

Figure 8: Sponsor's Angiotensin I Levels in Study MD02

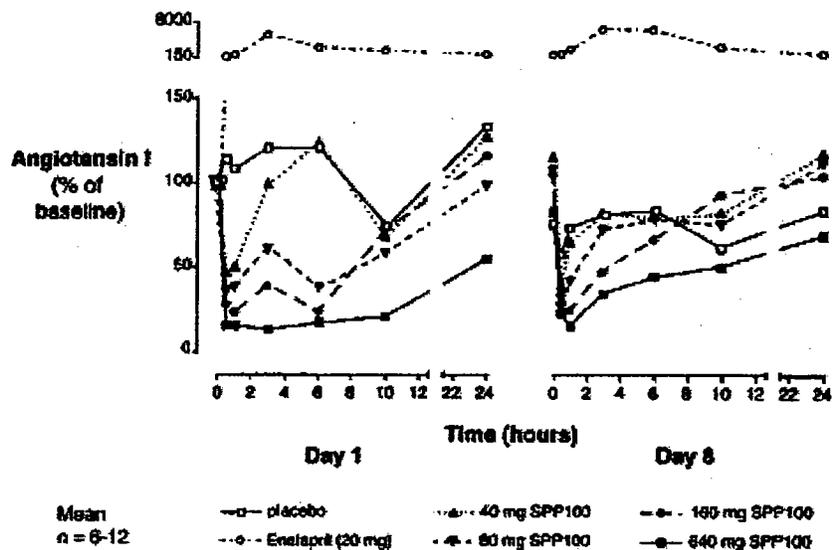


Figure 9: Sponsor's Angiotensin II Levels in Study MD02

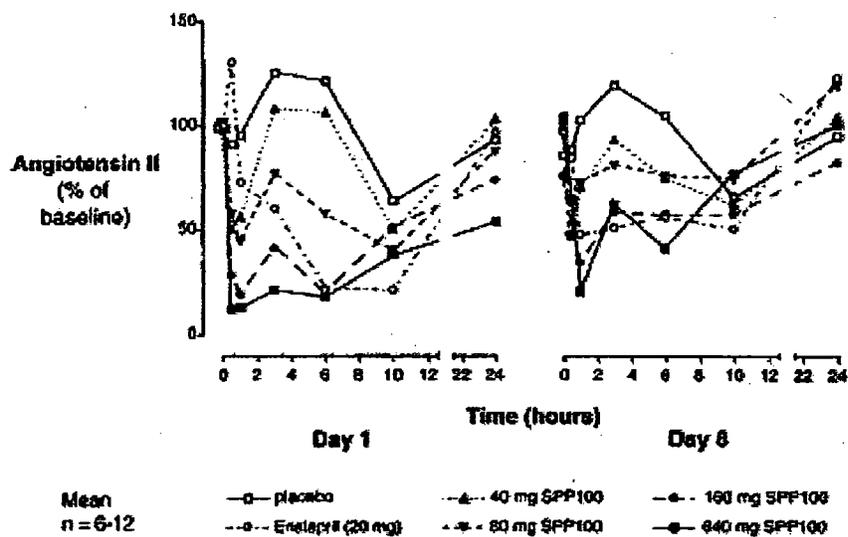
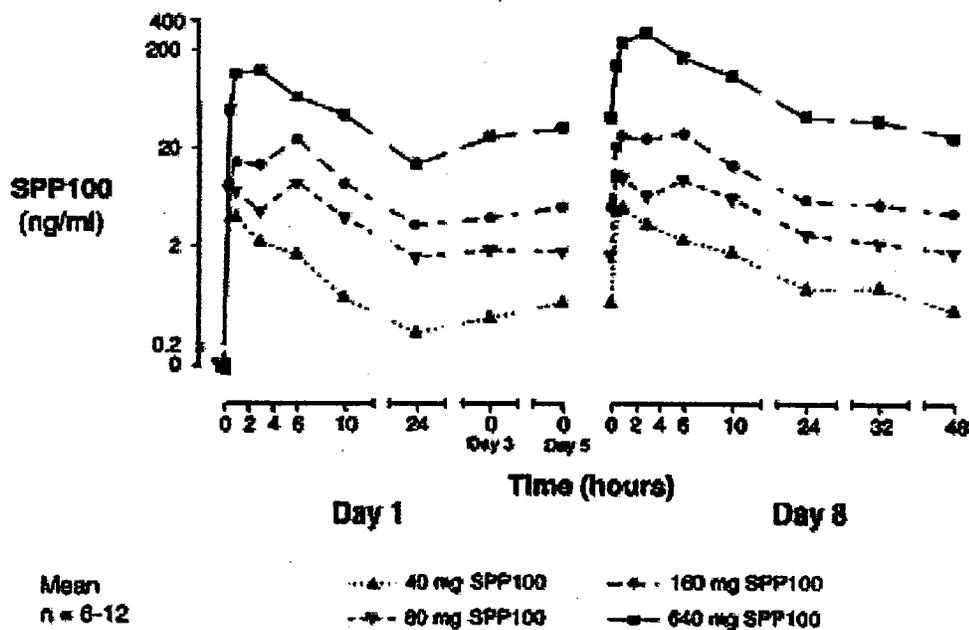


Figure 10: Sponsor's Aliskiren Levels in Study MD02



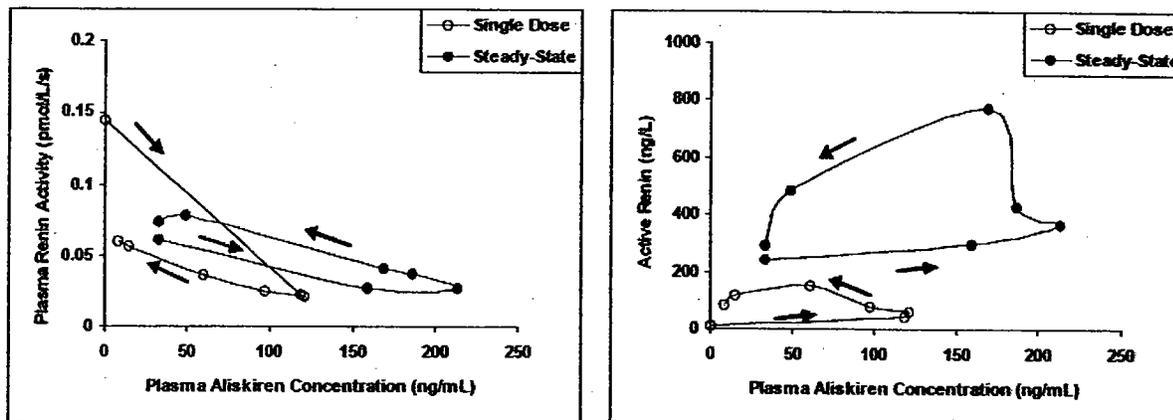
Plasma renin activity (PRA) and plasma renin concentration (PRC, active renin) were measured in two hypertension studies with aliskiren monotherapy groups, Study 2204 and Study 2308. In Study 2308, PRC increased by 52%, 102%, and 229% in the 150 mg, 300 mg, and 600 mg dose groups, respectively, while PRA increased by 20% in the placebo group and decreased by 80%, 81%, and 75% in the aliskiren 150 mg, 300 mg, and 600 mg dose groups. In Study 2204, treatment with all three aliskiren monotherapy doses was associated with reductions in PRA (54%, 65%, and 58% for the 75 mg, 150 mg, and 300 mg dose groups, respectively) and increases in PRC (160%, 192%, and 350% respectively).

COMMENT: The studies of RAAS hormones following aliskiren administration are consistent with renin inhibition. Plasma renin activity is reduced at trough with repeat dosing for all aliskiren dosages, but the angiotensin II levels are less consistently affected. Neither the drug level PK nor these studies justify once daily dosing. Note that in the hypertension studies PRA is reduced similarly at all aliskiren dosing levels, while PRC appears to show some dose response. This finding suggests to me that PRA may not be a good surrogate for aliskiren antihypertensive efficacy.

5.3 Exposure-Response Relationship

The effects of different doses of aliskiren upon RAAS hormones are presented in the previous section. Regarding concentration-response relationships, the sponsor presented the plots of renin vs. plasma aliskiren levels shown in Figure 11.

Figure 11: Sponsor's Renin vs. Plasma Aliskiren Levels in Study 2202



COMMENT: The hysteresis is readily apparent for active renin but marginal for plasma renin activity. Because plasma renin activity is the parameter that should be more closely related to pharmacodynamic action, the hysteresis is not impressive. Furthermore, whether any hysteresis is evident for angiotensin II levels is not shown. What the plasma renin activity vs. plasma aliskiren concentration plots show is a relatively flat concentration-response curve with even the trough levels showing substantial inhibition with repeat dosing. I think these data suggest the following:

- These PK and PD support daily dosing only in that plasma renin activity is inhibited at trough with repeat daily dosing.
- The plasma renin activity vs. plasma concentration curves are consistent with an IC_{50} of 0.6 nM (0.35 ng/mL) for aliskiren for inhibition of renin. This activity suggests that low dosages of aliskiren, given frequently or as a sustained release preparation, may be effective.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The proposed indication is the treatment of hypertension in adults.

6.1.1 Methods

The aliskiren development program in hypertension was large and the NDA submission included reports and data for the large number of studies tabulated in Section 4.2. There are many more studies demonstrating efficacy than the minimum of two required by the usual interpretation of the Food, Drug, and Cosmetic Act. For the primary evaluation of efficacy I summarize the results of five of the studies that have the usual study design as described in Section 6.1.3 for initial evaluation of an antihypertensive. I examine results of the other studies to answer other critical questions such as justification of the interdosing interval.

6.1.2 General Discussion of Endpoints

The primary endpoint in the pivotal studies was change from baseline in seated trough (i.e., prior to next treatment at the end of the 24-hour interdosing interval) cuff diastolic blood pressure. This endpoint is the usual one for trials of new antihypertensives. Seated trough cuff systolic blood pressure was analyzed as a secondary endpoint. BP measurements at the estimated peak blood levels were compared to the trough measurements in some studies and ambulatory blood pressure measurements (ABPM) were done in other studies to justify the once daily dosing.

6.1.3 Study Design

The initial aliskiren NDA submission included five studies incorporating variations on the typical study design for evaluating efficacy of antihypertensives: a randomized, double-blind, placebo-controlled trial of several dosages in mild-to-moderate hypertensives with an eight week endpoint of change from baseline in seated trough cuff DBP analyzed by a two-way analysis of covariance (ANCOVA) with treatment and region as factors, and baseline as a covariate. A statistical adjustment for multiple comparisons using Dunnett's procedure was used for studies including multiple aliskiren doses. The key secondary efficacy endpoint, change from baseline in seated trough cuff SBP, was analyzed similarly. To establish efficacy throughout the interdosing interval (24-hours) some studies incorporated BP measurements at estimated T_{max} and others incorporated ABPM substudies. These five typical studies are the primary evidence for antihypertensive efficacy of aliskiren.

In addition to the short-term trough BP endpoints, the aliskiren NDA submission also includes some double-blind, randomized withdrawals at the end of longer term studies to establish that efficacy is sustained long term. The submission also includes some studies in combination with other antihypertensives, to show efficacy in combination, some studies against active antihypertensive controls, to satisfy European regulatory requirements, and some studies in special populations, e.g., diabetics, the elderly.

For the details of the study designs and the individual study results, please see Appendix 10.1. I include only pertinent summary statistics in the integrated summary of efficacy (ISE) below.

6.1.4 Efficacy Findings

6.1.4.1 Primary Endpoint (DBP) and Major Secondary Endpoint (SBP)

The changes from baseline for seated trough cuff DBP for the five randomized, double-blind, placebo-controlled studies in the initial NDA submission are shown in Table 13 and the changes from baseline for seated trough cuff SBP are shown in Table 14.

Table 13: Reviewer's Placebo-Subtracted Changes from Baseline in Seated Trough Cuff DBP in the Five Pivotal Studies

Study	Median Group n	Placebo	Placebo-subtracted DBP change				Comment
			75	150	300	600	
1201	114	-3.3	-3.9*	-4.5*	-7.4*		Japanese
2201	130	-6.3		-3.0*	-5.5*	-5.2*	Different formulation
2203	177	-8.6	-1.7	-1.7	-3.7*		75, 150 encapsulated

Study	Median Group n	Placebo	Placebo-subtracted DBP change				Comment
			75	150	300	600	
2204	185	-6.9	-1.8	-2.0*	-3.4*		75, 150 encapsulated
2308	169	-4.9		-5.4*	-6.2*	-7.6*	

*p<0.05 vs. placebo by ANCOVA with Dunnett's procedure for multiple comparisons

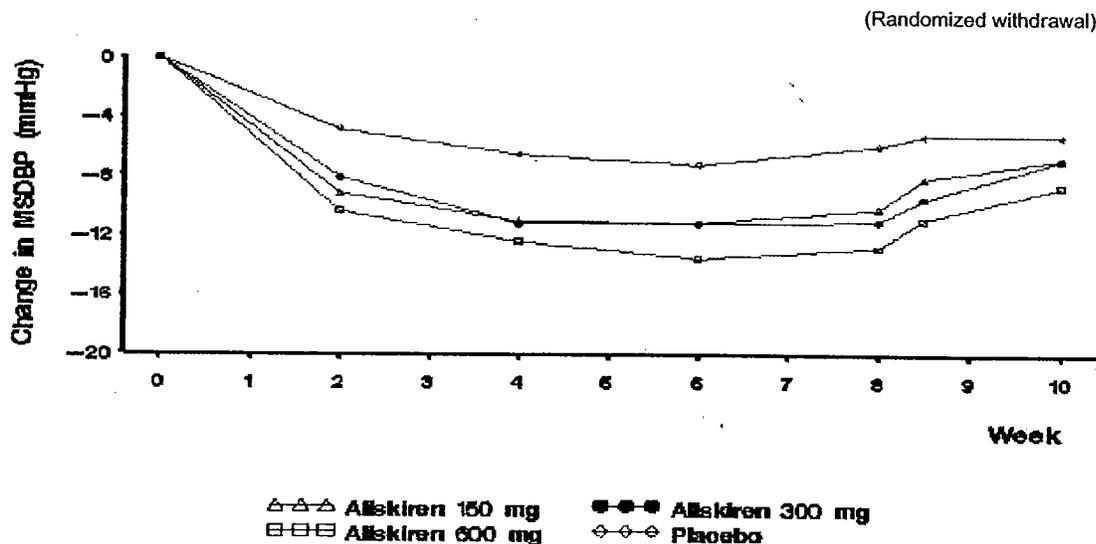
Table 14: Reviewer's Placebo-Subtracted Change from Baseline in Seated Trough Cuff SBP in the Five Pivotal Studies

Study	Median Group n	Placebo	Placebo-subtracted SBP change				Comment
			75	150	300	600	
1201	114	-2.9	-5.7*	-5.8*	-11.2*		Japanese
2201	130	-5.3		-10.5*	-10.4*	-7.2	Different formulation
2203	177	-10	-2.1	-2.1	-5.1*		75, 150 encapsulated
2204	185	-7.5	-1.9	-4.7*	-8.2*		75, 150 encapsulated
2308	169	-3.8		-9.2*	-10.9*	-12.0*	

*p<0.05 vs. placebo by ANCOVA with Dunnett's procedure for multiple comparisons

The BP reductions were typically seen after two weeks of therapy and maximal (at least for the to-be-marketed dosages) by four weeks. A typical time course for BP reductions, from Study 2308, is shown in Figure 12.

Figure 12: Sponsor's Changes from Baseline in DBP by Week in Study 2308



COMMENT: That some dosages of aliskiren have antihypertensive efficacy is shown clearly by the results in the above tables. I note the following:

- *The 75 mg dosage was statistically significantly superior to placebo only in the Japanese Study 1201. However, the effects of the 75 and 150 mg dosages are usually indistinguishable except for SBP in Study 2204.*

- *The 300 and 600 mg dosages are also not distinguishable. The 300 mg dosage is usually distinguishable from the 150 mg dosage.*
- *Any attempts at assessing dose-response may be confounded by formulation issues. The final market images were not used in any of the clinical trials and the market formulation was used in only one of the arms (aliskiren 300 mg arm of Study 2203) of the studies in Table 7 and Table 8.*
- *Study 2203, a large factorial study with valsartan, appears to have been confounded by a large placebo effect. The sponsor repeated this study with a similar one, Study 2327. Excluding Study 2203, the effect sizes are reasonable (i.e., reductions of 5-10/2-5 for 150 mg and 8-11/3-7 for 300 mg) and comparable to other antihypertensives.*

The critical issues for aliskiren efficacy in hypertension are not whether it works at all, but whether the proposed dosing interval is right and whether lower dosages than those proposed to be marketed are useful.

6.1.4.2 Long Term Efficacy

The sponsor evaluated long term efficacy of aliskiren by performing double-blind, randomized, placebo-controlled withdrawals in two long term studies: (1) Study 2302, an open label long term safety study; and (2) Study 2306, a 26-week, double-blind, randomized, active-controlled comparison of aliskiren to ramipril, allowing the addition of HCTZ. In Study 2302 the withdrawal was performed at 11 months in a subset of patients; 261 patients started the withdrawal and 250 completed it. I have summarized the withdrawal results in my review of Study 2302 in Appendix 10.1. The sponsor's changes 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. 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).

The sponsor did not submit Study 2306 in the initial NDA submission but did submit late in the review period a report and data for it. I did not review all aspects of this study but did examine AEs and the withdrawal results presented in the report. The withdrawal included 330 patients from the aliskiren regimen (170 to continuing and 163 to placebo) and 342 patients from the ramipril regimen (165 to continuing and 177 to placebo). The results for the withdrawal period for DBP are graphed in Figure 13 and the results for SBP in Figure 14.

