.1.9 Study 1201 - Dose-finding study of SPP100 in essential hypertension (in Japan)

10.1.9.1 Background

This is a Japanese dose-ranging study in essential hypertension.

10.1.9.2 Design and Conduct

This was an eight week, randomized, double-blind, double-dummy, placebo-controlled, parallel group, dose-ranging study. Patients had to have DBP 90-109 initially, 95-109 upon withdrawal, and SBP < 180. The study was conducted from August 31, 2004, to March 18, 2005, at 29 centers in Japan. Overall 455 patients were randomized equally to aliskiren 75, 150, or 300 mg or placebo and 434 patients completed the study. The patients were predominantly male (73%) and middle-aged (median age 53). The study consisted of a 4-week placebo withdrawal, an 8-week double-blind treatment, and a one-week withdrawal. The primary endpoint was trough cuff seated DBP (measured with an [redacted] device) at 8 weeks LOCF.

10.1.9.3 Efficacy Summary

The sponsor's results for the primary endpoint are shown in Table 114, the change in DBP by visit in Figure 36, and the change in SBP in Table 115.

Table 114: Sponsor's Change from Baseline in DBP in Study 1201

Time point	Treatment group	Placebo group N=115	75 mg group N=115	150 mg group N=112	300 mg group N=113
Week 0	n	115	115	112	113
	Mean (SD)	99.4 (3.9)	99.4 (4.0)	99.5 (4.0)	99.6 (4.4)
	Median	99.0	98.0	98.0	98.0
	Min, Max		[redacted]		
Endpoint	n	115	115	112	113
	Mean (SD)	96.3 (9.4)	92.3 (8.6)	91.8 (10.7)	88.9 (9.7)
	Median	97.0	93.0	92.5	88.0
	Min, Max		[redacted]		
Change (Endpoint – Week 0)	n	115	115	112	113
	Mean (SE)	−3.16 (0.73)	−7.17 (0.67)	−7.69 (0.84)	−10.66 (0.83)
	P value[a]	*P*<0.0001	*P*<0.0001	*P*<0.0001	*P*<0.0001
	Lsmean (SE)[b]	−3.26 (0.75)	−7.22 (0.75)	−7.75 (0.76)	−10.72 (0.75)
Difference in change between groups (SPP100 group − placebo group)	Lsmean	–	−3.96	−4.49	−7.46
	95% confidence interval	–	−6.03 to −1.89	−6.57 to −2.41	−9.54 to −5.38
	Test result	–	*P*=0.0002	*P*<0.0001	*P*<0.0001

Figure 36: Sponsor's Change in DBP by Visit in Study 1201

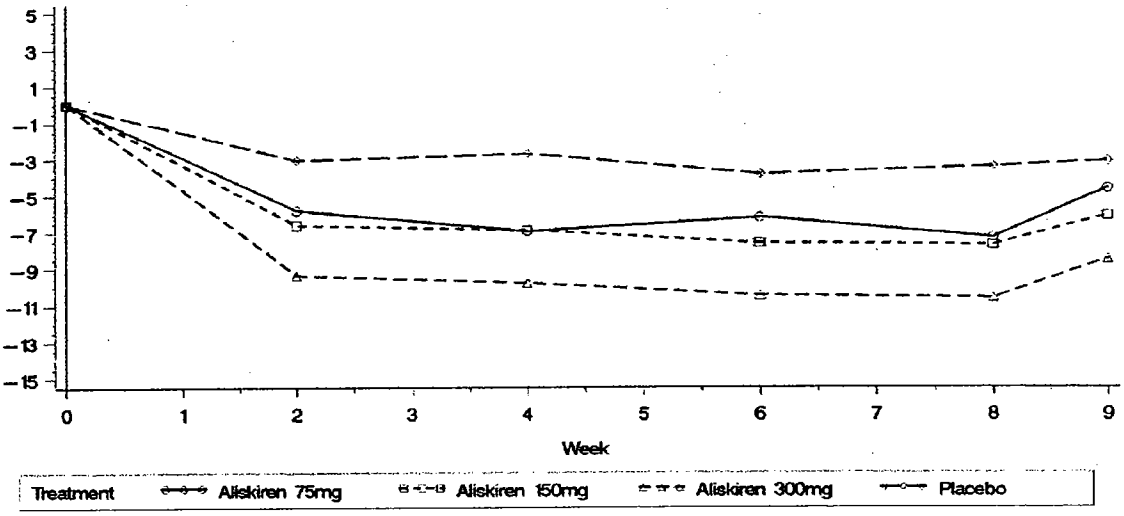


Table 115: Sponsor's Change from Baseline in SBP in Study 1201

Time point	Treatment group	Placebo group N=115	75 mg group N=115	150 mg group N=112	300 mg group N=113
Week 0	n	115	115	112	113
	Mean (SD)	155.4 (10.7)	152.7 (11.8)	155.6 (11.1)	155 (11.7)
	Median	155.0	152.0	155.0	155.0
	Min, Max				
Endpoint	n	115	115	112	113
	Mean (SD)	152.6 (14.7)	144.6 (12.9)	146.8 (16.5)	140.9 (17.0)
	Median	151.0	145.0	146.0	138.0
	Min, Max				
Change (Endpoint – Week 0)	n	115	115	112	113
	Mean (SE)	−2.84 (1.17)	−8.06 (1.18)	−8.83 (1.18)	−14.11 (1.29)
	P value[a)]	*P*=0.0168	*P*<0.0001	*P*<0.0001	*P*<0.0001
	Lsmean (SE)[b)]	−2.85 (1.17)	−8.57 (1.17)	−8.72 (1.18)	−14.09 (1.18)
Difference in change between groups (SPP100 group − placebo group)	Lsmean	–	−5.72	−5.87	−11.2
	95% confidence interval	–	−8.97 to −2.47	−9.13 to −2.61	−14.5 to −7.99
	Test result	–	*P*=0.0006	*P*=0.0009	*P*=0.0001

COMMENT: In this study all doses show a significant antihypertensive effect, although the 75 and 150 mg doses appear similar while the 300 mg dose shows a greater effect. The effect appears to be relatively complete by two weeks.

10.1.9.4 Safety Summary

There was one death, an aliskiren 150 mg patient who died from a drug overdose (a sudden death at home reported by his wife as related to a drug overdose). The overdose is described on the CRFs as related to a psychiatric drug prescribed prior to study initiation and a diagnosis of manic depressive psychosis is recorded. The SAE report has this description: "The investigator stated that a brief postmortem was performed but no forensic autopsy was conducted and a toxicology screen was 'probably not performed'. The investigator was unsure if this was an accidental or deliberate overdose and the medications the patient overdosed on were still unknown. The investigator confirmed that the patient did not overdose on study medication stating that all study medications were returned to the site. It was unknown if the patient's manic depressive illness contributed towards this event. The investigator stated that the medical examiner and the police were contacted on _ out they refused to provide details. In the absence of further information this event will therefore be considered as potentially related to Inderal, Seltouch, Paxil, Limas, Depas, and Benzalin." There is uncertainty about whether the patient was prescribed Inderal for hypertension or for bipolar disorder and whether the Inderal was stopped for the study. The patient's BP is described as well controlled.

COMMENT: Whether aliskiren contributed to this death is unclear.

One patient in the aliskiren 75 mg group also suffered a myocardial infarction, while a patient in the placebo group suffered a stroke. One patient in the 75 mg group experienced an AE of severe creatine kinase rise and one patient in the 300 mg group suffered severe potassium increase. The CK values for the patient with the CK increase are varied: 175 pre-treatment, 2381 day 1, 152 day 15, 110 day 29, and 9452 U/L day 57. CK increase AEs were reported in three 75 mg, one 300 mg, and two placebo patients.

One patient in the placebo group (baseline 159/107 to 168/109 at two weeks) and two patients on aliskiren discontinued because of increased BP. The BPs for the latter two patients are shown in Table 116.

Table 116: Sponsor's Time Course of BP in Aliskiren Patients Discontinuing for Increased BP in Study 1201

150 mg group:

Week	-4	-2	0	2	Discontinuation of study
Date of measurement	11/24/2004	12/04/2004	12/18/2004	12/30/2004	01/03/2005
MSDBP (mmHg)	105	102	106	108	114
MSSBP (mmHg)	155	159	161	170	191

300 mg group:

Week	-4	-2	0	2	4	6	Discontinuation of study
Date of measurement	12/04/2004	12/22/2004	01/07/2005	01/19/2005	02/01/2005	02/19/2005	03/05/2005
MSDBP (mmHg)	94	99	103	101	104	101	112
MSSBP (mmHg)	160	179	179	186	180	187	197

COMMENT: The two cases in Table 116 show that some patients do not respond to aliskiren. I explore whether such lack of control contributed to the two cases of stroke on aliskiren in other studies.

Overall, AEs were commonly reported in this study, about 50% of patients. Notable AEs include diarrhea in 3.5% of the 300 mg group (vs. 1% in the other groups) and ALT increases in about 4% of the 75 and 150 mg groups (but 2% in the 300 mg and placebo groups). Edema was not commonly reported, with one patient in the placebo group reporting facial edema.

COMMENT: The pattern of AEs in this Japanese study appears comparable to these seen in the studies in Western populations other than the absence of edema.

10.1.9.5 Conclusions

This study supports efficacy of aliskiren in hypertension. The AE profile in this Japanese population appears similar to that in the Western population except for edema.

10.1.10 Study 2302 - A 12 month, randomized, open-label, multicenter, study to assess the long term safety of aliskiren 150 mg alone and 300 mg alone or with the optional addition of hydrochlorothiazide (12.5 mg or 25 mg) in patients with essential hypertension

10.1.10.1 Background

This study provides longer term safety data for aliskiren use in hypertensives.

10.1.10.2 Design and Conduct

This was a randomized (to starting dose), open-label, titrated, international, multi-center study of aliskiren 150 and 300 mg with titrated-to-effect addition of hydrochlorothiazide (HCTZ) 12.5 or 25 mg. Patients in Study 2203 (aliskiren and valsartan combinations) could enter this study directly. Other patients were withdrawn from other antihypertensives for 2-4 weeks and then, if eligible with BP <180/90-109 and DBP variability ≤10, randomized 3:2 to aliskiren 150 or 300 mg. At months 2 and 3 investigators could increase aliskiren 150 to 300 or, for patients receiving 300, add HCTZ 12.5 mg or increase HCTZ to 25 mg to reach a target BP of <140/90. HCTZ could be down-titrated but aliskiren could not. At month 11 the first 320 patients on aliskiren alone were to undergo a randomized (current dosage or placebo), double-blind, placebo-controlled, one-month withdrawal. A 50% of these withdrawal patients were also to undergo ABPM at months 11 and 12. The primary evaluation for the whole study was regarding

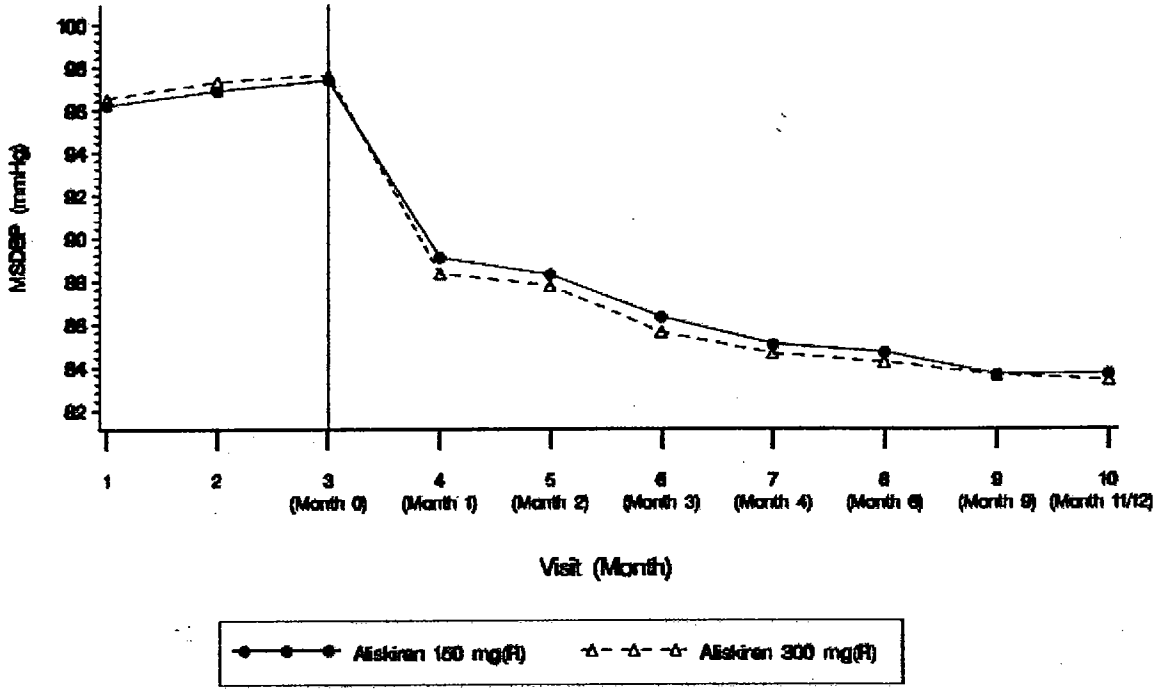
safety; the withdrawal was intended to show long-term efficacy. A sample size of 1500 was planned.

In the end 1955 patients were treated (1951 randomized) at 185 centers in 12 countries (50 centers in the US, 48 in Germany, 18 in Italy, 12 in Switzerland, 11 in Belgium 10 in Peru, 9 in the UK, 8 in Russia, 8 in Denmark, 5 in the Netherlands, 4 in Canada, and 2 in Iceland) from June 15, 2004, through October 13, 2005. Study 2203 accounted for 22% of the patients. Among all randomized patients 1624 (83%) completed the open-label period and 261 started and 250 patients finished the randomized withdrawal period. A slight majority of the patients were male (52.5%), predominantly white (86%). The median age was 56. Many patients were obese (about 38% BMI $\geq$ 30). Mean sitting BP at baseline was 153/97. These baseline characteristics were reasonably well balanced between the two baseline randomization groups. The mean exposure was 318.5 days, or about 1705 person-exposure years (PEYs) in total.

10.1.10.3 Efficacy Summary

The sponsor's graph of mean sitting DBP by initial randomization group and month is shown in Figure 37.