Figure 13: Sponsor's Mean Change from Withdrawal Baseline in DBP during the Withdrawal Period in Study 2306

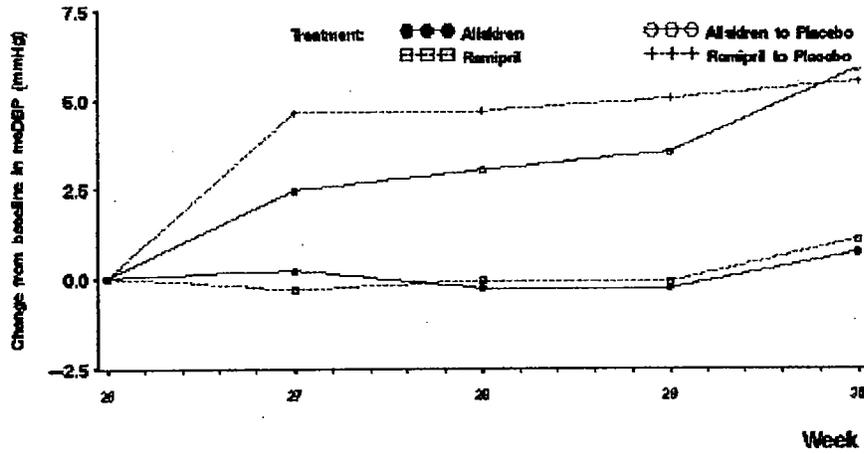
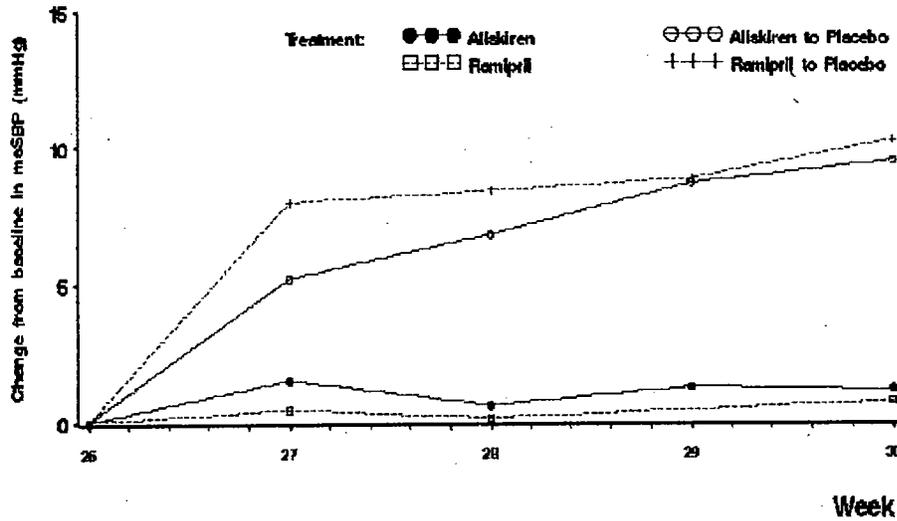


Figure 14: Sponsor's Mean Change from Withdrawal Baseline in SBP during the Withdrawal Period in Study 2306



In the Study 2306 withdrawal all withdrawals of active drug combinations were statistically significant (P about 0.001 or lower) except for changes in DBP with withdrawal of ramipril monotherapy.

COMMENT: The randomized withdrawals confirm that aliskiren has long term efficacy of at least 11 months. BP, at least the mean BP, appears to rise gradually after withdrawal of

aliskiren. The rate of rise following aliskiren withdrawal appears more gradual than following ramipril withdrawal.

6.1.4.3 Justification of Dosing Interval

While the sponsor justified testing once daily dosing based on what appear to me to be fallacious PK data interpretations, the critical issue regarding dosing intervals for antihypertensives is whether the BP control is reasonably constant throughout the interdosing interval. The traditional criterion for reasonably constant is relatively lax: The trough/peak effect (placebo-corrected BP reduction) should be > 0.5 . The sponsor performed cuff measurements at peak in one study and ABPM in others to demonstrate control throughout the interdosing interval.

Study 2201 is the one completed study with cuff measurements at multiple time points: 0, 2, 4, and 6 hours at 4 weeks and again at 8 weeks for a subset of patients (about 60 per group). I have summarized my analyses of the Study 2201 data in Appendix 10.1. My results show that, while aliskiren 300 and 600 mg had acceptable trough/peak ratios of 0.6 to 0.9, the ratios for aliskiren 150 mg were low, i.e., 0.3 to 0.4. Note that, from Table 13 and Table 14, the trough changes for aliskiren 150 mg for the entire study group were reasonable (-10.5/-3) and statistically significant. Note also that Study 2201 used a different formulation than the to-be-marketed formulation.

Study 2308 is the one completed study in general hypertensives with ABPM data. I have summarized my analyses of the Study 2308 data in Appendix 10.1. The ABPM data are erratic 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 results for 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.

Study 2324 is a study in elderly (age ≥ 65) hypertensives that included ABPM. I have also summarized my analyses of the Study 2324 APBM data in Appendix 10.1. They do not show a pronounced peak effect for aliskiren but, after a plateau, gradual diminishing of BP reductions during the second half of the interdosing interval. Aliskiren 75 mg was comparable to or slightly better than 150 mg and little different than 300 mg. Lisinopril 10 mg in this study showed superior BP control maintained throughout the interdosing interval, i.e., including at nighttime. The ratios of mean daytime to mean nighttime ambulatory BP for aliskiren range from 0.59 to 0.90.

COMMENT: The trough-to-peak cuff BP data suggest that BID dosing is preferable, while the ABPM data are weakly supportive of once daily dosing. The other data that are relevant are the withdrawal data: As summarized in Section 6.1.4.2, BP appears to rise gradually over several weeks following aliskiren withdrawal. The slow rise over several weeks upon withdrawal is the best evidence available that aliskiren once daily dosing is reasonable. That the sponsor did not explore twice daily dosing if unfortunate: Aliskiren has a definite dose-related toxicity—diarrhea. We do not know whether this toxicity would be better or worse with twice daily dosing than with once daily dosing.

6.1.4.4 Variability

Aliskiren shows high variability both intra- and intersubject for PK: intrasubject variability for C_{max} was 37-39% and for AUC 18-21%, and the intersubject variability for C_{max} was 36-75% and for AUC 29-50% (see Section 5.1 or the FDA clinical pharmacologist's review). Aliskiren also has a substantial food effect, with a high fat meal reducing AUC by 62-71% and C_{max} by 81-85%. Whether this PK variability translates into BP variability is an issue.

The sponsor, in response to a query from the FDA clinical pharmacology reviewer, provided its analysis of BP variability. The sponsor provided tables of statistics of the individual standard deviations of trough BP in patients treated with the same dose of aliskiren in Studies 2308 and 1201 at weeks 4, 6, and 8. These tables show similar mean individual standard deviations among the groups, about 4 (SD 2.5) for DBP and 6 (SD 4) for SBP. Similar tables including week 2 show slightly higher values.

A major limitation of the sponsor's analyses is that they analyze only trough data. As the Division discussed with the sponsor at pre-NDA meetings, we are more concerned about variability at peak. Study 2201 included measurements at peak at both four and eight weeks. I analyzed the Study 2201 data like the sponsor's analyses. I show my results in Table 15 through Table 18.

Table 15: Reviewer's Mean Individual Standard Deviation of DBP by Hour at Weeks 4 and 8 in Study 2201

Hour:	0	2	4	6
Aliskiren 150 mg	3.7	4.4	5.3	4.0
Aliskiren 300 mg	3.7	3.8	4.7	3.2
Aliskiren 600 mg	3.8	4.6	5.1	5.0
Irbesartan 150 mg	4.1	5.8	5.1	4.5
Placebo	4.1	3.8	4.3	4.0

Table 16: Reviewer's Mean Individual Standard Deviation of SBP by Hour at Weeks 4 and 8 in Study 2201

Hour:	0	2	4	6
Aliskiren 150 mg	6.3	6.8	7.0	7.0
Aliskiren 300 mg	5.0	6.2	6.6	4.6
Aliskiren 600 mg	6.0	6.3	7.8	6.2
Irbesartan 150 mg	6.4	8.1	7.5	7.3
Placebo	7.8	6.8	8.8	6.6

Table 17: Reviewer's Standard Deviations of Individual Standard Deviations of DBP by Hour at Weeks 4 and 8 in Study 2201

Hour:	0	2	4	6
Aliskiren 150 mg	2.8	4.0	3.5	2.8
Aliskiren 300 mg	3.0	3.3	3.7	2.7
Aliskiren 600 mg	2.6	3.9	3.7	3.2

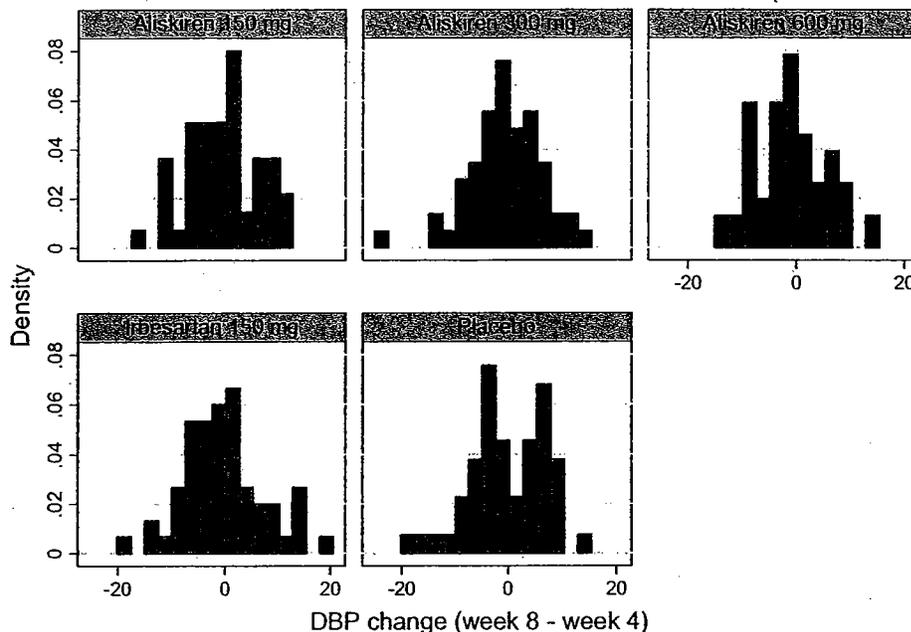
Hour:	0	2	4	6
Irbesartan 150 mg	3.4	4.7	4.3	4.0
Placebo	2.8	3.0	3.6	2.5

Table 18: Reviewer’s Standard Deviations of Individual Standard Deviations of SBP by Hour at Weeks 4 and 8 in Study 2201

Hour:	0	2	4	6
Aliskiren 150 mg	5.5	6.5	5.2	4.9
Aliskiren 300 mg	3.9	5.4	5.6	3.5
Aliskiren 600 mg	4.9	4.6	7.5	5.1
Irbesartan 150 mg	4.7	8.0	5.5	5.6
Placebo	4.5	5.8	6.3	4.4

Note that, as expected, SBP shows more variability than DBP. Placebo DBP and aliskiren 300 mg show the least variability, with both showing more variability at hours 2 and 4 than hours 0 or 6. Placebo SBP shows substantial variability. The aliskiren groups variability tends to peak at about hour 4, when BP also peaks. Irbesartan show more variability at hour 2 and, in fact, at hour 2 shows the greatest variability of any group at any time. It is informative to examine the distributions of changes in DBP from week 4 to week 8. I show some representative examples for DBP in Figure 15 through Figure 17.

Figure 15: Reviewer’s Distributions of Changes in DBP at Hour 0 (Trough) from Week 4 to Week 8 in Study 2201



Graphs by Treatment

Figure 16: Reviewer's Distributions of Changes in DBP at Hour 2 from Week 4 to Week 8 in Study 2201

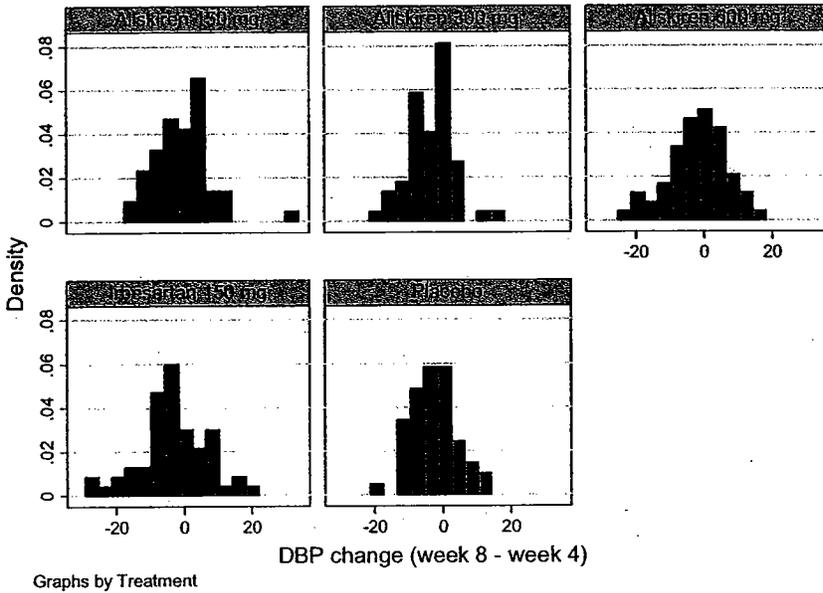
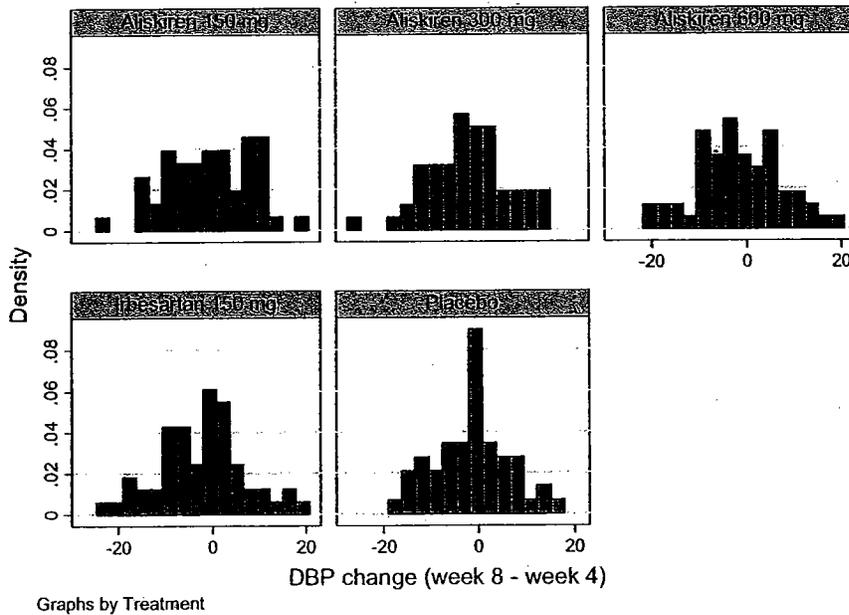


Figure 17: Reviewer's Distributions of Changes in DBP at Hour 4 from Week 4 to Week 8 in Study 2201



All of the active drug distributions are wider at hour 4 than at hour 0 (trough). There do not appear to be more extreme outliers for aliskiren than for irbesartan.

COMMENT: These data from trough and expected peak hours are reassuring that variability with aliskiren is not substantially different from that with irbesartan or even that with placebo. The major limitation is that the earliest measurements are at four weeks. Aliskiren accumulates, so even at trough at four weeks it has residual effects from the accumulation. Ideally I would like to see peak measurements of BP for the first week after initiating therapy. Another limitation is that the drug administration and the measurements were done in the clinic setting. The relationship to meals is probably more consistent than it is in routine daily life. An additional limitation is that Study 2201 did not use the to-be-marketed formulation.

6.1.4.5 Subgroups and Special Populations

Besides the usual issue of interpreting subgroup results, a special issue for analyzing subgroup results for hypertension studies using cuff BP measurements is how to perform placebo correction. Placebo effect may vary among subgroups as well as among studies. For example, I list the changes from baseline in BP for the placebo groups by study in Table 19.

Table 19: Reviewer's Mean Change from Baseline in BP for Placebo by Study

Study	SBP	DBP
1201	-2.8	-3.2
2201	-5.1	-6.5
2203	-9.1	-8.4
2204	-7.1	-7.0
2308	-2.9	-4.8

There do appear to be substantial differences in placebo effect by study. Hence I apply placebo corrections at least by study in the remainder of this section. Some subgroups also appear to have differences in placebo effect, as I show for gender in Table 20.

Table 20: Reviewer's Mean Change from Baseline in BP for Placebo by Study and Gender

Study	Female		Male	
	SBP	DBP	SBP	DBP
1201	-8.6	-7.6	-1.2	-1.9
2201	-7.3	-8.6	-2.9	-4.4
2203	-9.5	-8.3	-8.8	-8.5
2204	-8.3	-7.9	-6.1	-6.2
2308	-2.8	-5.0	-3.0	-4.6

Some studies, but not all, show a substantial difference in placebo effect by gender. Hence it seems reasonable to me to do placebo correction by both study and gender. I show such an analysis in Table 21.