Figure 37: Sponsor's Mean Sitting DBP by Month in Study 2302



Note that the decrease in DBP at the ends of month 1 and 2 (prior to any titration of drugs) is greater in the aliskiren 300 group than in the 150 mg group. Although not shown here, the decreases in SBP were similar. However, despite the greater mean decreases in the aliskiren 300

mg group, more patients in that group were treated with HCTZ at some time (56%) than in the aliskiren 150 group (38%). Rates of patients achieving control (<140/90) were slightly higher in the aliskiren 300 group as shown in Table 117.

Table 117: Reviewer's Rates of Control (Last BP <140/90) by Treatment Regimen in Study 2302

Aliskiren	Monotherapy	With HCTZ	All
150	68%	47%	60%
300	78%	51%	63%
Either	71%	49%	61%

COMMENT: The open-label nature of the 12-month treatment period makes it difficult to assess antihypertensive efficacy. There is a suggestion that aliskiren 300 mg is slightly more effective than aliskiren 150 mg. The greater use of HCTZ in the aliskiren 300 mg group illustrates the difficulties in interpreting open-label, titrated-to-effect studies: I interpret this effect as resulting from the fact that the initial titration step in the 300 mg group was to add HCTZ, while the initial step in the 150 mg group was to increase the dosage. (Although not shown here, the pattern of greater HCTZ use in the 300 mg group does not appear to vary much by country.)

The results of the blinded randomized withdrawal are more useful for showing efficacy than those from the open-label period. The sponsor's change from month 11 in mean sitting DBP during the withdrawal period are shown in Figure 38, the change in SBP in Figure 39, and the change in ambulatory DBP by hour in Figure 40.

Figure 38: Sponsor's Change from Month 11 in Mean Sitting DBP during Withdrawal Period in Study 2302

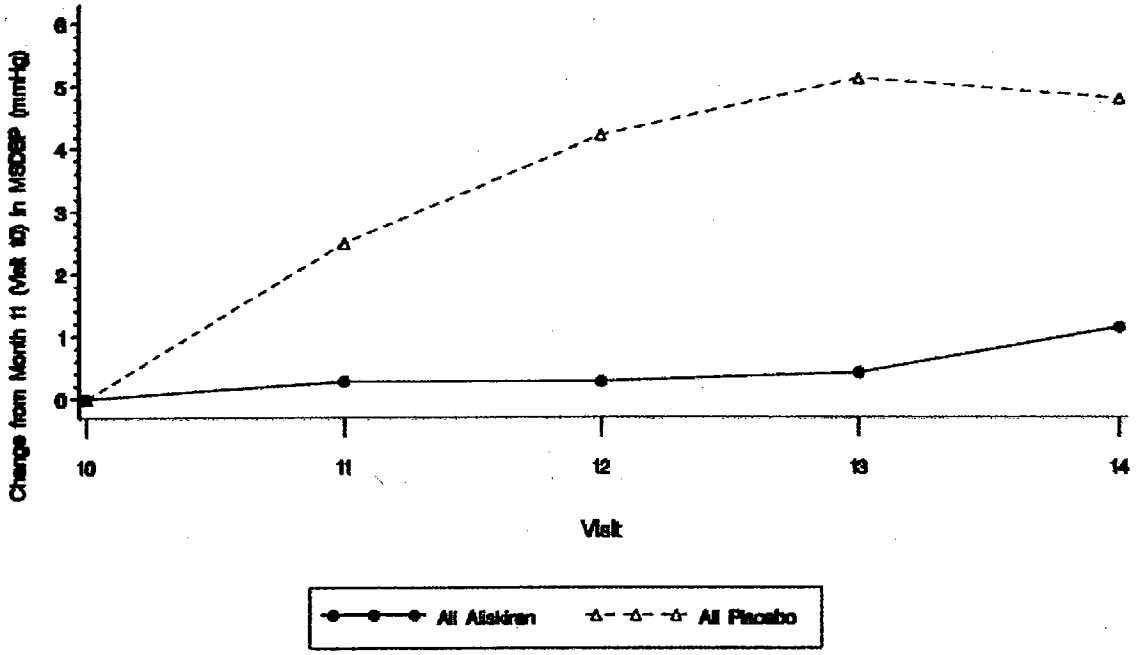
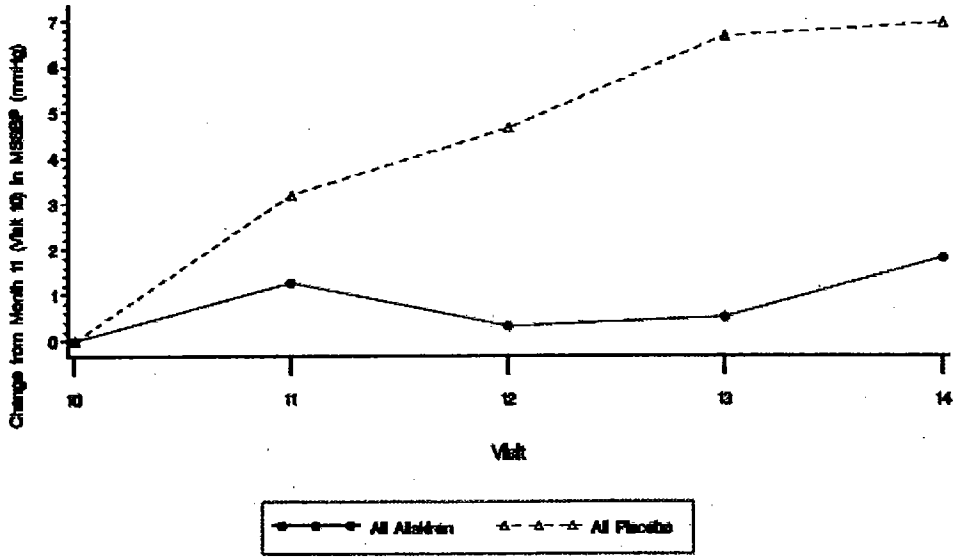
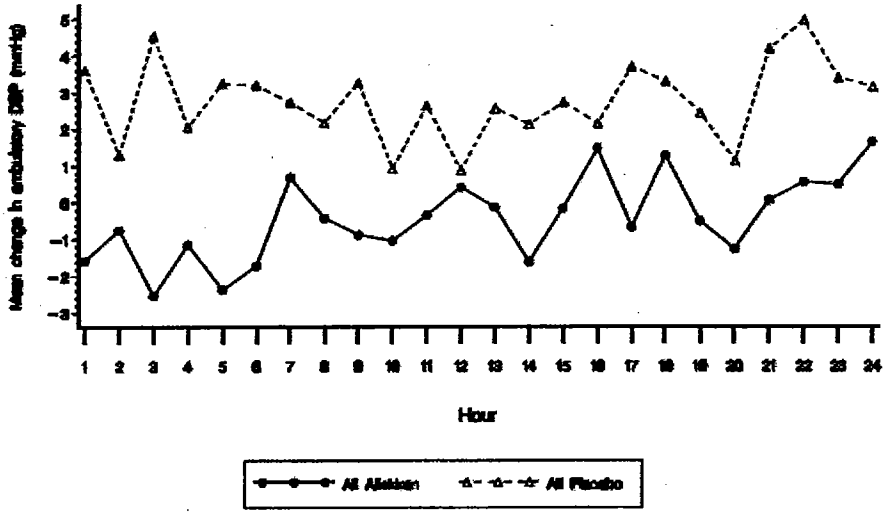


Figure 39: Sponsor's Change from Month 11 in Mean Sitting SBP during Withdrawal Period in Study 2302



The mean difference in DBP in the patients remaining on aliskiren from those switched to placebo was -3.8 mm Hg and in SBP was -5.5 ($p<0.0001$ for each).