Table 21: Reviewer’s Mean Placebo-Corrected Change from Baseline in BP by Dose and Gender in the Placebo-Controlled Studies

Dose	Female		Male	
	SBP	DBP	SBP	DBP
75	-1.3	-1.1	-3.6	-2.9
150	-5.5	-2.9	-5.9	-3.5
300	-9.4	-4.8	-9.0	-5.4
600	-12.6	-6.4	-10.7	-6.5

While there is the suggestion of a differential effect by gender for the 75 mg dosage, overall there do not appear to be differential BP reductions by gender. The ABPM data from Study 2308 also do not show consistent differences in daytime or nighttime BP control by gender.

COMMENT: These data do not show a consistent difference in antihypertensive effect by gender, but see also the results of multivariate analyses below.

The elderly (age ≥ 65) do not show consistent differences in placebo effect from younger patients. Hence I show the mean study placebo-corrected changes from baseline in BP by dose and age in the placebo-controlled studies in Table 22.

Table 22: Reviewer’s Mean Placebo-Corrected Change from Baseline in BP by Dose and Age in the Placebo-Controlled Studies

Dose	Age < 65		Age ≥ 65	
	SBP	DBP	SBP	DBP
75	-2.7	-1.9	-3.6	-3.4
150	-5.5	-2.9	-6.9	-4.8
300	-9.7	-5.2	-7.1	-4.4
600	-11.5	-6.6	-11.6	-6.4

Note that the elderly show a better response to the 75 mg and 150 mg doses than younger patients. There is no increment for the elderly at 300 mg, but one must be cautious about overinterpreting these subgroup results—given the greater response at 600 mg, the 300 mg results in the elderly are likely chance variation with inadequate sample sizes. The younger patients’ BPs show a dose-response from 75 to 600 mg, flattening in the 300 to 600 mg range. These results for the elderly are similar to those shown in Study 2324, whose enrollment was limited to patients aged ≥ 65 . In Study 2324 reductions with aliskiren 75 mg were slightly higher than those with aliskiren 150 mg and comparable to those with 300 mg. Please see Section 10.1.14.3 for the details.

COMMENT: The elderly show a reasonable response to aliskiren 75 mg and 150 mg. Younger patients show a dose-response through 300 mg and some incremental effect at 600 mg. Note that in the elderly AUC and C_{max} were increased by 57% and 28%, respectively.

Overall whites showed a slightly higher placebo effect than blacks and Asians showed the lowest. However, some of these differences may be related to the racial compositions of the

different studies, since interstudy placebo effect differences were great, e.g., Study 1201 had a low placebo effect and was exclusively Japanese. The estimates of placebo effects for blacks and Asians (other than in Study 1201) were highly variable, likely a result of insufficient numbers of these racial groups in most studies. I show the mean study-specific placebo-corrected changes from baseline in BP by dose and race (for whites, blacks, and Asians—the three races with sufficient numbers studied) in the placebo-controlled studies in Table 23 and the study and race-specific placebo corrected changes in Table 24.

Table 23: Reviewer’s Mean Study-Specific Placebo-Corrected Change from Baseline in BP by Dose and Race in the Placebo-Controlled Studies

Dose	White		Black		Asian	
	SBP	DBP	SBP	DBP	SBP	DBP
75	-2.2	-1.9	3.5	4.1	-5.7	-4.0
150	-6.0	-3.2	-1.3	0.4	-6.6	-4.6
300	-9.1	-4.7	-2.2	-1.0	-12.0	-7.5
600	-12.2	-6.8	-6.1	-2.8	-14.0	-9.7

Table 24: Reviewer’s Mean Study and Race-Specific Placebo-Corrected Change from Baseline in BP by Dose and Race in the Placebo-Controlled Studies

Dose	White		Black		Asian	
	SBP	DBP	SBP	DBP	SBP	DBP
75	-2.1	-1.7	-2.8	0.2	-8.8	-3.2
150	-6.5	-3.5	-5.5	-1.4	-3.7	-2.9
300	-9.6	-4.8	-6.1	-2.6	-12.7	-6.3
600	-12.3	-6.7	-8.7	-3.5	-11.2	-9.4

COMMENT: The BP changes by race appear to show three distinct patterns: Whites show a dose-response from 75 through 600 mg. Blacks appear to show a substantially lower response, while Asians show a better response at the 75 mg dose but the response plateaus for 300 to 600 mg. Whether blacks show much of a response at dosages lower than 600 mg is not clear from these data—the study-specific placebo-corrected results show minimal effects in blacks below 600 mg while the study and race-specific placebo-corrected results show progressive reductions in SBP that are reasonable starting at the 150 mg dosage.

While patients with severe renal dysfunction (e.g., estimated GFR 30 ml/min), some patients with moderate renal impairment were studied, i.e., in the placebo-controlled studies 216 patients, about 4%, had estimated GFR < 60. Because placebo effect did not clearly vary by renal function, I examined BP reductions by this GFR cutoff and show the results in Table 25.

Table 25: Reviewer's Mean Placebo-Corrected Change from Baseline in BP by Dose and GFR Cutoff 60 ml/min in the Placebo-Controlled Studies

Dose	GFR<60		GFR≥60	
	SBP	DBP	SBP	DBP
75	-2.2	-7.1	-4.2	-3.0
150	-4.7	-4.7	-5.8	-3.7
300	-9.0	-5.7	-9.2	-5.5
600	-15.9	-7.1	-9.4	-6.3

COMMENT: By this categorical analysis there is no clear pattern of increased effect in patients with reduced renal function. However, there appears to be substantial noise and hence the number of patients with reduced renal function studied in the placebo-controlled studies is too small to draw firm conclusions. Please see also the multivariate analyses below.

Because BP reductions may be related to more than one factor, e.g., age, race, I also explored multivariate analyses of BP. I show a multivariate regression analysis of DBP in Table 26 and of SBP in Table 27.

Table 26: Reviewer's Multivariate Regression of DBP Changes in the Placebo-Controlled Studies

Source	SS	df	MS	Number of obs = 3056		
Model	23937.912	21	1139.90057	F(21, 3034) =	17.09	
Residual	202405.247	3034	66.7123423	Prob > F =	0.0000	
Total	226343.159	3055	74.0894136	R-squared =	0.1058	
				Adj R-squared =	0.0996	
				Root MSE =	8.1678	

change in DBP	Coef.	Std. Err.	t	P> t	[95% Conf. Interval]	
baseline DBP	.1157314	.0420222	2.75	0.006	.0333365	.1981263
75	-2.535493	.5779985	-4.39	0.000	-3.668801	-1.402185
150	-3.226523	.5048877	-6.39	0.000	-4.216479	-2.236566
300	-4.896561	.5037824	-9.72	0.000	-5.88435	-3.908771
600	-5.980638	.6676031	-8.96	0.000	-7.289638	-4.671637
age≥65	-1.631466	.7837894	-2.08	0.037	-3.168278	-.0946545
age*drug	.7947509	.889133	0.89	0.371	-.9486132	2.538115
male	1.75877	.3078598	5.71	0.000	1.155136	2.362405
black	2.174234	1.074908	2.02	0.043	.0666121	4.281856
Asian	1.031504	1.015954	1.02	0.310	-.9605252	3.023532
native Amer.	.2708513	1.541203	0.18	0.861	-2.751057	3.292759
Pacific isl.	.9223481	4.096474	0.23	0.822	-7.109797	8.954493
other race	-.1853071	.7868563	-0.24	0.814	-1.728133	1.357518
black*drug	2.314801	1.250727	1.85	0.064	-.1375579	4.76716
Asian*drug	-1.877891	.8748022	-2.15	0.032	-3.593156	-.1626256
BMI	1123.734	284.7949	3.95	0.000	565.3231	1682.144
GFR	-.0274178	.0081637	-3.36	0.001	-.0434247	-.011411
Study 2201	-3.438039	.9436064	-3.64	0.000	-5.288212	-1.587867
Study 2203	-4.078195	.9074623	-4.49	0.000	-5.857498	-2.298892
Study 2204	-2.762789	.8882454	-3.11	0.002	-4.504413	-1.021165
Study 2308	-2.991385	.8162724	-3.66	0.000	-4.591888	-1.390882
intercept	-16.76366	4.399545	-3.81	0.000	-25.39005	-8.13727

Table 27: Reviewer’s Multivariate Regression of SBP Changes in the Placebo-Controlled Studies

Source	SS	df	MS	Number of obs = 3056		
Model	99277.2035	21	4727.48588	F(21, 3034) =	29.02	
Residual	494303.349	3034	162.921341	Prob > F =	0.0000	
				R-squared =	0.1673	
				Adj R-squared =	0.1615	
				Root MSE =	12.764	
Total	593580.552	3055	194.298053			

change in SBP	Coef.	Std. Err.	t	P> t	[95% Conf. Interval]	
baseline SBP	-.3083441	.0202085	-15.26	0.000	-.3479679	-.2687204
75	-3.198119	.9029973	-3.54	0.000	-4.968667	-1.427571
150	-4.891995	.7891909	-6.20	0.000	-6.439398	-3.344592
300	-8.089686	.7874148	-10.27	0.000	-9.633607	-6.545765
600	-9.409472	1.043319	-9.02	0.000	-11.45516	-7.363789
age≥65	4.957927	1.231049	4.03	0.000	2.544153	7.371701
age*drug	-2.834913	1.389407	-2.04	0.041	-5.559187	-.1106387
male	2.883605	.4789529	6.02	0.000	1.9445	3.82271
black	4.77559	1.679204	2.84	0.004	1.483097	8.068082
Asian	-1.461223	1.589626	-0.92	0.358	-4.578075	1.655629
native Amer.	-.8007619	2.409727	-0.33	0.740	-5.525625	3.924101
Pacific isl.	8.360477	6.402105	1.31	0.192	-4.192426	20.91338
other race	-.9080706	1.229667	-0.74	0.460	-3.319136	1.502995
black*drug	1.341924	1.954661	0.69	0.492	-2.49067	5.174517
Asian*drug	-1.882316	1.367286	-1.38	0.169	-4.563216	.7985845
BMI	1828.43	444.5591	4.11	0.000	956.7623	2700.097
GFR	-.0344003	.0127784	-2.69	0.007	-.0594554	-.0093452
Study 2201	-7.585215	1.485632	-5.11	0.000	-10.49816	-4.672267
Study 2203	-8.10524	1.42743	-5.68	0.000	-10.90407	-5.306412
Study 2204	-7.224116	1.39562	-5.18	0.000	-9.960573	-4.487659
Study 2308	-6.045528	1.283873	-4.71	0.000	-8.562878	-3.528178
intercept	42.68093	4.022261	10.61	0.000	34.7943	50.56756

COMMENT: In the multivariate regressions aliskiren shows a clear dose-response from 75 through 600 mg for both SBP and DBP. Blacks show a reduced response and Asians an increased response with a statistically significant interaction term with aliskiren (drug) use for Asians for DBP and almost statistically significant for blacks for DBP. The interaction term for age ≥ 65 and drug is statistically significant for SBP.

There do appear to be differences in response in various subgroups with aliskiren use. Blacks respond poorly to aliskiren monotherapy while Asians and the elderly may respond to lower doses. That blacks respond poorly is not surprising because other RAAS inhibitors show similar reduced efficacy in blacks. Unfortunately the sponsor did not study enough blacks in Study 2204, the large factorial trial of aliskiren with HCTZ, to establish that adding HCTZ improves BP control substantially as it does for other RAAS inhibitors—only 126 (<5%) of the patients completing Study 2204 were black.

6.1.4.6 Dose Response and Efficacy of Lower Dosages

An important question for any drug, and antihypertensives are no exceptions, is whether the marketed dosages are the optimal ones. Getting the dosage right is critical for aliskiren because aliskiren has a definite dose-related toxicity—diarrhea. At the high end the choice for the highest marketed dose seems obvious: At 300 mg once daily diarrhea rates are doubled but

- Some results of the sponsor's modeling are bizarre and inconsistent with the observed data. For example, the sponsor's model of diarrhea suggests 0 diarrhea rates for placebo and the lower aliskiren dosages for the elderly. The observed diarrhea rates are clearly nonzero for placebo and all aliskiren dosages. When queried about this anomaly, the sponsor responded that this anomaly was the result of weighting of values. The weighting was not documented in the original submissions on modeling. The weighting appears to be inappropriate and designed merely to get the results the sponsor wanted to see.
- All of the analyses suffer from a lack of specification: How exactly the models were performed is not provided.

For the reasons given above I can not rely upon the sponsor's modeling results.

COMMENT: While there may be some additional effect of the 600 mg dose particularly in whites, I do consider it reasonable to limit the high end dose to 300 mg because of the GI toxicity. At the low end the 75 mg dose
— however, 150 mg and 300 mg do appear to be more efficacious, so limiting marketing to those dosages is not totally unreasonable. At the low end I have more concerns about the dosing interval—I wonder whether low BID dosing (even 18 mg BID) would be useful in some patients.

6.1.4.7 Use with Other Antihypertensives

The sponsor conducted various studies of aliskiren in combination with other antihypertensives. The sponsor summarized the results of the aliskiren combination studies submitted with the initial NDA submission in Table 28 (DBP) and Table 29 (SBP).

COMMENT: Of these studies the one that provides the most useful information is Study 2204, a factorial study of aliskiren and HCTZ alone and in combination. This study provides substantial evidence that the combinations of aliskiren and HCTZ provide BP reductions greater than that produced by the corresponding monotherapies. The other studies have major limitations:

- *Study 2203 is a failed study in that it does not show that the effects of the combinations of aliskiren and valsartan exceed the monotherapies. As I discuss in Section 10.1.4, it may have failed because of a large placebo effect. The sponsor performed a similar study (Study 2327) and submitted it late in the initial review period (see below).*
- *Study 2305 has little value because it does not show that a combination of maximum labeled doses of aliskiren and amlodipine is more effective than the monotherapies. See Section 10.1.7 for more details.*
- *Study 2307 has a similar limitation to Study 2305: The study did not use the maximum labeled dose of the ACEI ramipril. See Section 10.1.8 for more details.*

Of these three latter studies two that are of particular interest are Study 2203 with valsartan and Study 2307 with ramipril because the two co-administered drugs also function through RAAS inhibition. Because ACEI work at the next step in the pathway after renin, one might speculate that ACEI and renin inhibitors like aliskiren might not be additive at maximal doses of each.

The sponsor has pursued studying aliskiren along with an ARB (valsartan) in another study, Study 2327.

Table 28: Sponsor's Least Square Mean Change from Baseline in msDBP (mm Hg) at Endpoint – Combination Therapy in Active or Placebo-controlled Studies (ITT Population)

	Aliskiren placebo	Aliskiren 75 mg	Aliskiren 150 mg	Aliskiren 300 mg
Study 2203*				
valsartan placebo	-8.59 (0.62)	-10.27 (0.62)	-10.28 (0.62)	-12.26 (0.62) ^p
valsartan 80 mg	-10.51 (1.07)	-11.84 (1.05) ^p	–	–
valsartan 160 mg	-11.01 (1.07) ^p	–	-12.07 (1.05) ^p	–
valsartan 320 mg	-11.28 (1.05) ^p	–	–	-12.93 (1.07) ^p
Study 2204				
HCTZ placebo	-6.93 (0.58)	-8.68 (0.59) ^p	-8.94 (0.59) ^p	-10.26 (0.60) ^p
HCTZ 6.25 mg	-9.07 (0.58) ^p	-10.76 (0.59) ^{p,h,a}	-10.36 (0.61) ^p	–
HCTZ 12.5 mg	-10.11 (0.59) ^p	-11.14 (0.59) ^{p,a}	-11.90 (0.59) ^{p,h,a}	-12.65 (0.59) ^{p,h,a}
HCTZ 25 mg	-9.37 (0.61) ^p	-11.46 (0.59) ^{p,h,a}	-12.65 (0.59) ^{p,h,a}	-14.26 (0.61) ^{p,h,a}
Study 2305				
amlodipine 5 mg	-4.84 (0.62)	–	-8.46 (0.60) ^{amlo}	–
amlodipine 10 mg	-8.04 (0.62)	–	–	–
Study 2307				
ramipril placebo	–	–	–	-11.32 (0.54)
ramipril 10 mg	-10.71 (0.54)	–	–	-12.78 (0.54) ^{a,r}

* 1 treatment group, valsartan 160 mg with HCTZ 12.5 mg, is not shown

HCTZ = hydrochlorothiazide

p = statistically significant vs. placebo (p <0.05)

h = statistically significant vs. component monotherapy HCTZ dose (p <0.05)

a = statistically significant vs. component monotherapy aliskiren dose (p <0.05)

r = statistically significant vs. component monotherapy ramipril dose (p <0.05)

amlo = statistically significant vs. component monotherapy amlodipine dose (p <0.05)

Table 29: Sponsor's Least Square Mean Change from Baseline in msSBP (mm Hg) at Endpoint – Combination Therapy in Active or Placebo-controlled Studies (ITT Population)

	Aliskiren placebo	Aliskiren 75 mg	Aliskiren 150 mg	Aliskiren 300 mg
Study 2203*				
valsartan placebo	-9.96 (0.96)	-12.13 (0.96)	-12.10 (0.95)	-15.05 (0.96) ^P
valsartan 80 mg	-11.23 (1.65)	-14.46 (1.62) ^P	–	–
valsartan 160 mg	-15.53 (1.65) ^P	–	-16.62 (1.62) ^{P, a}	–
valsartan 320 mg	-16.51 (1.62) ^P	–	–	-18.04 (1.65) ^P
Study 2204				
HCTZ placebo	-7.48 (0.92)	-9.37 (0.94)	-12.24 (0.94) ^P	-15.74 (0.95) ^P
HCTZ 6.25 mg	-10.95 (0.92) ^P	-14.29 (0.93) ^{P, h, a}	-15.31 (0.97) ^{P, h, a}	–
HCTZ 12.5 mg	-13.92 (0.93) ^P	-15.64 (0.93) ^{P, a}	-17.61 (0.94) ^{P, h, a}	-19.82 (0.95) ^{P, h, a}
HCTZ 25 mg	-14.30 (0.97) ^P	-17.32 (0.93) ^{P, h, a}	-19.47 (0.93) ^{P, h, a}	-21.22 (0.97) ^{P, h, a}
Study 2305				
amlodipine 5 mg	-4.96 (0.90)	–	-10.98 (0.88) ^{amio}	–
amlodipine 10 mg	-9.63 (0.90)	–	–	–
Study 2307				
ramipril placebo	–	–	–	-14.65 (0.86)
ramipril 10 mg	-11.99 (0.86)	–	–	-16.62 (0.87) ^r

Footnotes per Table 28

The sponsor provided a preliminary report for Study 2327 late in the review period. I have summarized the sponsor's findings in Section 10.1.15. The sponsor's results show highly statistically significant incremental reductions in BP at trough for the combinations of aliskiren and valsartan compared to the monotherapies. The incremental reductions for the 300/320 combination is reasonable, about -4/-3, compared to the monotherapies. The sponsor did not provide analyses comparing effects at peak.

COMMENT: Aliskiren use with HCTZ appears appropriate. While ideal evidence regarding use with amlodipine is lacking, the evidence is similar to that provided in initial submissions of other antihypertensives, and there is no mechanistic reason to believe that aliskiren should not behave with amlodipine similar to other RAAS inhibitors. The lack of evidence of efficacy with maximal doses of ACEIs is more problematic. The label should caution that the effects with full doses of ACEIs are unknown.

6.1.5 Clinical Microbiology

Clinical microbiology is not applicable for this oral formulation.

6.1.6 Efficacy Conclusions

Aliskiren clearly has anti-hypertensive efficacy, sustained for at least 11 months. In non-elderly whites aliskiren shows a dose-response in blood pressure reductions at trough from 75 mg through 600 mg once daily. The 600 mg dose can be rejected as a recommended dose more because of toxicity considerations, i.e., increased diarrhea, than for a total lack of incremental efficacy. At the low end, while the sponsor is proposing to market 150 mg as the lowest recommended dose,

Whether lower doses completely lack efficacy, particularly for the latter subgroups, has not been studied adequately.

The 24-hour interdosing interval is weakly supported by ABPM data but not by the available trough-to-peak cuff BP measurements or by the PK data. The slow rise on withdrawal also supports a sustained effect, at least for the trough effect. More information on effects throughout the interdosing interval would be helpful, and how BID dosing affects safety and efficacy would also be informative.

Variability in BP after several weeks administration of aliskiren appears does not appear problematic. Variability in BP upon initiation of therapy and variability due to the substantial food effect with varying timings of administration relative to meals has not been studied.

_____, it would be valuable to know how BP is affected at peak if the consistent relationship to breakfast is not maintained. It would also be valuable to know whether toxicity is affected by taking aliskiren with or without meals, or at bedtime rather than in the morning.

Aliskiren shows reduced efficacy in blacks. It shows greater efficacy at the lower doses in Asians and the elderly.

_____ but starting at 150 mg in these groups is a reasonable _____

Aliskiren use with HCTZ appears justified. There is inadequate evidence to recommend aliskiren administration with full doses of ACE inhibitors. There is also uncertainty regarding use with ARBs that may be resolvable when analysis of Study 2327 is completed. Use with beta blockers, which also act through RAAS inhibition, also needs study. For labeling the uncertainties regarding use with ACEIs _____ should be mentioned.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

Seven patients died in aliskiren groups in the completed trials and four patients who may be taking aliskiren died in the ongoing trials. One patient in a placebo group and three patients in active control groups died in the completed trials.

The following are brief narratives of the deaths in aliskiren groups in the completed trials:

1. A 44-year-old Japanese male in the aliskiren 150 mg group of Study 1201 died from a drug overdose on day 41--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 patient's BP is described as well controlled.
2. A 73-year-old white male in the aliskiren 150 HCTZ 25 group of Study 2204 died due to thoracic trauma from a traffic accident on day 58. The investigator reported this death as unrelated to study medication.
 3. A 74-year-old Hispanic white male in the aliskiren 150 mg group of Study 2302 died on day 27 of a ruptured aortic aneurysm. The patient's baseline BP (last recorded) was 159/96.
 4. A 79-year-old white female in the aliskiren 300 mg group of Study 2302 with a history of hyperlipidemia and also taking diclofenac died on day 296 of a MI. Her last BP on day 260 was 130/83.
 5. A 61-year-old female in the aliskiren 150 mg group (titrated to 300 mg) of Study 2302 without significant other comorbidities was found dead in bed on day 71. No autopsy was performed 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.
 6. A 77-year-old Hispanic male in the aliskiren 150 mg group (titrated to 300 mg) of Study 2302 with a 27 year history of hypertension but no other significant comorbidities 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.
 7. A 56-year-old white male in the aliskiren 300 mg group (with HCTZ 25 mg added) of Study 2302 with a history of tobacco abuse, coronary disease, and peripheral vascular disease 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: The deaths are the usual ones from cardiovascular disease in a hypertensive population plus some incidental ones (overdose, traffic accident). They do not distinguish aliskiren from placebo or active control. They do not suggest any rare or unusual problems with aliskiren.

7.1.2 Other Serious Adverse Events

Serious adverse events (SAEs) were uncommon, and the rates per 100 person exposure years (PEYs) were similar in the aliskiren groups and the control groups (both about 6 per 100 PEY).

The types of SAEs were varied, with the MedDRA high level categories with the most SAEs being ischemic coronary artery disorders (22, more frequent in control than aliskiren excluding the long term, uncontrolled Study 2302), abdominal and gastrointestinal infections (10, more common with aliskiren), and central nervous system hemorrhages and cerebrovascular accidents (12). I discuss gastrointestinal AEs in Section 7.1.3.3.1 and cerebrovascular accidents below.

7.1.2.1 Strokes and other thrombotic events

During the aliskiren development program strokes occurred, including several in patients under the age of 50. Hence scrutinizing strokes is appropriate. The following are brief narratives of the thirteen strokes occurring during active treatment with aliskiren:

1. A 61-year-old white male in the aliskiren 75/HCTZ 25 group of Study 2204 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.
2. A 59-year-old female in the aliskiren 75/HCTZ 12.5 group of Study 2204 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.
3. A 67-year-old white female in the 150 mg group of Study 2302 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.
4. A 63-year-old white male in the 150 mg group of Study 2302 (up-titrated to 300 mg after one month and also taking HCTZ for about 30 days) 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.
5. A 77-year-old Hispanic male in the aliskiren 150 mg group (titrated to 300 mg) of Study 2302 with a 27 year history of hypertension but no other significant comorbidities 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.

6. A 42-year-old Peruvian (“other” race and ethnicity) male in the 150 mg group of Study 2302 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.
7. A 59-year-old white female receiving aliskiren 300 mg/HCTZ 25 mg in Study 2302E1 suffered a stroke of the left middle cerebral artery on day 407 and was hospitalized. Imaging was not done. 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.
8. A 65-year-old diabetic black male in the 300 mg group of Study 2302 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 left atrial hypertrophy. The diagnosis was an acute left pontine CVA. His BP on day 92 was 160/189 and on day 120 was 159/99.
9. A 48-year-old white female in the 150 mg group of Study 2302 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 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.
10. A 48-year-old white female in the aliskiren 150/ramipril 5 combination group of Study 2307 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.
11. A 66-year-old white female in the aliskiren/ramipril combination group of Study 2307 suffered severe right arm paresis on day 7 and was hospitalized. Study medication was discontinued and metoprolol started. She recovered by day 17. No diagnosis of stroke or TIA was made.
12. A 63-year-old Japanese male in the 75 mg group of Study — suffered lightheadness for 3 days and a “mild brainstem infarction” (diagnosed by CAT scan and MRI) on day 361. His BPs throughout the year were reported as 140-150/80-90.

13. A 60-year-old Japanese female in the 75 mg group of Study — experienced numbness in her right arm and difficulty walking upon awakening on day 246. She was hospitalized and an initial MRI showed lacunar infarcts and a second MRI showed a pontine infarct that was thought to be causing her symptoms. Her last BP 22 days prior to the event was 135/78 and on admission was 126/64.

In addition to events during active treatment, a 67-year-old white male in the aliskiren 150/HCTZ 6.25 group of Study 2204 suffered a stroke 19 days after discontinuing the study. His BP was poorly controlled throughout the study (164-185/101-114).

The following are brief narratives of other events that may be cerebrovascular ischemia:

1. A 51-year-old white, diabetic male in the aliskiren 75/HCTZ 12.5 group of Study 2204 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.
2. A 50-year-old white male receiving aliskiren 300 mg in Study 2302 experienced two isolated, transient (5-10 minute) episodes of paresthesia in his left arm and left side of face on day 25. He was diagnosed as a TIA. One month prior his BP was 164/84 and one week after it was a maximum of 174/118 on 24-hour ABPM.
3. A 61-year-old female in Study 2302 (150 mg group initially) without significant other comorbidities was found dead in bed on day 71. No autopsy was performed 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.
4. A 75-year-old male in the aliskiren/ramipril combination group of Study 2307 suffered a TIA on day 4. Treatment was not discontinued.
5. A 44-year-old Japanese female in Study — (who had completed Study 1201) was treated with escalating doses of aliskiren to 300 mg and then amlodipine was added on day 54 (BP 143-154/92-94). On day 61 she was unable to hold a pencil or write with her right hand. While a peripheral nerve palsy was suspected, MRI showed a lesion suggestive of an old infarction in the right putamen. An MRI is also described as showing lacunar infarcts in the right basal ganglia and bilateral corona radiata. She was withdrawn from the study. On day 63 her BP was 145-159/87-90.
6. A 56-year-old white female in the aliskiren 300 mg group of Study 2302 suffered a sixth cranial nerve paresis on day 50. Treatment was not discontinued. She also had an AE of temporal arteritis treated with prednisone on day 118.

In comparison, one patient in a placebo group, a 69-year-old Japanese female in Study 1201, suffered a stroke confirmed by MRI on day 21.

The stroke events are impossible to interpret without an understanding of the drug exposures associated with them. The stroke rates in the individual studies by person years of exposure (PEYs) are shown in Table 30.

Table 30: Reviewer's Stroke Rates in the Aliskiren Studies

Study	Placebo			Aliskiren		
	PEYs	Strokes/ 100 PEY	*Possible Strokes/ 100 PEY	PEYs	Strokes/ 100 PEY	*Possible Strokes/ 100 PEY
1201†	16	6.1	6.1	50	0	0
2201	38	0	0	58	0	0
2203	60	0	1.7	103	0	1
2204	108	0	0	294	0.7	1.7
2302				1763	0.4	0.6
2303	8	0	0	18	0	0
2305	39	0	0	21	0	0
2307	40	0	0	79	2.5	2.5
2308	23	0	0	74	0	0
2323	251	0	1.2	264	0	0
2324	12	0	0	29	0	3.5

*Possible Strokes = definite strokes plus possible strokes; †Japanese study

If only placebo-controlled trials are considered, then the stroke rate per 100 PEY is 0.4 (1 stroke) in the combined control groups and 0.35 (2 strokes) in the aliskiren groups. However, the only placebo stroke occurred in a Japanese study (1201). If this study is excluded (as the sponsor usually treats the Japanese studies separately), then the stroke rate is 0.38 in the combined aliskiren groups vs. 0 in the combined control groups. If all controlled trials are included except for the Japanese study, then the stroke rate is 0.43 (4 strokes) vs. 0.

For an Aliskiren External Expert Panel the sponsor compared stroke rates in the aliskiren development program to those in the valsartan development program (Table 31) and tabulated stroke rates in randomized controlled trials of mild to moderate hypertension in the literature (Table 32).

Table 31: Sponsor's Comparison of Stroke Rates in the Aliskiren and Valsartan Development Programs

	Long-term uncontrolled studies		All studies		
	Diovan program † (protocols 11/31)	Aliskiren (studies 2302/1202)	Diovan program †	Aliskiren ‡	Aliskiren (worse case-scenario)*
Nº patients on active treatment (N)	775	2300	11132	7138	9289
PY exposure to treatment	704.9	2047.7	2901.4	2758.7	3485.8
Mean exposure	332d	325.2d	95.1d	141.2 days	132.1 d
Stroke/TIA cases&Incidence rate					
Nº Strokes cases	2	8	9	12	16
Nº TIA cases	1	2	4	2	4
Nº Stroke/TIA	3	10	13	14	20
IR Stroke per 1000 py (95%CI)	2.8 (0.3-10.3)	3.9 (1.7-7.7)	3.1 (1.4-5.9)	4.3 (2.2-7.6)	4.6 (2.6-7.4)
IR Stroke/TIA per 1000 py (95%CI)	4.3 (0.9-12.4)	4.9 (2.3-9.0)	4.5 (2.4-7.7)	5.0 (2.8-8.6)	5.7 (3.5-8.9)

‡ Includes Aliskiren patients in completed RCT and in long-term uncontrolled studies

† Diovan program includes any active treatment.

* Worse Case-scenario: Including 4 Strokes and 1 TIA in ongoing trials that are blinded to treatment and the estimated exposure to Aliskiren in ongoing studies.



Table 32: Sponsor's Stroke Rates in Randomized Controlled Trials of Mild to Moderate Hypertension in the Literature

	HOT (1998)	INSIGHT (2000)	CAPPP (1999)	NORDIL (1999)	ELSA (2002)
Patients (N)	19193	6321	10985	10881	2334
Mean follow-up (y)	3.8	3.5	6.1	4.5	3.7
Patient-years	71051	21991	67239	48992	7255
Mean age (y)	61.5	65	52.5	60.4	56
%Women	47	53.7	46.5	51.4	46
Countries	Multinational	Israel/Europe	Sweden/Finland	Sweden/Norway	Europe
Cardiovascular risk factors	DM: 8.0% Smoking: 15.8%	Hyperchol:52.0%; Smoker: 28.3%; DM: 20.6%	DM: 5.2% Smoking: 22.1%	DM: 6.7% Smoking: 22.4%	Smoking: 20.1%
Previous CV events	Stroke: 1.2%; MI: 1.5%; OtherCHD:5.9%	MI: 6.2%; CHD:6.4%	MI:0.9%; CHD:0.7%; Stroke: 0.4% HF:0.1%	MI:2.1; Other CHD:2.5%; Stroke: 1.5%; TIA:1.1%	Major cardiovascular: 2.4%
Stroke/TIA cases	294/NA	141/50	342/56	355/81	23/NA
Incidence rate Stroke (per 1000 PY)*	4.13	6.4	5.1	7.2	3.2
Incidence rate Stroke/TIA (per 1000 PY)	NA	8.7	5.9	8.9	NA

HOT Hansson L Lancet 1998;351:1755-62; INSIGHT Brown M Lancet 2000;356:366-372; CAPPP Hansson L Lancet 1999;353:611-616; NORDIL Hansson L Lancet 2000;356:359-365; ELSA Zanchetti A Circulation 2002;106:2422-2427

HOT all hypertensive patients had their BP under control; NA: Not available Py: patient-year

Because strokes are frequently associated with other cardiovascular thrombotic events, such as MIs, it is worth commenting on MI rates here. MIs were uncommon, i.e., 16 diagnosed and 8 additional possible. MIs were less frequent in the aliskiren arms (0.13%) than in the control arms (0.2%). Conversely, diagnosed angina cases were slightly more frequent with aliskiren (0.19%) than with control (0.13%). If all possible angina and MI cases are considered, then the rates with aliskiren (0.32%) and control (0.36%) are similar but still favor aliskiren.

COMMENT: The numbers of strokes, and the occurrences of strokes in three individuals under age 50, have been of concern in the aliskiren development program. The difficulty in interpreting the strokes has been that most of the strokes, and the exposure, are in the long-term, uncontrolled Study 2302. Whether the controlled trials show a difference in stroke rates between aliskiren and control depends upon whether the Japanese study is included or excluded; regardless, there are few events in the controlled trials so that the confidence intervals for any estimates are wide.

The sponsor's comparisons of stroke rates in the aliskiren development program to those in the valsartan development program and to those in published studies are reassuring that the aliskiren stroke rates are not anomalously high. I performed a similar comparison to the most recently approved new molecular entity for hypertension, eplerenone (NDA 21-437). The stroke rates in the eplerenone program, taken from the clinical review posted on the FDA external website, are shown in Table 33.

Table 33: Reviewer's Stroke Rates from NDA 21-437, Eplerenone in Hypertension

	Active Control	Coadmin	Mono-therapy	Placebo	Any E*	No E*
N	339	309	961	376	1270	715
PEY	69.6	44.9	182.5	78.9	227.4	148.5
Strokes=patients with strokes	2	2	7	0	9	2
Strokes/100 PEY	2.9	4.5	3.8	0.0	4.0	1.3

*E = eplerenone; PEY = patient exposure year

Note that the eplerenone program also had no strokes with placebo and that the stroke rates per 100 PEY for both eplerenone and active control (3-4) exceed those seen in the aliskiren development program (about 0.4 for aliskiren in both the controlled trials and the uncontrolled long-term safety study.) If anything these comparative data are more suggestive of a potential risk with eplerenone, but eplerenone was subsequently shown to have a mortality benefit in one population (MI patients with systolic dysfunction).

Similarly, the aliskiren stroke rates compare favorably to another recent submission: In the LIFE study of losartan vs. atenolol (with added HCTZ) in patients with left ventricular hypertrophy (LVH), the rates of patients suffering strokes were 1.2/100 PEY with losartan±HCTZ and 1.7/100 PEY with atenolol±HCTZ; the rates of stroke events were 1.4 and 2.0 respectively. Because the LIFE patients were selected for having one high risk factor (LVH),

it is not surprising that the stroke rate was higher in LIFE, but it is still reassuring that the stroke rate in the aliskiren development program is substantially lower.