Figure 40: Sponsor's Mean Change in Ambulatory DBP at the End of the Withdrawal Period in Study 2302



COMMENT: The BP results during the withdrawal period confirm that aliskiren has an antihypertensive effect sustained for at least one year. The ABPM data suggest that the effect is reasonable for the 24-hour interdosing interval.

10.1.10.4 Safety Summary

Overall AEs were reported in about 65% of patients with similar rates in both initial dosage groups and with or without the addition of HCTZ. The common AEs and AEs by organ class were not substantially different among the groups, e.g., nasopharyngitis, headache, dizziness, back pain, and bronchitis were the five most common AEs. Diarrhea, the sixth most common AE, was more frequent in the 300 mg group, but the differences in the rates for diarrhea were similar to the differences in rates of other AEs, some more frequent in the 150 mg group.

Deaths, SAEs, and discontinuations may be more revealing than the overall AEs. The sponsor's tabulation of the rates of these serious events is shown in Table 118.

Table 118: Sponsor's Rates of Death, SAEs, and AE Discontinuations in Study 2302

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

Brief descriptions of the deaths are as follows:

- The aliskiren 150 mg death was a 74-year-old Hispanic white male who died on day 27 of a ruptured aortic aneurysm. The patient's baseline BP (last recorded) was 159/96.

- The three aliskiren 300 mg deaths were the following:

    - A 79-year-old white female with a history of hyperlipidemia and also taking diclofenac who died on day 296 of a MI. Her last BP on day 260 was 130/83.

    - A 61-year-old female (150 mg group initially) without significant other comorbidities who was found dead in bed on day 71. No autopsy was preformed and death was attributed to "natural causes". Her baseline BP was 170/106, 160/96 on day 28 and 150/93 on day 56, at which time aliskiren was increased from 150 to 300.

    - A 77-year-old Hispanic male (150 mg group initially) with a 27 year history of hypertension but no other significant comorbidities who died on day 102 of a stroke. His baseline BP was 173/93 and his last recorded BP on day 91 was 158/91, so aliskiren was increased from 150 to 300. He presented on day 92 with dizziness, confusion, headache, and hypertension but no BPs are reported. The next day a CAT scan showed an intracerebral hemorrhage in the posterior fossa for which he underwent surgery. He became comatose post-op.

- The aliskiren 300/HCTZ 25 death was a 56-year-old white male with a history of tobacco abuse, coronary disease, and peripheral vascular disease who died suddenly at home on day 308. An autopsy showed severe coronary atherosclerosis with calcification, three-vessel disease with acute plaque erosion and non-occlusive thrombus in mid left anterior descending artery and occlusion of right coronary artery. The investigator reported this event as a MI. His last recorded BP was 171/91 on day 279.

COMMENT: In the absence of a placebo control these deaths are concerning but difficult to interpret. What impress me are the two deaths (sudden and stroke) shortly after uptitrations from aliskiren 150 to 300.

Noteworthy among the discontinuations were four discontinuations for MI in the 150 group and five in the 300 mg group and four discontinuations for stroke in the 150 group and one in the 300 mg group. The MIs, other than the two diagnosed fatal ones described above, were the following:

- A 52-year-old female in the 300 mg group presented with chest pain on day 180 and was diagnosed as having a non-Q wave MI. An ECG showed lateral ischemia. Angiography showed a systolic reduction of the LAD due to myocardial bridging. Echo showed an ejection fraction of 59%. Her BP two months earlier was 129/77.

- A 50-year-old white male in the 300 mg group was hospitalized with dyspnea on day 161. His blood pressure was 110/80. His ejection fraction was 30% with hypokinesis of the left ventricular. The SAE report lists a CK of 452 and a CK-MB of 32.1 with dates of eight days after the event.

COMMENT: There is also a suspected MI described below regarding discontinuations for lab value abnormalities. Without a control group these MIs are difficult to interpret. I address MI rates in the controlled studies in the ISS.

The strokes other than the fatal one described above were the following:

- A 67-year-old white female in the 150 mg group also treated with HCTZ was hospitalized with dysarthria and leftward deviation of the tongue on day 304. She also had hypokalemia. Her BP was 150/100. Echo and cranial imaging did not demonstrate occlusion or an ischemic lesion. She was rehospitalized with recurrent symptoms on day 334 and recovered by day 340.

- A 68-year-old white male in the 150 mg group fell and became unconscious for a short while on day 302. He had facial nerve paralysis and a head wound and was hospitalized with a stroke. He was reported as completely recovered nine days later. At day 274 his BP was 140/73. No additional details are provided.

- A 42-year-old Peruvian ("other" race and ethnicity) male in the 150 mg group with recent onset hypertension developed a right faciobrachial hemiparesis on day 77 and was hospitalized. Tomography revealed an infarct in the left thalamic region. MRI showed signs of recent ischemic infarction affecting the lenticular nucleus with extension to the corona radiata of the left cerebral hemisphere. There was a lacunar infarction in the pons. There were no visible signs of vascular malformation. Two weeks prior to the stroke his BP was 121/85. On the day of the stroke his BP was 150/105. Pulse was 78-84 with no mention of arrhythmias. He had undergone a hemorrhoidectomy one week prior to the stroke and on the night before he strained for a bowel movement with subsequent headache and weakness.

- A 65-year-old diabetic black male in the 300 mg group also receiving HCTZ suffered a stroke (loss of balance and one-sided weakness) on day 157. He was hospitalized with an initial BP of 185/113. An ECG showed sinus rhythm, LVH, and LAH. The diagnosis was an acute left pontine CVA. His BP on day 92 was 160/189 and on day 120 was 159/99.

- A 48-year-old white female in the 150 mg group experienced left-sided weakness and paresthesias intermittently and was hospitalized on day 69. Her BP the next day was 151/109 and pulse 76, while her BP on day 29 was 139/88 and pulse 84. Because she had intermittent tachycardia, 24-hour Holter monitoring was done that recorded normal sinus rhythm or sinus tachycardia. A CT scan showed a small, 1 cm, hypodense focus in the right frontal subcortical white matter. A MRI showed a showed a small area of acute infarct involving the posterior right frontal region and a small area of abnormality involving the lenticular striate distribution and external capsule on the right side.

COMMENT: I analyze stroke rates in the ISS.

A SAE of angioneurotic edema was reported for a patient receiving aliskiren 300 mg/HCTZ 25 mg. After being on open-label study medication for 372 days, this patient (a 47 year old Caucasian female) experienced itching and edema of the left ear which quickly spread to the lips and eyes. Inspiratory stridor was also present. The investigator diagnosed angioneurotic edema and prescribed prednisolone and an antihistamine. On the following day, the facial edema had become more symmetric and her chin was red. No rash was present. Bronchial stridor had decreased but rhonchi were present. The patient completed the study (4 more days) without interruption of study drug. She was seen one day after study completion and had made a full recovery.

COMMENT: I examine all potential angioneurotic edema cases in the ISS.