I have also examined the stroke case reports for any characteristics (BP rebound, atrial fibrillation, etc.) suggesting a common etiology. There is evidence of lack of control in some of the patients, and location of the strokes in many patients (i.e., brainstem) suggests a hypertensive etiology. There is no pattern suggesting an action other than, if the patient's BP is not controlled, then other antihypertensives should be used.

While the strokes in patients under 50 remain concerning, there is no hard evidence that aliskiren produces a stroke rate higher than controls or higher than that seen in other antihypertensive drug development programs. The lack of evidence for a detrimental effect upon MI rates is also reassuring that aliskiren does not have some pro-thrombotic effect. There are several on-going studies that will provide further data regarding the effects of aliskiren upon stroke. I do not believe that the evidence regarding stroke is suspicious enough to withhold approval at this time, and I believe the on-going studies will be sufficient to confirm or refute whether additional studies are needed.

7.1.2.2 Seizures

There is one other neurological SAE that occurred rarely but is worthy of comment: seizures. Two seizures were reported in aliskiren cases that were not explained by a history of epilepsy or a detectable concurrent cause. (There was also one "epileptic fit" in an aliskiren patient with a history of epilepsy who was continued on aliskiren post-seizure without further reports of seizures.) Brief narratives for these cases are the following:

1. A 74-year-old white male in the aliskiren 150 mg group of Study 2302 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 and no concomitant medications. A CAT scan five days later and an EEG 22 days later were normal.
2. A 69-year-old white male in the aliskiren group of Study 2327 suffered a sudden loss of consciousness with tonic-clonic "cramps" on day 3. He was hospitalized with a diagnosis of grand mal. BP was 147/81. His past medical history included only hypertension and hyperuricemia treated with allopurinol. Imaging studies and EEG were not mentioned in the initial report provided. The investigator attributed the seizure to study drug because he could not identify any other contributing factors.

COMMENT: These two cases are remarkable because the investigators did not identify any contributing factors. While only two cases, I can not rule out a contribution of aliskiren to the seizures. In the preclinical studies, convulsions were seen in one male rat given 2 gm by gavage for an in vivo micronucleus assay.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Adverse events leading to study drug discontinuation were uncommon, occurring in about 3% of both aliskiren and control groups. In the placebo-controlled trials discontinuations (including ones for uncontrolled hypertension) were more frequent with placebo (2.4%) than in the aliskiren arms (2%).

7.1.3.2 Adverse events associated with dropouts

Types of AEs causing dropouts were varied and not distinguished by substantial rate differences among treatment groups with the exception of headaches: Discontinuation for headache was uncommon but more frequent for placebo (about 1%) than for aliskiren groups (about 0.3%).

7.1.3.2.1 *Angioedema*

While the more frequent causes for discontinuation were not distinguishing, some of the rare causes for discontinuation are of clinical interest. One of the rare but potentially life-threatening AEs associated with other drugs that inhibit the renin-angiotensin system is angioedema. Angioedema was observed in a few aliskiren-treated patients. The following are brief narratives of the aliskiren angioedema cases:

1. A 53-year-old white female in the aliskiren/valsartan 300/320 mg group of Study 2203 developed ankle and periorbital edema and weight gain (2.6 kg) on day 5. She was discontinued on day 8. She had a prior history of angioedema.
2. A 61-year-old diabetic white male in the aliskiren 75 mg group of Study 2204 developed feet and hands edema and dyspnea on about day 9. On day 36 he was also noted to have eyelid edema. At about day 49 aliskiren was discontinued and furosemide given with slight improvement. Other medications included gliclazide and pioglitazone. BP appears to have been poorly controlled, i.e., about 173/101 at baseline and 169/109 at day 51. The investigator confirmed that there was no evidence of heart failure at baseline and suspected angioedema.
3. A 46-year-old white female in the aliskiren 150 mg group of Study 2302 was titrated to aliskiren 300 mg/HCTZ 25 mg. After being on open-label study medication for 372 days, this patient 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. Other medications included HCTZ, citalopram, tramadol, and paracetamol.
4. A 57-year-old white female in the aliskiren 150 mg arm of Study 2306 developed swelling of the lips and tongue, dyspnea and throat tightness on day 23. She was diagnosed with angioedema, prednisolone was started, and she was advised to stop study

drug. By day 28 she was feeling better, prednisolone was discontinued, and study drug restarted. She re-experienced her symptoms on day 34 and study drug was discontinued. She started perindopril without recurrence of symptoms.

The rate of the angioedema cases in the completed studies (the first three cases above) was 0.4 per thousand. The rate per 100 person exposure years (PEYs) was 0.1.

One patient in the valsartan 160 mg group of Study 2203 also developed angioedema. This 27-year-old white female presented with moderate facial edema on day 28 “without any complication.” Drug was discontinued and the edema resolved in about a week without additional therapy. This patient had a history of a similar episode with an ACE inhibitor.

There were 29 other cases of edema involving the face, hands, or whole body with aliskiren. Of these three cases (starting on days 2, 6, and 55) on aliskiren 150 or 300 mg were severe enough that the patient was discontinued. Another aliskiren patient discontinued on day 17 because of an allergic skin reaction of the face (no other details known).

COMMENT: Aliskiren appears to be associated with angioedema. The rate is low, but the rate of 0.4 cases per 1000 calculated above is likely an underestimate: About double this rate of patients discontinued because of upper body edema. The rate appears to be comparable to that seen with ACE inhibitors.

7.1.3.2.2 Rhabdomyolysis/myositis

Another rare but potentially serious AE that now appears in the labels for angiotensin receptor blockers is rhabdomyolysis. The following are brief narratives for patients treated with aliskiren who developed CK rises or AEs of possible rhabdomyolysis or myositis.

1. A 50-year-old Asian male in the aliskiren group of Study 2307 developed “subclinical rhabdomyolysis” on day 57 (at the end of the study). Creatine kinase (CK) at baseline was 114 and at end of study 384 (ULN 232) with creatinine stable (105-114, ULN 106).
2. A 32-year-old black male in the aliskiren 150 mg group of Study 2203 developed CK rises associated with other symptoms: He had a baseline CK level of 230 U/L (ULN 308) 25 prior to randomization. Three days later, he complained of severe fatigue. On 12-Jun-2004, fifteen days later, the patient’s severity of fatigue changed to mild and, in addition, the patient complained of muscle tenderness in both quadriceps. In the interim he also complained of a sore throat, sinus congestion and back ache. On day 2 he was noted to have an elevated CK level of 493 U/L. On day 5 he developed a sore throat and swollen glands that lasted three days. The muscle tenderness resolved on day 34 but the fatigue continued. Study drug was stopped on day 45 and a CK level obtained on day 46 was > 4X ULN (1275 U/L). The patient was discontinued from the study that day due to the abnormal laboratory result. Fatigue remained ongoing. A repeat CK lab drawn two weeks after discontinuing study drug was 3633 U/L. A subsequent CK level was normal (262 U/L). Concomitant medication taken during the study included Benadryl, multivitamin and potassium.

3. A 38-year-old Asian male in the aliskiren 150/HCTZ 25 mg group of Study 2204 had AEs reported of chronic hepatitis and myositis on day 8 but continued to finish the study. His screening CK was 227, but it was 5841 on day 1, 281 on day 8, and 915 on day 57; his ALTs ranged between 34 and 53 and creatinines 89-100 µmol/L throughout the study.
4. A 48-year-old white female in Study 2302 discontinued on day 189 because of an elevated CK (CK 408 with ALT 34). No other details are provided.
5. A 55-year-old white male in Study 2302 developed a CK of 659 and ALT of 56-62 and discontinued. No other details are provided.

A 59-year-old Asian male in the ramipril 10 mg group in Study 2307 had “suspected myositis” at the final study visit on day 58. His CK was 463 (2X ULN) as compared to 210 at baseline. No other details are provided.

COMMENT: While rare, these events suggest that rhabdomyolysis may occur with aliskiren as has been noted for angiotensin receptor blockers (ARBs) in post-marketing reports. The reported cases were not severe and were not associated with renal dysfunction, so that any threat from rhabdomyolysis with aliskiren should be minimal. It does appear relevant that the events in the aliskiren program, including the one in a ramipril group, occurred predominantly in Asians. Many of the post-marketing reports of rhabdomyolysis with ARBs were Japanese. So this AE appears most relevant to the Asian U.S. population.

7.1.3.3 Other significant adverse events

7.1.3.3.1 Gastrointestinal AEs

The dose-limiting toxicity for aliskiren in humans is gastrointestinal (GI) toxicity. The propensity of aliskiren for producing GI adverse effects at higher dosages was shown in Study CRD16, “Aliskiren - A Phase I, Double -Blind, Placebo-Controlled, Ascending Multiple Oral Dose, Safety, Tolerability and Pharmacokinetic Study in Healthy Male Subjects”. In that study doses of 850, 1200, and 1800 mg were given fasting to cohorts of six healthy male subjects as a single dose and then for eight days. GI AEs were frequent and dose-related as shown in Table 34.

Table 34: Subjects with GI Adverse Events in Study CRD016

Adverse event	Aliskiren dose			
	0	850	1200	1800
Diarrhea	0%	0%	50%	67%
Loose stools	0%	0%	17%	50%
Abdominal pain upper	0%	33%	50%	33%
Abdominal pain NOS	0%	17%	33%	50%
Abdominal pain lower	0%	17%	0%	0%
Nausea	0%	33%	33%	50%

Aliskiren also produces GI toxicity at lower doses. The rates of various GI AEs in the aliskiren monotherapy arms compared to placebo are shown in Table 35.

Table 35: Reviewer's GI AEs in the Aliskiren Monotherapy Arms

Dose	Diarrhea		Colitis		Abdominal pain		Dyspepsia		GE reflux*	
	% pts	/100 PEY	% pts	/100 PEY	% pts	/100 PEY	% pts	/100 PEY	% pts	/100 PEY
0	1.3%	9.1	0.0%	0.0	1.7%	11.8	1.7%	11.8	0.1%	0.9
75	1.1%	7.3	0.2%	1.2	1.6%	11.0	1.1%	7.3	0.2%	1.2
150	1.4%	9.5	0.0%	0.0	1.6%	11.1	1.9%	12.7	0.6%	4.0
300	2.2%	16.1	0.2%	1.8	2.2%	16.1	1.7%	12.5	0.2%	1.8
600	10.1%	68.9	0.0%	0.0	2.7%	18.4	2.7%	18.4	0.3%	2.3
Any	2.6%	12.8	0.1%	0.6	2.2%	10.5	2.1%	10.1	0.4%	2.0

*GE reflux = gastroesophageal reflux

If any aliskiren use (including use in combination) is compared to no aliskiren use (including active controls), there were higher rates of colitis with aliskiren use (0.3% vs. 0.07%, 0.9/100 PEY vs. 0.3/100 PEY).

Discontinuations for diarrhea alone were rare, occurring in two placebo and five aliskiren patients (about 0.06-0.07%). In addition one patient in an aliskiren 150/HCTZ 6.25 arm discontinued for colitis (diffuse inflammatory bowel disease.) on day 29.

The median start day for diarrhea in the aliskiren arms was day 31 (with wide variation among the doses) vs. day 18 in the placebo arm; median start day was day 12 in the 600 mg group. Colitis occurred later (median start day about day 85 in the aliskiren monotherapy arms, day 46 for all aliskiren use. Median start time for abdominal pain was similar in aliskiren monotherapy and placebo groups (about day 41).

Diarrhea rates in the aliskiren monotherapy arms by demographic subgroups are shown in Table 36.

Table 36: Reviewer's Percent of Patients with Diarrhea AEs in the Aliskiren Monotherapy Arms by Demographic Subgroups

Demographic subgroup	Aliskiren dose				
	0	75	150	300	600
male	1.3%	1.2%	1.0%	2.0%	9.0%
female	1.3%	0.8%	2.0%	2.4%	11.5%
age<65	1.4%	1.1%	1.1%	2.3%	9.5%
age≥65	0.7%	1.0%	2.2%	2.0%	13.2%
white	1.0%	0.5%	1.0%	1.9%	10.3%
black	2.9%	5.3%	3.2%	1.8%	7.0%
Asian	2.0%	0.8%	1.9%	3.9%	9.7%

The descriptions of the diarrhea AEs (and other AEs) on the case report forms were brief, e.g., "diarrhea", or "loose stools". In response to an FDA query the sponsor asked investigators to complete a more detailed diarrhea description form. The sponsor's summary of the diarrhea descriptions from these forms is the following:

"Review of the cases suggested three syndromes described as diarrhea. The first and most common was a very brief (1 to several days) self-limited episode of loose and/or watery frequent stools without blood or mucous. This was sometimes attributed to gastroenteritis or food poisoning and similar syndromes were sometimes described in family members or guests at an event. The second was better described as a change in bowel habits toward looser stools and was again described as mild. This was in some cases longer lasting. A third and much less common syndrome was a bowel movement 1 to 2-3 hours after taking the pill."

Five of the aliskiren diarrhea cases had colonoscopies performed for which the reports were obtained. The sponsor's summary of these cases is shown in Table 37.

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Table 37: Sponsor's Colonoscopy Results for Aliskiren Diarrhea Cases

Study No.-Center No.- Patient ID	Treatment	Start Date/ End Date of Treatment	Start Date/ End date of Diarrhea	Colonoscopy Date	Biopsy Report Date	Results
*SPP100A2204-0222-00004	aliskiren 300 mg	21-Dec-2004/ 17-Feb-2005	04-Feb-2005/ continuing at the time of the last study visit	—	12-Apr-2005	stenosing tumor surrounded by extensive granulating inflammation; mucous adenocarcinoma
*SPP100A2307-0087-00002	aliskiren/tramipol 300/ 10mg	27-Feb-2005/ 24-Apr-2005	30-Mar-2005/ 08-Apr-2005	—	—	erosive gastritis without gastric ulcer; some diverticulum in sigmoid with focal mild hemorrhagic areas in the right colon and much more in sigmoid; patient on chronic ASA
SPP100A2204-0509-00014	aliskiren/HCTZ 75/25mg	23-Mar-2005/ 16-May-2005	31-Mar-2005/ 01-Apr-2005	—	—	sigmoid diverticulosis and polyp, internal hemorrhoids diffuse diverticulosis; grade II-III internal hemorrhoids
SPP100A2302-0227-00006	aliskiren 300mg	22-Sep-2004/ 14-Sep-2005	23-Jan-2005/ 06-Feb-2005 02-Jul-2005/ 03-Sep-2005	— (extirpation of the polyp)	2-Sep-2005 19-Oct-2005	polyp & diverticulum; adenomatous polyp hyperplastic colonic polyp; no atypical cells
SPP100A2302-0552-00010	aliskiren 300mg	30-Sep-2004/ 25-Sep-2005	01-Oct-2004/ 02-Oct-2004	—	—	normal

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COMMENT: GI toxicity with aliskiren appears to be dose-related. What the lower threshold is for GI toxicity is not absolutely clear: By percentages of patients affected even the 150 mg dose may exceed placebo, while by rates per 100 PEY greater GI toxicity is apparent only for the 600 mg dosage. In some demographic subgroups (women, the elderly) diarrhea rates appear increased at the 150 mg dose. While, as the sponsor notes, diarrhea was typically mild and rarely led to discontinuation, there is one important question that can not be answered in the development program: Do the aliskiren GI effects have any worrisome long term sequelae such as cancer? Aliskiren causes colonic hyperplasia with chronic administration in rats. This adverse effect has been attributed to a local irritant effect of aliskiren in the gut with high doses in rats and considered to be not relevant to humans. Conversely, marmosets also develop diarrhea (and vomiting) at high oral doses but do not show GI histopathologic changes. However, the above results document that aliskiren causes increased rates of diarrhea in humans at dosages including the proposed to be marketed dosage; the etiology of the diarrhea is unknown. The few colonoscopies reported in the trials are not revealing. The sponsor is

currently conducting a colonic biopsy study in humans. This study should be helpful in providing information to answer this important question.

7.1.3.3.2 Cancer

In the aliskiren monotherapy arms four cancers were reported, one breast cancer in a 600 mg group and one colon cancer and one prostatic cancer in aliskiren 300 mg groups, and another colon cancer in an aliskiren 75 mg group, vs. no cancers in the placebo groups. If any vs. no aliskiren use is compared, then the rates of patients with cancer were similar between aliskiren (0.23%) and no aliskiren (0.19%) and the rates per 100 PEY were lower in the aliskiren groups (about 0.5/100 PEY) than in the no aliskiren groups (about 1.2/100 PEY). GI cancers were reported in five aliskiren patients as described in Table 38.

Table 38: Reviewer's GI Cancers in the Aliskiren Arms

Study	Demographics	Dose	Cancer	Start day
2204	69WM	300	Colon	59
2324	71WF	75	Colon	56
—	59AM	75	Rectal	75
—	54AM	75	Rectal	330
2302	62WF	150	Ileal stromal tumor	341

For comparison, colon cancer was also reported at 57 days in a HCTZ 25 mg patient in Study 2204, a gastric cancer at 10 days in a blinded HCTZ/placebo patient in Study 2323, and a descending colon tumor at 83 days in a HCTZ patient in Study 2323.

COMMENT: It is difficult to envision an etiologic mechanism for truly increased cancer rates in the short-term aliskiren monotherapy studies. The most logical explanation for the three cancers discovered after short-term treatment with aliskiren, besides chance, is that the GI AEs associated with aliskiren use lead to increased rates of GI procedures such as colonoscopy. The rectal cancer detected at day 330 and the ileal stromal tumor at day 341 are more concerning. However, the exposure in this development program, even though large compared to other antihypertensive programs, is insufficient to answer the question of whether long-term use of aliskiren could lead to increased rates of GI cancers.

7.1.3.3.3 Cough

If cough rates are compared in the aliskiren monotherapy arms, then there appears to be slighter higher rates of cough with aliskiren than with placebo except for the aliskiren 600 mg groups (for which exposure was low) as shown in Table 39.

Table 39: Reviewer's Cough AEs in the Aliskiren Monotherapy Arms

Dose	Cough	
	% pts	/100 PEY
0	0.6%	4.6
75	0.9%	6.1
150	1.5%	10.3
300	1.1%	8.4

Dose	Cough	
	% pts	/100 PEY
600	0.3%	2.3
Any	1.3%	6.2

Discontinuations for cough were rare, i.e., among the aliskiren monotherapy arms only one patient in an aliskiren 300 mg group discontinued for cough, and three other subjects in other aliskiren arms discontinued for cough.

In the three studies directly comparing aliskiren to an ACEI (2307 against ramipril and 2303 and 2324 against lisinopril), rates of cough with aliskiren were lower than with the ACEI as shown in Table 40. Three patients on an ACEI (0.7%) and one aliskiren patient (0.15%) discontinued due to cough.

Table 40: Reviewer's Patients with Cough AEs in the Studies with ACEI Arms

Study	Aliskiren	ACEI	Aliskiren+ ACEI
2303	0.8%	1.7%	
2307	2.1%	4.7%	1.8%
2324	0.7%	2.3%	
All	1.3%	3.8%	1.8%

COMMENT: Aliskiren appears to be associated with a slightly higher rate of cough than placebo but lower than that seen with ACEI. Whether aliskiren actually moderates the rate of ACEI-induced cough when used in combination with an ACEI needs confirmation in an independent study.

7.1.3.3.4 Hyperkalemia and renal dysfunction

While aliskiren use leads to a small increase in mean potassium levels, overt hyperkalemia AEs were rare: three cases with aliskiren (all in 300 mg groups) vs. one with placebo. Abnormalities in potassium and renal function detected by the lab screenings were more frequent but still uncommon as shown in Table 41.

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Table 41: Sponsor's Selected Abnormal Lab Values for Potassium and Renal Function in the Placebo-controlled Studies

Parameter	Placebo	Ali 75mg	Ali 150mg	Ali 300mg	Ali 600mg	Mono	AI/ARB	AI/HCTZ	AI/AI	ARB	HCTZ	ARB/ HCTZ
	N= 781 Total n (%)	N= 478 Total n (%)	N= 774 Total n (%)	N= 768 Total n (%)	N= 296 Total n (%)	N=2316 Total n (%)	N= 178 Total n (%)	N=1484 Total n (%)	N=3958 Total n (%)	N= 311 Total n (%)	N= 555 Total n (%)	N= 59 Total n (%)
Potassium (mmol/L)												
> 5.5	702 4 (0.6)	430 3 (0.7)	703 5 (0.7)	702 7 (1.0)	282 0 (0.0)	2117 15 (0.7)	164 2 (1.2)	1171 6 (0.5)	3452 23 (0.7)	289 0 (0.0)	445 4 (0.9)	54 0 (0.0)
< 3.5	702 23 (3.3)	430 2 (0.5)	703 9 (1.3)	702 7 (1.0)	282 6 (2.1)	2117 24 (1.1)	164 1 (0.6)	1171 21 (1.8)	3452 46 (1.3)	289 3 (1.0)	445 14 (3.1)	54 0 (0.0)
BUN (mmol/L)												
> 14.28	753 0 (0.0)	468 0 (0.0)	754 0 (0.0)	754 1 (0.1)	286 0 (0.0)	2262 1 (0.0)	173 0 (0.0)	1437 0 (0.0)	3872 1 (0.0)	301 0 (0.0)	549 0 (0.0)	58 0 (0.0)
Creatinine (umol/L)												
> 176.8	753 0 (0.0)	468 1 (0.2)	754 0 (0.0)	754 1 (0.1)	286 0 (0.0)	2262 2 (0.1)	173 0 (0.0)	1437 0 (0.0)	3872 2 (0.1)	301 0 (0.0)	549 0 (0.0)	58 0 (0.0)

Total=number of patients with lab measurement, n=number of patients meeting the criteria, %=(n/Total)*100

The sponsor notes that in combination with an ARB the incidence of hyperkalemia was slightly higher (1.2%) than monotherapy, and in combination with an ACEI in a diabetic population the rate was 5.5%, compared to 2.6% for therapy with ramipril alone.

COMMENT: Overall hyperkalemia and renal dysfunction do not appear to be clinically significant problems for aliskiren. The exception, as the sponsor notes, is combination therapy with ACEIs particularly in diabetics. A similar concern, in diabetics with renal dysfunction, was noted for the aldosterone antagonist eplerenone.

7.1.3.3.5 Anemia

As noted by the sponsor, mean decreases in hemoglobin and hematocrit of approximately 0.08 g/dl and 0.16 volume percent, respectively, were observed in aliskiren-treated patients. The rates of anemia AEs in the aliskiren monotherapy arms are shown in Table 42.

Table 42: Reviewer's Anemia AEs in the Aliskiren Monotherapy Arms

Dose	Anemia	
	% pts	/100 PEY
0	0.0%	0.0
75	0.2%	1.2
150	0.0%	0.0
300	0.2%	1.2
600	0.3%	2.3
Any	0.1%	0.6

COMMENT: Similar reductions in hemoglobin and hematocrit are seen with ACEI and ARB use and are noted in their labels. The reductions are said to be "rarely of clinical significance". The larger development programs, such as this for aliskiren and the large LIFE study with losartan, suggest that the slight mean reductions may have more clinical relevance than the minimizations in labels suggest.

7.1.3.3.6 Hyperuricemia, gout, and renal stones

Aliskiren monotherapy produced small median increases in serum uric acid levels (about 6 $\mu\text{mol/L}$) while HCTZ produced larger increases (about 30 $\mu\text{mol/L}$). The combination of aliskiren with HCTZ appears to be additive (about a 40 $\mu\text{mol/L}$ increase). The increases in uric acid do appear to lead to slight increases in uric acid related AEs (gout, renal stones) as shown in Table 43.

Table 43: Reviewer's Uric Acid Related AEs in the Aliskiren Monotherapy Arms

Dose	Elevated uric acid		Gout		Renal stone	
	% pts	/100 PEY	% pts	/100 PEY	% pts	/100 PEY
0	0.1%	0.9	0.1%	0.9	0.0%	0.0
75	1.1%	7.3	0.0%	0.0	0.4%	2.4
150	0.2%	1.6	0.1%	0.8	0.1%	0.8
300	0.4%	3.0	0.2%	1.8	0.3%	2.4
600	0.0%	0.0	0.3%	2.3	0.0%	0.0
Any	0.4%	2.0	0.2%	0.8	0.2%	1.2

While HCTZ leads to greater median increases in uric acid levels than aliskiren, HCTZ had few elevated uric acid AEs (0.08%) and similar rates for gout (0.2%) and renal stones (0.3%) AEs.

COMMENT: Aliskiren raises serum uric acid levels slightly and this increase does appear to lead to slight increases in gout and renal stone rates. The effects are similar to those seen with HCTZ. There is a suggestion of a dose-response for gout but not for renal stones or elevated uric acid.

7.1.3.3.7 Rash

Aliskiren is associated with an increased rate of rashes, but not urticaria, as shown in Table 44.

Table 44: Reviewer's Rash and Urticaria AEs in the Aliskiren Monotherapy Arms

Dose	Rash		Urticaria	
	% pts	/100 PEY	% pts	/100 PEY
0	0.3%	1.8	0.3%	1.8
75	0.5%	3.7	0.2%	1.2
150	1.2%	7.9	0.3%	1.3
300	0.9%	6.6	0.2%	0.9
600	1.7%	11.5	0.0%	0.0
Any	1.0%	4.8	0.2%	1.1

The descriptions of the rashes are short and varied and I could not characterize a typical aliskiren rash from the descriptions on the CRFs. Rash was reported as resulting in aliskiren discontinuation for 15 cases (vs. one for lisinopril).

COMMENT: Aliskiren is associated with increased rate of rash.

7.1.4 Other Search Strategies

I did not employ any other search strategies.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

I scrutinized the SAEs and AE discontinuations in the individual study reports. For any unusual events (e.g., grand mal seizure without an explanatory cause) or repetitive AEs (e.g., strokes), I recoded the events based on the investigator's verbatim text for the event as well as the sponsor's encoding in the SAS AE data sets. I used my recodings for the AE analyses above.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The sponsor encoded the AEs using MedDRA. I recoded the unusual events and repetitive AEs from the investigator's verbatim text and checked my recodings against the sponsor's. I did not find any blatant problems with the sponsor's encoding. I did encounter the usual problem of events that should be lumped in analyses coded to multiple MedDRA preferred terms (e.g., what I reference as stroke is encoded by six different MedDRA preferred terms: Brain stem ischaemia, Cerebral haemorrhage, Cerebral infarction, Cerebrovascular accident, Monoparesis, and Stroke).

7.1.5.3 Incidence of common adverse events

For common adverse events the sponsor tabulated event rates in the placebo-controlled studies, Studies 1201, 2201, 2203, 2204, and 2308. This approach for estimating the incidence of common adverse events is preferred. (The sponsor also tabulated event rates for all-controlled studies and for the long term safety study.)

7.1.5.4 Common adverse event tables

The sponsor tabulated rates of common adverse events in Table 45.

Table 45: Sponsor's AEs $\geq 2\%$ in Any Group in the Placebo-Controlled Studies

	Placebo N= 781 n (%)	Ali 75mg N= 478 n (%)	Ali 150mg N= 774 n (%)	Ali 300mg N= 768 n (%)	Ali 600mg N= 296 n (%)	Mono Ali N=2316 n (%)	Ali/ARB N= 178 n (%)	Ali/ HCTZ N=1464 n (%)	Ali All N=3958 n (%)	ARB N= 311 n (%)	HCTZ N= 555 n (%)	ARB/ HCTZ N= 59 n (%)
Any Adverse Event	314 (40.2)	193 (40.4)	290 (37.5)	309 (40.2)	130 (43.9)	922 (39.8)	54 (30.3)	591 (40.4)	1567 (39.6)	104 (33.4)	226 (40.7)	13 (22.0)
Preferred term												
Headache	68 (8.7)	31 (6.5)	42 (5.4)	44 (5.7)	15 (5.1)	132 (5.7)	9 (5.1)	98 (6.7)	239 (6.0)	13 (4.2)	39 (7.0)	0 (0.0)
Nasopharyngitis	45 (5.8)	34 (7.1)	33 (4.3)	29 (3.8)	5 (1.7)	101 (4.4)	4 (2.2)	56 (3.8)	161 (4.1)	3 (1.0)	21 (3.8)	0 (0.0)
Diarrhoea	9 (1.2)	6 (1.3)	9 (1.2)	18 (2.3)	28 (9.5)	61 (2.6)	6 (3.4)	24 (1.6)	91 (2.3)	5 (1.6)	11 (2.0)	0 (0.0)
Dizziness	17 (2.2)	6 (1.3)	9 (1.2)	19 (2.5)	8 (2.7)	42 (1.8)	2 (1.1)	35 (2.4)	79 (2.0)	7 (2.3)	13 (2.3)	0 (0.0)
Fatigue	12 (1.5)	11 (2.3)	5 (0.6)	13 (1.7)	7 (2.4)	36 (1.6)	8 (4.5)	13 (0.9)	57 (1.4)	6 (1.9)	6 (1.1)	0 (0.0)
Upper respiratory tract infection	12 (1.5)	4 (0.8)	7 (0.9)	13 (1.7)	7 (2.4)	31 (1.3)	1 (0.6)	16 (1.1)	48 (1.2)	2 (0.6)	4 (0.7)	0 (0.0)
Back pain	11 (1.4)	7 (1.5)	12 (1.6)	7 (0.9)	3 (1.0)	29 (1.3)	4 (2.2)	21 (1.4)	54 (1.4)	10 (3.2)	6 (1.1)	1 (1.7)
Oedema peripheral	5 (0.6)	5 (1.0)	6 (0.8)	7 (0.9)	6 (2.0)	24 (1.0)	1 (0.6)	13 (0.9)	38 (1.0)	5 (1.6)	6 (1.1)	0 (0.0)
Constipation	5 (0.6)	5 (1.0)	1 (0.1)	5 (0.7)	6 (2.0)	17 (0.7)	0 (0.0)	12 (0.8)	29 (0.7)	0 (0.0)	3 (0.5)	0 (0.0)
Influenza	5 (0.6)	1 (0.2)	9 (1.2)	5 (0.7)	2 (0.7)	17 (0.7)	0 (0.0)	33 (2.3)	50 (1.3)	0 (0.0)	6 (1.1)	0 (0.0)

Studies included: [Study 1201], [Study 2201], [Study 2203], [Study 2204] and [Study 2308]

COMMENT: Most of these AEs are incidental findings common in the study populations and the general population and unrelated to study drug. The significant exception is diarrhea, discussed in Section 7.1.3.3.1.

7.1.5.5 Identifying common and drug-related adverse events

The AEs that appear to be drug-related are discussed in Sections 7.1.2.2, 7.1.3.2, and 7.1.3.3.

7.1.5.6 Additional analyses and explorations

Additional analyses of AEs are presented in Sections 7.1.2, 7.1.3.2, and 7.1.3.3.

7.1.6 Less Common Adverse Events

Analyses of less common AEs are presented in Sections 7.1.2, 7.1.3.2, and 7.1.3.3.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

The development program included typical safety lab testing (chemistry, hematology, and urinalysis) at baseline and end of study. In addition, because aliskiren affects the renin-angiotensin system, additional testing for renal function and potassium levels was done. Some studies also incorporated special testing for renin-angiotensin system parameters, e.g., renin, angiotensin 2 levels.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

The sponsor analyzed changes in lab values for the placebo-controlled and for all controlled studies. These sets of studies are reasonable to analyze for lab value changes.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

Lab tests that showed changes in measures of central tendency in the aliskiren groups were hemoglobin (decreases, with corresponding decreases in hematocrit and RBC), creatinine and urea (increases), potassium (increases), and uric acid (increases). The changes from baseline in the placebo-controlled studies in hemoglobin are shown in Table 46, in creatinine in Table 47, in urea in Table 48, in potassium in Table 49, and in uric acid in Table 50. Patterns of changes in all controlled trials were similar to those seen in the placebo-controlled trials.

Table 46: Sponsor's Changes from Baseline in Hemoglobin (g/L) in the Placebo-controlled Studies

Treatment	n	Baseline			Endpoint			Post baseline Change from baseline		
		Mean	SD	Median	Mean	SD	Median	Mean	SD	Median
Placebo (N=781)	738	144.7	13.43	145.0	145.9	13.24	146.0	1.2	6.75	1.0
Ali 75mg (N=478)	459	145.3	12.91	146.0	145.1	12.98	145.0	-0.2	5.96	0.0
Ali 150mg (N=774)	742	145.6	12.33	146.0	145.4	12.64	146.0	-0.1	6.39	0.0
Ali 300mg (N=768)	736	145.5	13.47	146.0	144.3	13.45	145.0	-1.2	6.35	-1.0
Ali 600mg (N=296)	284	144.4	14.01	144.5	142.0	13.33	142.0	-2.4	6.82	-3.0
Mono Ali (N=2216)	2221	145.4	13.21	146.0	144.6	13.11	145.0	-0.8	6.55	-1.0
Ali/ARB (N=175)	166	143.9	12.15	145.0	142.0	12.54	143.0	-1.9	7.47	-2.0
Ali/HCTZ (N=1464)	1422	145.2	13.50	145.5	144.8	13.21	145.0	-0.4	6.88	-1.0
All Ali (N=3953)	3809	145.2	13.28	146.0	144.5	13.13	145.0	-0.7	6.75	-1.0
ARB (N=311)	292	142.2	13.02	141.0	140.8	11.73	140.0	-1.4	6.56	-2.0
HCTZ (N=555)	540	144.9	14.26	146.0	145.6	14.65	146.0	0.7	7.39	1.0
ARB/HCTZ (N=59)	57	146.8	10.80	146.0	144.4	10.54	144.0	-2.4	6.26	-3.0

Table 47: Sponsor's Changes from Baseline in Serum Creatinine ($\mu\text{mol/L}$) in the Placebo-controlled Studies

Treatment	n	Baseline			Endpoint			Post baseline Change from baseline		
		Mean	SD	Median	Mean	SD	Median	Mean	SD	Median
Placebo (N=781)	753	77.75	15.287	78.70	78.38	15.488	79.00	0.62	8.101	0.00
Ali 75mg (N=478)	468	76.16	16.262	75.05	76.71	17.124	76.00	0.56	8.539	0.00
Ali 150mg (N=774)	754	78.59	16.160	79.56	79.67	16.199	79.60	1.09	8.062	0.00
Ali 300mg (N=768)	754	77.14	16.646	77.00	78.38	17.090	78.35	1.23	8.025	0.00
Ali 600mg (N=296)	286	79.85	15.102	79.56	80.75	15.527	79.60	0.89	8.243	0.00
Mono Ali (N=2316)	2262	77.76	16.250	78.00	78.76	16.656	79.56	1.00	8.172	0.00
Ali/ARB (N=178)	172	79.01	16.526	78.00	79.46	15.821	79.00	0.46	8.647	0.00
Ali/HCTZ (N=1464)	1437	78.90	16.484	78.70	81.32	16.992	79.60	2.42	9.575	1.70
All Ali (N=2958)	2872	78.24	16.355	78.70	79.74	16.786	79.60	1.50	8.775	0.00
ARB (N=311)	301	79.70	16.599	79.56	80.86	16.919	79.56	1.16	9.009	0.00
HCTZ (N=555)	549	77.94	15.455	77.80	79.73	16.214	79.60	1.79	8.347	0.80
ARB/HCTZ (N=59)	58	79.19	14.927	78.00	82.74	16.226	81.50	2.55	8.321	2.50