A 74-year-old white male in the 150 mg group experienced a tonic/clonic convulsion for ten minutes followed by unconsciousness for 30 minutes on day 124, eleven days after being uptitrated to 300 mg. He had no prior history of seizures. A CAT scan five days later and an EEG 22 days later were normal. Another patient in the aliskiren 150 mg group, a 52-year-old male with a history of epilepsy, had an epileptic fit on day 187. He was not discontinued and completed the study through one year.

COMMENT: The isolated, unexplained seizure case could be dismissed as random. However, see the ISS for the description of a second case.

There were reportedly eight discontinuations for lab value increases. However, many of these patients had baseline abnormalities as shown in Table 119.

Table 119: Reviewer's Discontinuations for Lab Abnormalities in Study 2302

Center/subject	Demographics	Lab Abnormality
91/00004	42WM	Baseline ALT 90

Center/subject	Demographics	Lab Abnormality
92/00019	65OM	Baseline ALT 93
99/00001	49WM	Suspected MI "ed CK"?
134/00016	33WM	Baseline ALT 89
139/00015	48WF	CK 408, ALT 34
139/00024	52WM	ALT 94 with tiredness
534/00003	40BM	CK baseline 1105
534/00012	55WM	CK 659, ALT 62-56

COMMENT: Five cases have baseline abnormalities or another explanation, i.e., the suspected MI. What the other three cases represent is difficult to determine—they could be mild viral infections. However, the CK elevations with minimal ALT elevations are interesting. I examine CK rises in the ISS.

10.1.10.5 Conclusions

The blood pressure results during the withdrawal period confirm that aliskiren has an antihypertensive effect sustained for at least one year. The strokes in this uncontrolled trial are concerning and will be examined in the Integrated Summary of Safety in view of the total drug exposure.

10.1.11 Study 2302E1 - A 4 month extension to a 12 month, randomized, open-label, multicenter, study to assess the long term safety of aliskiren 150 mg alone and 300 mg alone or with the optional addition of hydrochlorothiazide (12.5 mg or 25 mg) in patients with essential hypertension

10.1.11.1 Background

This study is an extension to Study 2302 and was intended to provide more safety data for patients taking aliskiren 300 mg and HCTZ 25 mg. The study report and data were submitted with the 120 safety update.

10.1.11.2 Design and Conduct

This was an open-label, uncontrolled study. Patients who completed at least eight months of treatment with aliskiren 300 mg and HCTZ 25 mg in Study 2302 were eligible. Of 250 patients planned, 198 were eventually enrolled. Patients took two aliskiren 150 mg tablets and one HCTZ 25 mg capsule at the same time each morning without regard to food intake for the four month treatment period. BP and safety labs were evaluated at the end of the treatment period. About 96% (189) of the patients completed the study. They were predominantly white (94%) and evenly distributed between the genders (50% male) with a mean age of 57. About 49% were obese (BMI $\geq$ 30) and 47% met criteria for the metabolic syndrome.

10.1.11.3 Efficacy Summary

The mean BP at the original baseline (not the start of this extension) was 159/99; the mean BP at the end of this extension was 142/89. The mean BP in this group was similar through the original study period and the extension.

COMMENT: Because of the lack of a control and the fact that this study population is a group selected for having completed at least eight months of therapy, the BP results are difficult to interpret.

10.1.11.4 Safety Summary

About 49% of the patients experienced at least one AE during the study. The common non-serious AEs were typical of a study population with similar age and comorbidity and not clearly drug-related, e.g., bronchitis, nasopharyngitis, and headache were the most frequent AEs. No patients died but six patients experienced SAEs. The SAEs included one polyneuropathy and one stroke. The stroke occurred in a 59-year-old white female on day 407. BP on that day was reported as 220/120, although at the completion of Study 2302 about six weeks earlier it had been 147/90.

Noteworthy among changes in lab values were increases in uric acid. An increase in mean uric acid of 31.4 umol/L from baseline to the end of study was observed as was the shift from normal to high value in a portion of the patients (41% in any post-baseline visit and 22% at the endpoint). Gout or exacerbation of gout was reported in five patients.

10.1.11.5 Conclusions

This study provides little useful information regarding efficacy. The one stroke in this small study is concerning. Gout may also be a potential problem with the combination of aliskiren and HCTZ.

10.1.12 Study 2303 - An eight-week, randomized, double-blind, multi-center, active controlled, parallel group study to evaluate the safety and efficacy of an aliskiren based regimen compared to a lisinopril based regimen in patients with uncomplicated severe hypertension

10.1.12.1 Background

This study was designed to meet European Union regulatory requirements. The study report and data were submitted with the 120 safety update.

10.1.12.2 Design and Conduct

This was a multicenter, randomized, double-blind, double-dummy, active-controlled, parallel group study of aliskiren compared to lisinopril with the potential addition of hydrochlorothiazide in adult patients with uncomplicated moderately severe hypertension (DBP 105-119). Eligible patients were randomized to receive aliskiren 150 mg or lisinopril 20 mg in a 2:1 ratio. Patients were titrated to goal BP (BP < 140/90) following these three steps:

Step 1: aliskiren 150 mg or lisinopril 20 mg.
Step 2: aliskiren 300 mg or lisinopril 40 mg.
Step 3: aliskiren 300 mg + HCTZ 25 mg or lisinopril 40 mg + HCTZ 25 mg.

Visits occurred at week 1, 2, 4, 6, and 8 with BP measured by cuff approximately 24 hours after the last dose. A sample size of 180 was planned, 183 patients were randomized, and 165 (90%) completed—11% with aliskiren and 7% with lisinopril. All but one patient were white, a little more than half were male (57%), and the mean age was 55 years. The mean baseline BP was 163/108.

10.1.12.3 Efficacy Summary

The mean decrease at 8 weeks (LOCF) was slightly lower with aliskiren (-20.0/-18.5) than with lisinopril (-22.3/-20.1). A slightly higher percentage of aliskiren patients had HCTZ added (54%) than lisinopril patients (45%) while the percentage on the high dose alone was similar in both groups (about 20%).

10.1.12.4 Safety Summary

Overall a higher percentage of patients in the aliskiren group experienced AEs than in the lisinopril group (32% vs. 29%). Organ systems with more AEs in the aliskiren group was skin and subcutaneous disorders (4.8% vs. 0%) and respiratory and thoracic (3.2% vs. 1%), with neither organ system showing a clear pattern of AEs for aliskiren. One patient in each group reported an AE of cough. There were no deaths reported, and just over 3% of patients in each group discontinued for an AE. The discontinuations for aliskiren were for headache, hypotension, dysesthesia, and pruritus. One patient in the lisinopril group discontinued for an MI.

10.1.12.5 Conclusions

Aliskiren in this study was similar to but perhaps slightly less effective than lisinopril. Aliskiren may have slightly more minor AEs, while differences in SAEs are too small to evaluate.

10.1.13 Study 2323 - A twenty six-week, randomized, double-blind, parallel group, multicenter, active controlled, dose titration study to evaluate the efficacy and safety of aliskiren compared to HCTZ with the optional addition of amlodipine, followed by a second twenty six weeks of blinded treatment, in patients with essential hypertension

10.1.13.1 Background

Per the study report, "The study was conducted to support regulatory submissions seeking approval to market aliskiren worldwide for the treatment of hypertension." The preliminary study report and data, excluding the second twenty-six week period (which is on-going), were submitted with the 120 safety update.