Table 48: Sponsor's Changes from Baseline in Blood Urea Nitrogen (mmol/L) in the Placebo-controlled Studies

Treatment	n	Baseline			Endpoint			Post baseline Change from baseline		
		Mean	SD	Median	Mean	SD	Median	Mean	SD	Median
Placebo (N=781)	753	5.09	1.576	5.00	5.12	1.602	5.00	0.02	1.127	0.00
Ali 75mg (N=478)	468	5.32	1.489	5.00	5.42	1.402	5.40	0.11	1.165	0.10
Ali 150mg (N=774)	754	5.05	1.639	5.00	5.17	1.692	5.00	0.12	1.211	0.00
Ali 300mg (N=768)	754	5.03	1.713	5.00	5.26	1.785	5.20	0.18	1.246	0.10
Ali 600mg (N=296)	286	4.44	1.618	4.60	4.61	1.699	4.60	0.17	0.999	0.17
Mono Ali (N=2316)	2262	5.04	1.651	5.00	5.18	1.686	5.10	0.14	1.189	0.10
Ali/ARB (N=178)	172	5.76	1.561	5.70	5.36	1.689	5.70	0.10	1.294	0.10
Ali/HCTZ (N=1464)	1437	5.44	1.322	5.30	5.91	1.547	5.70	0.46	1.258	0.40
All Ali (N=2958)	2872	5.22	1.570	5.20	5.48	1.674	5.40	0.27	1.235	0.30
ARB (N=311)	301	4.72	1.905	4.70	4.90	1.942	5.00	0.18	1.119	0.17
HCTZ (N=555)	549	5.42	1.344	5.30	5.79	1.490	5.70	0.37	1.210	0.40
ARB/HCTZ (N=59)	58	5.15	1.251	5.10	6.16	1.587	6.15	0.98	1.301	1.00

Table 49: Sponsor's Changes from Baseline in Potassium (mmol/L) in the Placebo-controlled Studies

Treatment	n	Baseline			Endpoint			Post baseline Change from baseline		
		Mean	SD	Median	Mean	SD	Median	Mean	SD	Median
Placebo (N=781)	702	4.22	0.416	4.30	4.26	0.397	4.20	-0.02	0.294	0.00
Ali 75mg (N=478)	430	4.34	0.377	4.30	4.33	0.369	4.40	0.04	0.275	0.10
Ali 150mg (N=774)	703	4.28	0.390	4.20	4.32	0.399	4.30	0.04	0.290	0.00
Ali 300mg (N=768)	702	4.22	0.393	4.20	4.32	0.382	4.20	0.05	0.270	0.00
Ali 600mg (N=296)	282	4.23	0.391	4.20	4.29	0.390	4.20	0.05	0.299	0.10
Mono Ali (N=2316)	2117	4.22	0.389	4.30	4.32	0.387	4.20	0.05	0.282	0.00
Ali/ARB (N=178)	164	4.30	0.379	4.20	4.37	0.251	4.30	0.06	0.279	0.10
Ali/HCTZ (N=1464)	1171	4.35	0.391	4.40	4.28	0.392	4.30	-0.10	0.401	-0.10
All Ali (N=2958)	2452	4.32	0.392	4.30	4.31	0.399	4.30	-0.00	0.294	0.00
ARB (N=311)	289	4.27	0.339	4.30	4.29	0.355	4.20	0.01	0.272	0.00
HCTZ (N=555)	445	4.37	0.335	4.40	4.26	0.411	4.20	-0.12	0.380	-0.10
ARB/HCTZ (N=59)	54	4.22	0.322	4.20	4.22	0.399	4.20	-0.00	0.222	0.00

Table 50: Sponsor's Changes from Baseline in Serum Uric Acid (µmol/L) in the Placebo-controlled Studies

Treatment	n	Baseline			Endpoint			Post baseline Change from baseline		
		Mean	SD	Median	Mean	SD	Median	Mean	SD	Median
Placebo (N=781)	746	350.67	84.019	345.00	350.57	83.262	345.00	-0.10	48.726	0.00
Ali 75mg (N=478)	461	347.42	81.855	345.00	350.76	86.409	345.00	3.34	48.386	0.00
Ali 150mg (N=774)	748	350.32	82.189	345.00	357.58	87.741	350.00	7.26	47.032	6.00
Ali 300mg (N=768)	746	349.90	85.723	344.98	355.56	86.483	350.00	5.66	49.071	6.00
Ali 600mg (N=296)	286	351.64	88.941	340.00	355.65	79.044	350.47	4.01	47.609	5.97
Mono Ali (N=2216)	2241	349.75	84.147	345.00	355.26	85.960	350.00	5.51	48.062	6.00
Ali/ARB (N=178)	167	347.09	88.492	350.00	357.11	86.956	351.00	10.02	48.970	10.00
Ali/HCTZ (N=1464)	1424	325.32	81.611	330.00	372.14	91.024	270.00	36.81	54.434	40.00
All Ali (N=2958)	2822	344.27	83.672	340.00	361.61	88.268	356.90	17.34	52.729	17.90
ARB (N=311)	295	347.27	82.402	344.98	354.54	82.992	350.00	7.26	47.058	10.00
HCTZ (N=555)	541	325.51	85.905	330.00	362.24	94.217	360.00	27.73	57.169	30.00
ARB/HCTZ (N=59)	57	345.60	86.762	330.00	377.30	85.244	270.00	31.70	55.185	40.00

COMMENT: The mean and median changes for these lab values are small and similar to or less than those seen with other antihypertensives. However, some of the changes appear to have small but detectable clinical impacts upon the AE profile for aliskiren. Please see Section 7.1.3.3 for a discussion of the possible clinical impacts.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

The sponsor defined the criteria for notable laboratory values and for shift tables shown in Table 51.

Table 51: Sponsor's Criteria for Notable Laboratory Values

Laboratory Variables	Low	High
Hematology		
Hemoglobin	>20% decrease	>50% increase
Hematocrit	>20% decrease	>50% increase
RBC count	>20% decrease	>50% increase
WBC count	>50% decrease	>50% increase
Platelet count	>50% decrease	>75% increase
Biochemistry		
Sodium	>5% decrease	
Potassium	>20% decrease	>20% increase
Chloride	>10% decrease	>10% increase
Calcium	>10% decrease	>10% increase
Creatinine		>50% increase
BUN		>50% increase
Glucose	>50% decrease	>50% increase
SGOT (ALT)		>150% increase
SGPT (AST)		>150% increase
Alkaline phosphatase		>100% increase
Total bilirubin		>100% increase
Uric acid		>50% increase
CK		>300%

By these criteria there are only rare outliers or shifts from normal to abnormal values and no suggestive patterns of abnormalities in the aliskiren groups (HCTZ did show a greater frequency of hypokalemia). Because aliskiren inhibits the renin-angiotensin system, the sponsor also examined effects upon renal function and potassium closely. The most revealing analysis is shown in Table 52.

Table 52: Sponsor’s Rates of Potassium, BUN, and Creatinine Abnormal Values in the Controlled Studies

Parameter	Placebo N= 781 Total n (%)	Mono Ali N=2598 Total n (%)	Ali/ARB N= 178 Total n (%)	Ali/HCTZ N=1464 Total n (%)	Ali/CCB N= 187 Total n (%)	Ali/ACE N=277 Total n (%)	Ali/Ali N=4704 Total n (%)	ARB N=311 Total n (%)	HCTZ N=555 Total n (%)	CCB N= 357 Total n (%)	ACE N= 278 Total n (%)	ARB/HCTZ N= 59 Total n (%)
Potassium (mmol/L)												
> 5.5	702 4 (0.6)	2394 21 (0.9)	164 2 (1.2)	1171 8 (0.5)	166 0 (0.0)	273 15 (5.5)	4168 44 (1.1)	289 0 (0.0)	445 4 (0.9)	314 1 (0.3)	273 7 (2.6)	54 0 (0.0)
< 3.6	702 23 (3.3)	2394 20 (1.2)	164 1 (0.6)	1171 21 (1.8)	166 5 (3.0)	273 3 (1.1)	4168 59 (1.4)	289 3 (1.0)	445 14 (3.1)	314 21 (6.7)	273 7 (2.6)	54 0 (0.0)
BUN (mmol/L)												
> 14.28	753 0 (0.0)	2541 4 (0.2)	173 0 (0.0)	1437 0 (0.0)	166 0 (0.0)	273 1 (0.4)	4590 5 (0.1)	301 0 (0.0)	549 0 (0.0)	314 0 (0.0)	274 0 (0.0)	58 0 (0.0)
Creatinine (umol/L)												
> 178.8	753 0 (0.0)	2541 5 (0.2)	173 0 (0.0)	1437 0 (0.0)	166 0 (0.0)	273 1 (0.4)	4590 6 (0.1)	301 0 (0.0)	549 0 (0.0)	314 0 (0.0)	274 1 (0.4)	58 0 (0.0)

Total=number of patients with lab measurement, n=number of patients meeting the criteria, %=(n/Total)*100
 Studies included: [Study 1201], [Study 2201], [Study 2203], [Study 2204], [Study 2308], [Study 2305] and [Study 2307]

The one figure that stands out in the above table is the 5.5% rate of potassium >5.5 with combined aliskiren/ACEI use. The sponsor notes that aliskiren/ACEI use was all in Study 2307 in diabetics. In that study the rate of potassium ≥ 6 mmol/L was 2.2% (6 of 273 patients, 2 of whom only had values above 6 mmol/L at screening). No patients were discontinued from this study due to elevated potassium levels.

COMMENT: With the exception of the potassium changes in Study 2307 in diabetics, the lab value outlier changes are not revealing. Note that hyperkalemia in diabetics (with reduced renal function) was problematic in another antihypertensive development program (eplerenone, another RAAS inhibitor). While the lab value shifts aren’t revealing, the AE rates related to some of the shifts are as presented in Section 7.1.3.3.

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

There were no marked outliers for lab abnormalities other than the CK increases discussed in Section 7.1.3.2.2, and there were several dropouts for CK rises as discussed in that section. One patient in Study 2302, a 52-year-old white male, discontinued with tiredness and an ALT of 94 on day 176. No other details are provided.

COMMENT: Aliskiren appears to rarely be associated with lab abnormalities leading to discontinuation.

7.1.7.4 Additional analyses and explorations

I did not perform any additional analyses or explorations other than those presented above.

7.1.7.5 Special assessments

Special assessments for renal function and potassium are addressed in Section 7.1.7.3.2. I did not identify any other laboratory value concerns for which special assessment are needed.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Blood pressure and pulse were routinely measured at most visits for the efficacy evaluations. Weight was typically measured during baseline and at the end. Temperature and respirations were not routinely recorded. I discuss changes in BP in the ISE. I present an overview of changes in other vital signs below.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

The most appropriate sets of studies for drug-control comparisons are the placebo-controlled studies and all monotherapy arms of the controlled studies.

7.1.8.3 Standard analyses and explorations of vital signs data

Aliskiren has no detectable effect upon pulse rates at trough as shown in Table 53.

Table 53: Reviewer's Mean Changes from Baseline in Pulse Rate in the Monotherapy Arms of the Placebo-controlled Trials and All Monotherapy Arms

Dose	Placebo-controlled	All monotherapy
0	-0.5	-0.5
75	-0.4	-0.4
150	0.0	0.0
300	-0.4	-0.4
600	0.0	0.0

Aliskiren did not appear to have any consistent effect upon body weight as shown in Table 54.

Table 54: Reviewer's Mean Changes from Baseline in Body Weight (kg) in the Monotherapy Arms of the Placebo-controlled Trials

Dose	No diarrhea	Any diarrhea	All
0	-0.1	0.3	-0.1
75	-0.1	0.1	-0.1
150	0.0	-0.3	0.0
300	0.1	0.0	0.1
600	-0.6	0.2	-0.5

Body weight also did not vary consistently between those patients who experienced diarrhea and those who did not in the monotherapy arms. In the long term Study 2302, patients overall experienced a slight mean weight gain over the course of the study (0.4 kg) that was similar in the patients experiencing diarrhea (0.6 kg) to those that did not (0.4 kg).

COMMENT: Aliskiren does not appear to have any effects upon heart rate or body weight.

7.1.8.4 Additional analyses and explorations

I did not perform any additional analyses of vital signs.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

ECGs were typically recorded at baseline and at end of study in the hypertension trials; however, these ECGs were not analyzed systematically. The sponsor did perform a thorough QTc study (Study 2208) per ICH E14 guidance. That study provides the primary evidence regarding possible effects of aliskiren upon ECG parameters.

The following is the sponsor's summary of the preclinical CV safety findings: "No effects on the rate and force of contraction of isolated guinea pig atria were observed up to concentrations of 10 μ M. Measurement of action potential duration, triangulation, reverse use-dependency, instability, the proarrhythmia index, coronary flow and inter-ventricular conduction in the isolated rabbit heart model showed that aliskiren did not modify the measured parameters at concentrations between 1 and 100 μ M using different stimulation rates. The investigation of the effects of aliskiren on cloned hERG channels expressed in mammalian cells revealed a very shallow dose-response over a 100-fold concentration range (10, 100 and 1000 μ M) that did not achieve 50% inhibition. The lowest concentration tested had no significant effect.

"Effects of aliskiren on cardiovascular, respiratory and renal systems were evaluated in the rat in vivo. After intravenous administration to anaesthetized rats at doses of 0.3, 1 and 3 mg/kg, aliskiren induced dose-dependent transient (recovery after 20 minutes) reductions in both systolic and diastolic BP and a concurrent slight fall in HR. These effects were most probably due to the pharmacological mechanism of action of aliskiren. There were no significant effects on the electrocardiogram. In conscious rats, no significant effects on Cl⁻, Na⁺ and K⁺ excretion and urine volumes or on respiratory rate, tidal volume and minute volume were observed after single intravenous doses up to 3 mg/kg."

COMMENT: The preclinical findings do not suggest an arrhythmogenic potential for aliskiren.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

Study 2208, the thorough QTc study, is the most appropriate study for drug-control comparisons. I summarize the results of that study below based on a review of the study by the Division's Interdisciplinary Review Team for QT Studies.

Study 2208 was entitled "A randomized, double blind, multiple oral dose study to evaluate the effects of SPP100 on cardiac safety in healthy subject versus placebo with positive control." It was a multi-center, double-blind (aliskiren vs. placebo), parallel-group, placebo and active (moxifloxacin) controlled, multiple-dose study in healthy volunteers. Overall 283 subjects were randomized to receive 300 mg aliskiren, 1200 mg aliskiren, 400 mg moxifloxacin, or placebo once daily in the fasted state for seven days. Holter ECGs were recorded at 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, and 23 h at baseline and at 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 14, 23 h post-

dose on day 7. PK samples were collected at 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 23, 36, 48, and 72 h on day 7. The average of three ECGs (recorded within five minutes of the time point) was used to determine cardiac intervals at each time point. When provided, the lead II rhythm strip was used for assessment of conduction intervals to make interval duration measurements on three consecutive beats. If a rhythm strip was not provided, as many measurements as possible (1-2) were performed from one of the available leads (II or V5). For QTc the sponsor used both the Fridericia and an individual QT vs. heart rate regression correction formula.

7.1.9.3 Standard analyses and explorations of ECG data

The central tendency analysis of QTc interval data was performed in two ways: (1) time-matched analysis, and (2) time-averaged analysis. The time-matched analysis was the primary analysis. For the time-matched analysis the sponsor adjusted post dose QTc by the average of all the baseline values; therefore, the sponsor did not perform a true time matched baseline adjustment. The Division QTc team performed the following analysis. For each subject, they subtracted the QTc value at each time point at baseline from the QTc value at the same time point on day 7 and then they averaged over all the subjects in each group. Their results are shown in Table 55.

Table 55: Division QTc Team's Time-Matched Mean QTc Changes in Study 2208

Time	Baseline adjusted mean dif of 300 mg & placebo	1-sided 95% Upper Bound	Baseline adjusted mean dif of 1200 mg & placebo	1-sided 95% Upper Bound	Baseline adjusted mean dif of Moxi & placebo	1-sided 95% Lower Bound (*)
0	1.32	4.78	4.80	8.82	4.62	-0.83
0.5	-0.39	3.47	0.95	4.50	10.63	4.75
1	1.12	4.37	-1.36	1.82	12.04	6.74
1.5	0.26	3.78	-0.05	3.31	13.67	8.42
2	-1.03	2.53	-0.13	3.27	12.03	6.26
3	2.80	5.98	2.56	6.04	15.94	11.10
4	1.47	5.07	2.81	6.35	13.90	8.49
5	0.35	3.81	0.00	3.75	7.11	1.51
6	1.54	5.16	0.63	4.15	10.04	5.21
8	2.80	6.07	0.91	4.19	10.74	5.56
10	1.23	4.73	1.08	4.21	9.90	4.72
12	2.21	5.27	3.50	6.11	5.88	1.14
14	0.72	4.13	1.21	4.70	3.61	-2.17
23	2.98	6.85	5.84	9.28	8.94	3.68

* With Bonferroni adjustment

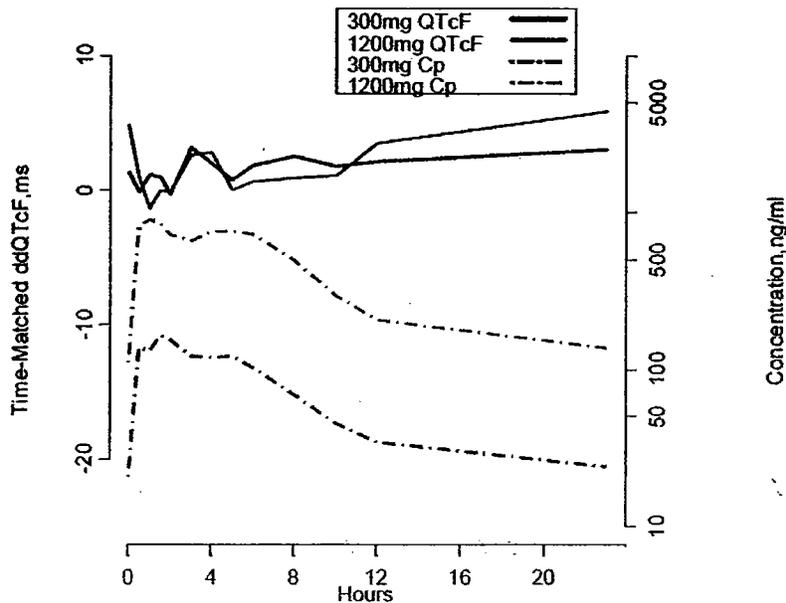
COMMENT: The conclusions of the Division QTc team were as follows: "Since there are at least one time point where the lower bound of the adjusted one-sided 95% confidence interval for the baseline adjusted mean difference of moxifloxacin and placebo is above five msec, the assay sensitivity was established. Since all the one-sided 95% upper bounds for the baseline

adjusted mean difference of the drug (300 mg and 1200 mg) and placebo are below 10 msec, a negative thorough QT/QTc study can be claimed."