10.1.13.2 Design and Conduct

This was a randomized, double-blind, parallel-group, multicenter, active-controlled, dose titration study in patients with mild to moderate hypertension (DBP 90-109). It included a washout period, a single-blind placebo-controlled run-in, then a six week randomized double-blind, placebo-controlled period (monotherapy aliskiren 150 mg, HCTZ 12.5 mg--force titrated after three weeks to aliskiren 300 mg or HCTZ 25 mg--or placebo) and then a 20 week double-blind period with aliskiren 300 mg or HCTZ 25 mg and optional open-label amlodipine. Patients initially receiving placebo were re-randomized after six weeks to the aliskiren or HCTZ treatment arm. At least 1100 patients were planned for randomization in a 2:2:1 ratio (aliskiren, HCTZ, placebo, respectively). The single-blind, placebo run-in period enrolled 1275 patients, of whom 1124 (88%) were randomized and 978 (87%) completed. One center (47) failed a site audit, so results are analyzed with and without that site. The patients were predominantly white (99%) with a majority of males (55%) and a mean age of 56.

10.1.13.3 Efficacy Summary

The following summarizes the BP results at the various time points:

- At week 6, aliskiren 300 mg (-15.5/-10.7) was significantly superior to placebo (-7.8/-7.3) and had better mean reductions than HCTZ 25 (-12.5/-8.9).
- At week 12 (prior to the addition of amlodipine), aliskiren 300 mg (-17.4/-12.2) was significantly superior to HCTZ 25 mg (-14.7/-10.3).
- At week 26 (after the addition of amlodipine), BP reductions were similar between the aliskiren (-20.3/-14.6) and HCTZ (-18.6/-14.3) groups. About 40% of aliskiren patients and 44% of HCTZ patients received amlodipine.

COMMENT: Aliskiren 300 mg compares favorably to HCTZ 25 mg in antihypertensive efficacy on trough measurements.

10.1.13.4 Safety Summary

During the first six week period rates of AEs were similar for aliskiren (26%), HCTZ (25%), and placebo (29%). Aliskiren patients reported more skin and subcutaneous tissue disorders (3%) than HCTZ or placebo (about 1%). For the entire double-blind period AE rates were similar for aliskiren and HCTZ, about 50%, without few differences in patterns. Skin disorders were more commonly reported in aliskiren patients (6.2%) than HCTZ patients (4.8%) while headaches were more commonly reported in HCTZ patients (about 8 vs. 5%).

No deaths were reported during the double-blind period (although one patient died after discontinuing during the placebo run-in period.) SAEs were infrequent and similar in the two groups (about 1.7%), while more patients discontinued on HCTZ (5.2%) than on aliskiren (3.7%). Two aliskiren discontinuations are of interest:

- One patient in the aliskiren group, a 69-year-old white male with a history of COPD, CHD, hypercholesterolemia, and polyneuropathy, developed severe, whole body edema starting on day 55. Aliskiren was discontinued and furosemide was given.

- One patient, a 67-year-old white female, developed "moderate" burning stomach pain starting on day 3. Aliskiren was discontinued and the event was classified as serious, although the patient was not reported to be hospitalized.

Regarding lab values, greater mean increases in uric acid were observed in the HCTZ group (30.4 vs. 4.9 μmol/L). Mean potassium increased in the aliskiren group (0.13 mmol/L) and decreased in the HCTZ group (-0.23 mmol/L).

COMMENT: Aliskiren appears to have been tolerated similarly to HCTZ. It is somewhat reassuring that strokes were not reported with aliskiren in this larger, longer term controlled study. The discontinuations are reminders that aliskiren may cause GI disturbances and angioedema.

10.1.13.5 Conclusions

In this study aliskiren 300 mg compared favorably to HCTZ 25 mg in antihypertensive efficacy on trough measurements and in safety.

10.1.14 Study 2324 - An 8-week, randomized, double-blind, parallel-group, multicenter study assessing the efficacy and safety of aliskiren 75 mg, 150 mg, and 300 mg in patients ≥ 65 years of age with essential hypertension, using 24-hour ABPM with lisinopril 10 mg as a reference

10.1.14.1 Background

Per the study report, "The present Phase III study was designed to meet the criteria set forth by European Union (EU) regulatory authorities to evaluate the overall safety and efficacy of an aliskiren-based regimen in a patient population ≥ 65 years of age with essential hypertension with lisinopril as a reference ..." The study report and data were submitted with the 120 safety update.

10.1.14.2 Design and Conduct

This was an 8-week, randomized, double-blind, parallel multicenter study with lisinopril 10 mg as a reference and 3 doses of aliskiren 75 mg, 150 mg and 300 mg in patients ≥ 65 years of age with essential hypertension. Study medication was to be taken at 8:00 a.m. without regard to food. The study had three periods: (1) screening/washout period, (2) a single-blind placebo run-in period, and (3) a double-blind treatment period. A total of 356 patients were planned for randomization (stratified by age < or ≥ 75) with 355 patients actually randomized. A total of 354 patients were included in the ITT population. The primary endpoint was mean 24-hour SBP on ABPM. Baseline demographics and other characteristics varied somewhat among the groups. The aliskiren 150 mg group had slightly fewer age ≥ 75 (45% vs. overall 49%) while the

lisinopril group had more age ≥ 75 (52%), more females (66% vs. overall 59%), and slightly higher mean ambulatory SBP (149 vs. 147-148). Race was balanced at about 87% white, 13% Asian.

10.1.14.3 Efficacy Summary

The reductions in mean 24-hour ambulatory SBP were similar in the aliskiren groups (-8.4, -7.1, and -8.7 for 75, 150, and 300 mg respectively) without a dose response and less than for lisinopril (-10.2). The reductions in mean ambulatory DBP were also similar in the aliskiren groups (-4.5, -3.6, and -3.9 for 75, 150, and 300 mg respectively) without a dose response and less than for lisinopril (-6.3). The median reductions by hour in DBP are shown in Figure 41 and the median reductions by hour in SBP in Figure 42. Trough cuff BPs were more similar in all groups (-13/-5.5, -13.5/-6.2, -14.5/-6.4, and -14.9/-5.4 for aliskiren 75, 150, and 300 mg and lisinopril 10 mg respectively.)

Figure 41: Reviewer's Median Change from Baseline in Ambulatory DBP by Hour in Study 2324

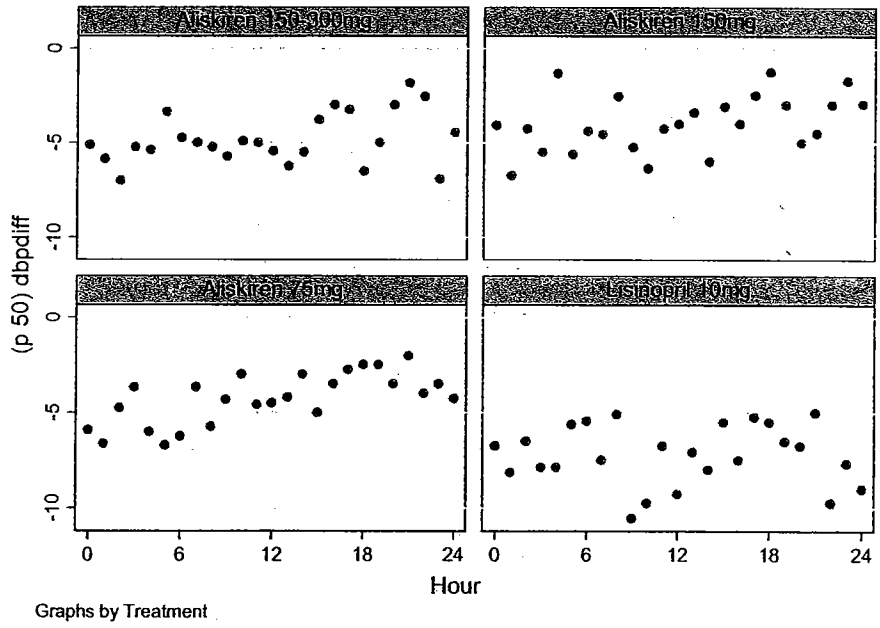


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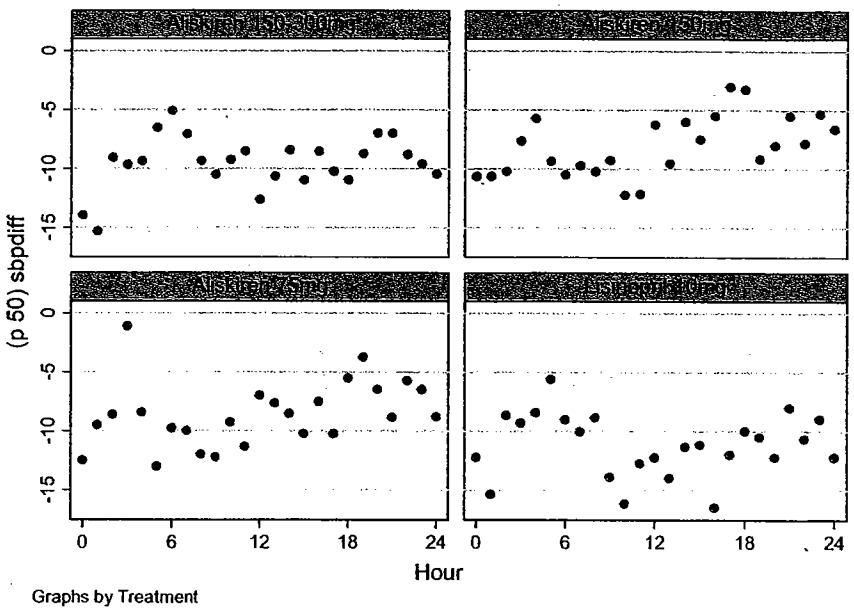
Figure 42: Reviewer's Median Change from Baseline in Ambulatory DBP by Hour in Study 2324



Mean BP reductions in the aliskiren groups were greater during the day than at night, while BP reductions with lisinopril were similar by day and night as shown in Table 120.

Table 120: Reviewer's Mean BP by Day and Night in Study 2324

Group	SBP			DBP		
	Day	Night	Ratio	Day	Night	Ratio
aliskiren 75 mg	-9.8	-7.5	0.77	-6.0	-4.1	0.68
aliskiren 150 mg	-8.9	-5.8	0.65	-4.6	-2.7	0.59
aliskiren 300 mg	-9.2	-8.3	0.90	-5.1	-4.1	0.80
lisinopril 10 mg	-11.5	-12.1	1.05	-7.7	-7.1	0.92

Day = 0600-2200; Night = 2200-0600; Ratio = night/day

COMMENT: In this study aliskiren fails to show a dose-response for the range 75-300 mg and appears to be slightly less effective, both with regard to the magnitude of the BP reduction and BP reduction at night, than lisinopril 10 mg. While blood pressure reductions were less at night with aliskiren, they appear to be within the trough-to-peak ratios considered acceptable for once daily dosing.

10.1.14.4 Safety Summary

Overall AEs were reported in 31% of patients. The AE rate is highest for aliskiren 150 mg (40.5%) and lowest for aliskiren 300 mg (24.5%). There were no obvious patterns to the AEs

except diarrhea was more frequent with the aliskiren 150 and 300 mg dosages. There were two cough AEs in the lisinopril group and one on aliskiren 150 mg and another on aliskiren 300 mg.

There were no deaths. SAEs were rare, with one TIA SAE in the aliskiren 150 mg group and one prostate cancer in the 300 mg group. In addition to the TIA SAE, an AE of a "mild" visual field defect was also reported in an 81-year-old Asian male on day 50.

10.1.14.5 Conclusions

Aliskiren failed to show a dose response on ABPM and appears slightly less effective than lisinopril 10 mg. Its safety profile does not appear greatly different than lisinopril's, but the one TIA and the visual field defect AE again raise the question of whether aliskiren has a propensity for cerebrovascular events.

10.1.15 Study 2327 - An 8-week randomized, double-blind, parallel group, multi-center, placebo and active controlled dose escalation study to evaluate the efficacy and safety of aliskiren (150 mg and 300 mg) administered alone and in combination with valsartan (160 mg and 320 mg) in patients with hypertension

10.1.15.1 Background

This study is a second factorial study of aliskiren and valsartan alone and in combination because a similar study, Study 2203, failed. It was submitted late in the initial review period. Hence I am including my brief summary of it here but I have not had time to review it completely.

10.1.15.2 Design and Conduct

This was a randomized, double-blind, placebo-controlled factorial study with a forced doubling of initial doses at four weeks and evaluations at four and eight weeks. It enrolled the usual patients with mild-to-moderate essential hypertension (office cuff DBP 95-109) with mean 8-hour ABPM DBP > 90 as an inclusion criterion. It studied the proposed to-be-marketed doses of aliskiren and the highest labeled dose of valsartan. The study plan is shown in Figure 43.

Figure 43: Sponsor's Study 2327 Plan

Phase	Pre-randomization				Double-Blind Treatment				
Period	Screening / Washout	Single-blind Placebo Run-in			Initial four-weeks of treatment		Final four-weeks of treatment		
Visit	1[1,2]	2[2]	3	4	5[3]	6	7[4]	8	9
Duration[5]	1-2 week(s)	2 weeks	1 week	1 day or 1 week	4 weeks		4 weeks		
Day[6]	-28 or -42	-21 or -28	-7 or -14	-1 or -7	1	15	29	43	56
Randomization					X				
Rx group 1		Placebo			Aliskiren 150 mg o.d.		Aliskiren 300 mg o.d.		
Rx group 2		Placebo			Valsartan 160 mg o.d.		Valsartan 320 mg o.d.		
Rx group 3		Placebo			Aliskiren 150 mg / Valsartan 160 mg o.d.		Aliskiren 300 mg / Valsartan 320 mg o.d.		
Rx group 4		Placebo			Placebo		Placebo		

[1] If the patient was required to be tapered off the current anti-hypertensive medication then the tapering was to occur at Visit 1. The patient was to be washed out of their anti-hypertensive medication for at least 1 week prior to Visit 2.

[2] For currently untreated patients Visit 1 and Visit 2 were combined into one Visit.

[3] Visit 5 consisted of 2 days. Randomization occurred on the second day of Visit 5.

[4] Titration occurred at Day 29 (Visit 7) of double-blind treatment.

[5] Duration refers to the time between current visit and next Visit.

[6] If the placebo run-in period was extended for 1 week to meet randomization criteria then, Visit 1 became Day -42 (if the duration between Visit 1 and Visit 2 was 2 weeks), Visit 2 became Day -28, Visit 3 became Day -14 and Visit 4 became Day -7.

Approximately 1784 patients (446 in each of the 4 treatment arms) were to be randomized from approximately 194 centers in the US and Europe. The primary endpoint was change from baseline in seated trough cuff DBP at eight weeks, with SBP as a secondary endpoint. A subset of approximately 500 patients (125 per treatment arm) were to be enrolled into the 24-hour ABPM at visit 5, with the goal of 400 patients (100 per treatment arm) completing both 24-hour ABPM evaluations (at visits 5 and 9).

In the end 1797 patients were randomized; 459 patients were randomized to placebo; 437 patients to the aliskiren group, 455 to the valsartan group, and 446 to the aliskiren/valsartan group. Of the randomized patients, 89% (1601) completed the double-blind treatment phase. Rates of premature discontinuation were lowest in the combination group (8.3%), and highest in the placebo group (13.7%). The increased rate of discontinuation in the placebo group was accounted for by an increase in patients who discontinued due to unsatisfactory therapeutic effect. Few patients discontinued due to adverse events; the incidence was lower in the

combination group (7 patients, 1.6%) compared with placebo (10 patients, 2.2%), aliskiren monotherapy (11 patients, 2.5%), or valsartan monotherapy (11 patients, 2.4%).

The mean age was 52 with 12.5% 65 or older. Males comprised 61% of the study population. Regarding race, 75% were white and 15% black. The average baseline BP was about 154/100. Baseline characteristics were reasonably balanced among the four randomization groups.

10.1.15.3 Efficacy Summary

The sponsor's analysis of the primary endpoint (DBP) is shown in Table 121 and of the secondary endpoint (SBP) in Table 122.

Table 121: Sponsor's Change from Baseline in DBP at Week 8 in Study 2327

Treatment Group	N	LSM change from baseline(SE)	
Placebo	455	-4.07 (0.41)	
Aliskiren	430	-9.02 (0.42)	
Valsartan	453	-9.69 (0.41)	
Aliskiren/Valsartan	438	-12.17 (0.41)	
Pairwise Comparison	**LS M difference in change from baseline (SE)**	**95% CI for LSM difference**	**P-Value+**
Aliskiren vs. Placebo	-4.95 (0.58)	(-6.07, -3.82)	<.0001*
Valsartan vs. Placebo	-5.62 (0.57)	(-6.73, -4.51)	<.0001*
Aliskiren/Valsartan vs. Placebo	-8.09 (0.57)	(-9.22, -6.97)	<.0001*
Aliskiren/Valsartan vs. Aliskiren	-3.15 (0.58)	(-4.29, -2.01)	<.0001*
Aliskiren/Valsartan vs. Valsartan	-2.47 (0.57)	(-3.60, -1.35)	<.0001*

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

Least square means, confidence intervals, and p-values were from an ANCOVA model containing treatment, region, and baseline.

+ P-Values and treatment comparisons were evaluated at the average baseline level.

* Indicates statistical significance at 0.05 level

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Table 122: Sponsor's Change from Baseline in SBP at Week 8 in Study 2327

Treatment Group	N	LSM change from baseline(SE)	
Placebo	455	-4.56 (0.65)	
Aliskiren	430	-12.96 (0.67)	
Valsartan	453	-12.75 (0.65)	
Aliskiren/Valsartan	438	-17.20 (0.67)	
Pairwise Comparison	**LSM difference in change from baseline (SE)**	**95% CI for LSM difference**	**P-Value+**
Aliskiren vs. Placebo	-8.40 (0.93)	(-10.22, -6.58)	<.0001*
Valsartan vs. Placebo	-8.20 (0.91)	(-9.99, -6.40)	<.0001*
Aliskiren/Valsartan vs. Placebo	-12.64 (0.92)	(-14.45, -10.8)	<.0001*
Aliskiren/Valsartan vs. Aliskiren	-4.24 (0.94)	(-6.07, -2.40)	<.0001*
Aliskiren/Valsartan vs. Valsartan	-4.44 (0.92)	(-6.26, -2.63)	<.0001*

SE=Standard Error; LSM=Least Squares Mean; CI=Confidence Interval
Least square means, confidence intervals, and p-values were from an ANCOVA model containing treatment, region, and baseline.
+ P-Values and treatment comparisons were evaluated at the average baseline level.
* Indicates statistical significance at 0.05 level.
Source: PT-Table 14.2-2.1b

While I have not included them in this brief summary, changes in cuff BP at week 4 also showed efficacy of the combination over the components and placebo and mean 24-hour ABPM showed similar efficacy. The sponsor did not include trough-to-peak ratios or daytime/nighttime analyses in the preliminary report.

COMMENT: The trough results are encouraging if validated. More informative would be similar analyses at peak.

10.1.15.4 Safety Summary

I did not review safety in this study in detail. I did examine it for unusual SAEs and incorporated my findings in the ISE, e.g., one case of unexplained grand mal convulsions occurred in an aliskiren patient in this study. I do note that diarrhea was uncommon but slightly more frequent in the aliskiren arm (2.3%) than placebo (1.1%), although diarrhea in the combination arm was similarly low (0.9%). There was one more case of cough in the aliskiren arms (4 each) than in the arms without aliskiren (3 each).

10.1.15.5 Conclusions

This study needs to be analyzed completely and the results validated.

15 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

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/s/

Thomas Marciniak
12/7/2006 11:37:52 AM
MEDICAL OFFICER

Interdisciplinary Review Team for QT Studies
Addendum to QT Study Review

NDA	21985
Brand Name	Rasilez
Generic Name	Aliskiren
Sponsor	Novartis
Indication	Hypertension
Dosage Form	Oral tablet
Therapeutic Dose	150 mg, 300 mg
Duration of Therapeutic Use	Chronic Use
Application Submission Date	10 Feb 2006
Review Classification	Standard
Clinical Division	Division of Cardiovascular and Renal Products

1.0 INTRODUCTION

This review is an addendum to a prior QT study review. In the original QT study review (9/25/2006), ECGs were not available to the review team; however, 12-lead recordings were subsequently uploaded into the ECG warehouse. The purpose of this addendum is to evaluate ECGs submitted to the ECG warehouse as part of study SPP100A2208 (thorough QT study) in order to verify appropriateness of QT measurement.

2.0 ECG ANALYSIS

24,564 ECGs were uploaded from 307 subjects. A sampling of at least 50 ECGs was reviewed.

According to the ECG warehouse statistics, 0.83% of ECGs included annotations in multiple leads. However, from a visual inspection, it appears that the QT interval was measured in only one lead per 12-lead ECG; the annotation in the other lead was made for P waves only. According to the study report, leads II or V5 were used for QT measurement. This reviewer found several instances where lead V2 or V3 was used instead (in these ECGs, the T waves were flattened in leads II and V5 and the QT interval may have been difficult to measure in the pre-specified leads).

ECG Quality:

Upon visually reviewing a subset of selected ECGs with the greatest amount of "noise," this reviewer concurs with the ECGs measurements made by the Sponsor.

3.0 SUMMARY OF FINDINGS

A sampling of ECGs was reviewed in the ECG warehouse to verify appropriateness of QT measurements. From this sampling, this reviewer concurs with the sponsor's measurements of QT intervals.

This review serves to finalize the preliminary conclusions made by the QT team in the QT study review dated 9/25/2006.

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