7.1.9.4 Additional analyses and explorations

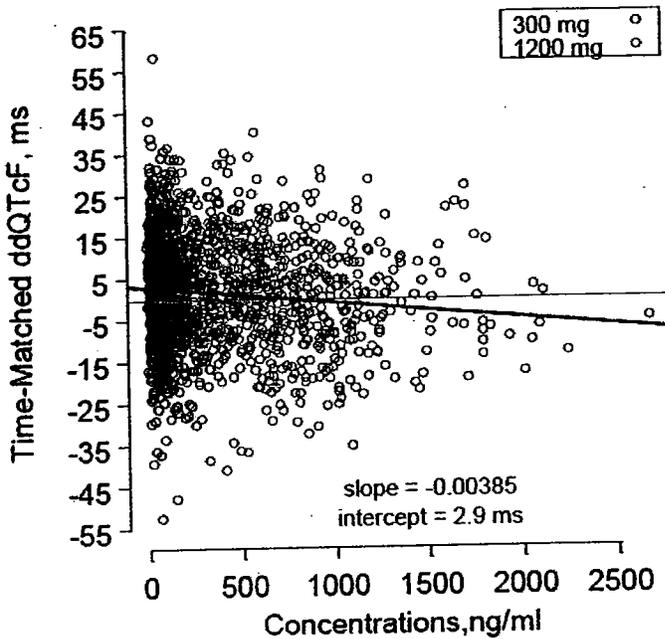
The Division QTc team also examined relationships between aliskiren plasma concentrations and QTc intervals. The time courses of QTc changes and aliskiren plasma concentrations are shown in Figure 18 and the relationship between QTc changes and aliskiren plasma concentrations is shown in Figure 19.

Figure 18: Division QTc Team's Time Courses of Mean ddQTcF Intervals and Mean Aliskiren Plasma Concentrations in Study 2208



**APPEARS THIS WAY
ON ORIGINAL**

Figure 19: Division QTc Teams Aliskiren Concentration and ddQTcF Relationship in Study 2208



COMMENT: There is no apparent relationship between aliskiren plasma concentrations and QTc changes. Aliskiren does not appear to have an appreciable effect upon QTc.

7.1.10 Immunogenicity

Aliskiren is a small molecule that by itself should have little immunogenic potential. Aliskiren did not show a pattern of increase adverse events of potentially immunogenic etiology, e.g., aliskiren was not associated with increased rates of urticaria compared to placebo.

7.1.11 Human Carcinogenicity

I discuss aliskiren's potential for human carcinogenicity in Section 7.1.3.3.2.

7.1.12 Special Safety Studies

The sponsor is currently performing a special safety study involving pre and post treatment colonic biopsies in subjects treated with aliskiren 300 mg. The sponsor is conducting this study to determine whether humans develop colonic hyperplasia as was seen in a rat study. This study has not been completed yet.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

The potential for AEs and rebound effects was studied in a 1-week monitored washout period in Study 1201, for 4 days following withdrawal from randomized placebo-controlled therapy in Study 2201, for two weeks following treatment with placebo, aliskiren 150, 300, and 600 mg/day

in Study 2308, and during a 4-week randomized double-blind placebo-controlled withdrawal from open-label aliskiren at doses of 150 or 300 mg/day given for 11 months in Study 2302. In each of these circumstances there was a gradual reduction of drug effect as demonstrated by a gradual return toward baseline of the blood pressure and plasma renin activity. Blood pressure was monitored at four days in Study 2308 to detect potential early rebound and weekly in Study 2302. I summarize the results of the withdrawal phases in the ISE. In the dose finding Study 2201, the sponsor defined rebound as either DBP or SBP greater than baseline at any time during the withdrawal. In subsequent studies the sponsor defined rebound as a rise of > 5 mm Hg for diastolic and >10 mm for systolic. Neither of these definitions produced results that suggestive of rebound on withdrawal of aliskiren treatment. AEs were infrequent during the randomized withdrawal from Study 2302 and similar between the treatment groups. There were no SAEs or deaths during withdrawal.

Preclinical and clinical studies have not indicated any potential for dependence. There is no reason to suspect potential for abuse in humans.

7.1.14 Human Reproduction and Pregnancy Data

Seven pregnancies occurred during the aliskiren clinical trials, four in aliskiren patients. Two of the pregnant aliskiren patients elected to continue the pregnancy and the disposition of the pregnancy in a third is unknown. The dispositions of the patients and pregnancies that were continued or whose status is unknown are as follows:

1. A 31-year-old black female in the aliskiren 300 mg group of Study 2203 had a positive pregnancy test result 42 days after starting study drug. The patient discontinued study drug. Nine days prior to the expected delivery date the patient gave birth by normal vaginal delivery to a male, weight 3.8 kg and height 54 cm, with no abnormalities. No abnormalities were noted in the patient during the delivery process.
2. A 29-year-old black female in the aliskiren/HCTZ 150/12.5 mg group of Study 2204 was diagnosed on day 38, and she discontinued from the study due to the pregnancy. This patient had a history of pre-term labor. She experienced pre-term labor at 25 weeks and was hospitalized. She delivered a normal female at 26 weeks by Caesarean section.
3. A 31-year-old "other race" female in the clinical pharmacology Study 2218 taking aliskiren/amlodipine 300/10 mg was found to have a positive pregnancy test result on study day 48. The subject was immediately discontinued from the study. During follow-up of this event, the subject indicated that the pregnancy would be terminated; however, after several failed attempts to contact the subject, the study center could not obtain proof of termination documentation.

COMMENT: While there have not been definite fetal abnormalities reported following pregnancies detected during aliskiren use, the experience with human pregnancies is obviously limited. The sponsor is proposing a black box warning in the label regarding use in pregnancy as is currently included in the labels for ACEIs and ARBs. Including the black box warning is a reasonable, conservative approach.

7.1.15 Assessment of Effect on Growth

Aliskiren has not been studied in children.

7.1.16 Overdose Experience

There were no reports of overdose with aliskiren in the clinical trials.

7.1.17 Postmarketing Experience

Aliskiren has not been marketed.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

The aliskiren development program is a large development program for an antihypertensive. The exposure substantially exceeds the minimum ICH recommendations for a chronic drug. It includes several randomized, double-blind, placebo-controlled trials as well as randomized, double-blind, active-controlled trials.

COMMENT: While the exposure is substantial particularly for short-term trials, one limitation is that the controlled long-term exposure is not.

7.2.1.2 Demographics

The sponsor's tabulation of the demographics in the placebo-controlled studies (included in the original NDA submission) is shown in Table 56 and in all controlled studies in Table 57.

Table 56: Sponsor's Demographics in the Placebo-controlled Studies

Treatment Group	Number of Patients	Age (yrs) Mean	Sex (%)		Race (%)			
			Male	Female	Caucasian	Black	Asian	Other*
Placebo	783	54.4	59.3	40.7	66.5	8.8	19.3	5.4
Ali 75mg	478	54.5	58.8	41.2	67.4	4.0	25.3	3.3
Ali 150mg	774	54.1	61.2	38.8	68.0	8.1	19.0	4.9
Ali 300mg	770	54.7	57.1	42.9	69.0	6.5	19.0	5.5
Ali 600mg	296	54.4	56.1	43.9	68.9	14.5	10.5	6.1
Mono Ali	2318	54.4	58.7	41.3	68.3	7.5	19.2	5.0
Ali/ARB	178	56.7	54.5	45.5	89.9	8.4	0.0	1.7
Ali/HCTZ	1471	54.6	54.0	46.0	86.1	4.2	2.7	7.0
All Ali	3967	54.6	56.8	43.2	75.9	6.4	12.2	5.6
ARB	311	56.0	52.7	47.3	83.3	13.2	0.3	3.2
HCTZ	558	55.2	54.5	45.5	85.3	5.6	2.2	7.0
ARB/HCTZ	59	56.9	61.0	39.0	89.8	8.5	0.0	1.7
Total	5678	54.7	56.7	43.3	76.1	7.0	11.4	5.5

Studies included: [Study 1201], [Study 2201], [Study 2203], [Study 2204] and [Study 2308]

* Including Native American, Pacific Islander, and Other categories.

Table 57: Sponsor's Demographics in All Controlled Studies

Treatment Group	Number of Patients	Age (yrs)	Sex (%)		Race (%)			
		Mean	Male	Female	Caucasian	Black	Asian	Other*
Placebo	783	54.4	59.3	40.7	66.5	8.8	19.3	5.4
Mono Aii	2000	55.0	58.4	41.6	70.7	6.9	17.9	4.5
Aii/ARB	178	56.7	54.5	45.5	89.9	8.4	0.0	1.7
Aii/HCTZ	1471	54.6	54.0	46.0	86.1	4.2	2.7	7.0
Aii/CCB	187	52.7	56.1	43.9	88.4	18.2	11.2	2.1
Aii/ACE	277	59.5	60.6	39.4	92.4	2.2	5.4	0.0
All Aii	4713	55.1	56.9	43.1	77.4	6.3	11.5	4.8
ARB	311	56.0	52.7	47.3	83.3	13.2	0.3	3.2
HCTZ	558	55.2	54.5	45.5	85.3	5.6	2.2	7.0
CCB	358	53.8	52.2	47.8	69.8	17.3	11.2	1.7
ACE	278	59.9	59.7	40.3	91.0	2.5	6.5	0.0
ARB/HCTZ	59	56.9	61.0	39.0	89.8	8.5	0.0	1.7
Total	7060	55.2	56.7	43.3	77.4	7.3	10.8	4.5

Studies included: [Study 1201], [Study 2201], [Study 2203], [Study 2204], [Study 2308], [Study 2305] and [Study 2307]

Note that blacks comprised only about 7% (n=398) of the placebo-controlled study populations. Also, the mean ages in the sponsor's tabulations don't convey what percentages of the study populations were elderly. In the placebo-controlled trials about 20% were 65 or older and almost 4% were 75 or older; the percentages are slightly higher in all the hypertension studies (25% and 6%).

COMMENT: While the elderly are represented reasonably, a higher representation of blacks is desirable to define better aliskiren activity in this subgroup in which other RAAS inhibitors have shown reduced activity and in which adverse effects such as angioedema are more common.

7.2.1.3 Extent of exposure (dose/duration)

The sponsor's summary of numbers of patients exposed for the initial NDA submission is the following:

- A total of 3,958 patients received aliskiren for a planned 8 weeks in the placebo-controlled studies.
- A total of 4,704 patients received aliskiren in all-controlled studies.
- A total of 6,398 patients received aliskiren in all-controlled studies and the uncontrolled, long-term Study 2302.

The sponsor's analysis of the duration of exposure by aliskiren regimen is shown in Table 58.

Table 58: Sponsor's Duration of Exposure to Study Drug by Aliskiren Regimen in All Controlled Studies and Long-Term Study 2302 (Safety Population)

Duration of exposure (days)	Placebo n (%)	All 75mg n (%)	All 150mg n (%)	All 300mg n (%)	All 600mg n (%)	Mono All ^a n (%)	All/ARB n (%)	All/HCTZ n (%)	All/CCB n (%)	All/ACE n (%)	All All n (%)
≥1	900 (100)	486 (100)	2204 (100)	2412 (100)	297 (100)	4359 (100)	178 (100)	2334 (100)	187 (100)	277 (100)	6398 (100)
>14	855 (95.0)	486 (95.9)	2142 (97.2)	2355 (97.8)	287 (98.6)	4246 (97.4)	173 (97.2)	2278 (97.6)	185 (98.9)	267 (96.4)	6224 (97.3)
>28	767 (85.2)	452 (93.0)	1884 (85.5)	2058 (85.3)	282 (94.9)	4149 (95.2)	171 (96.1)	2241 (96.0)	182 (97.3)	263 (94.9)	6100 (95.3)
>42	691 (78.8)	443 (91.2)	1764 (80.0)	1730 (71.7)	279 (93.9)	4072 (93.4)	168 (94.4)	2220 (95.1)	59 (31.6)	253 (91.3)	5885 (92.0)
>56	275 (30.6)	142 (29.2)	1220 (55.4)	1249 (51.8)	133 (44.8)	2649 (60.8)	58 (32.6)	1301 (55.7)	0 (0.0)	92 (33.2)	3322 (51.9)
>6 months	0 (0.0)	0 (0.0)	411 (18.6)	525 (21.8)	0 (0.0)	965 (22.1)	0 (0.0)	734 (31.4)	0 (0.0)	0 (0.0)	1714 (26.8)
>12 months	0 (0.0)	0 (0.0)	241 (10.9)	194 (8.0)	0 (0.0)	586 (13.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1236 (19.3)
>14 months	0 (0.0)	0 (0.0)	5 (0.2)	9 (0.4)	0 (0.0)	45 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	110 (1.7)

*Duration of exposure to aliskiren treatment regimens is cumulative for patients who entered [Study 2302] from [Study 2203].

^aOne patient in study 2302 who took aliskiren 450 mg is included.

Exposure to different dose levels within a titrated treatment regimen is counted in the individual treatment groups. As a result, the exposure numbers in the Mono All and All All treatment groups are not a direct sum of the exposure numbers in the individual treatments, but represent cumulative exposure to any aliskiren treatment.

All All: all aliskiren monotherapy treatment groups and all aliskiren combination treatment groups.

In addition to the studies submitted with the initial NDA submission, the sponsor also submitted data for four additional studies with the 120-day safety update. Altogether the sponsor submitted the raw safety data for eleven (combining Study 2302 with its extension 2302E1) studies in hypertension. The person-exposure years for these eleven studies are shown in Table 59.

Table 59: Reviewer's Person-Exposure-Years (PEYs) for the Studies in Hypertension with Raw Data Submitted

Study	Person-Exposure-Years	
	Control	Aliskiren
1201	16	50
2201	38	58
2203	60	103
2204	108	294
2302	0	1762
2303	8	18
2305	39	21
2307	40	79
2308	23	74
2323	251	264
2324	12	29
Total	596	2752

COMMENT: The exposure in the aliskiren trials exceeds the ICH minimum recommendations. One limitation of the aliskiren exposure is that the majority of it, largely in Study 2302, is uncontrolled. This lack of control makes it difficult to answer definitively whether aliskiren has a detrimental effect upon strokes, although the stroke rates suggest that the stroke events are the result of studying a hypertensive population rather than a problem with aliskiren. The other question that is answerable with the development program exposure is whether aliskiren GI

effects can produce a higher cancer rates; however, addressing carcinogenesis issues is impossible with clinical study sizes in any development program.

Limiting the dosages studied to 300 mg at the high end is reasonable because diarrhea becomes prominent at higher dosages. Greater exposure at the low end, i.e., 75 mg or lower, would be helpful in defining better the efficacy of the lower dosages, particularly in subgroups such as the elderly.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

There are no secondary clinical data sources.

7.2.2.1 Other studies

I am not aware of studies of aliskiren other than those submitted with the NDA.

7.2.2.2 Postmarketing experience

Aliskiren has not been marketed.

7.2.2.3 Literature

I did Pubmed searches for “aliskiren” and “renin inhibitors” and also examined related references for pertinent references identified by these primary searches. I did not identify any aliskiren studies not submitted with the NDA nor did I find any publications on safety issues with aliskiren or other renin inhibitors.

7.2.3 Adequacy of Overall Clinical Experience

The overall clinical experience appears to have been adequate for estimating common (e.g., diarrhea) and uncommon (e.g., angioedema) problems with aliskiren. While more controlled exposure would be helpful in defining better effects upon stroke, the overall experience is adequate for concluding that rates of stroke in the aliskiren development program do not exceed those seen in other antihypertensive programs. The carcinogenesis potential of aliskiren is not completely defined, but clinical trials to do so are too large to conduct pre-marketing. A greater representation in blacks in the clinical trials would have been helpful to provide better estimates of efficacy and safety in this subgroup as discussed in Section 7.2.1.2.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Pre-clinical testing was adequate with one notable exception: It would be helpful to know whether aliskiren is an ACE inhibitor in addition to being a renin inhibitor. Knowing whether aliskiren inhibits ACE would be helpful in understanding its adverse effects and its potential for use with approved ACE inhibitors.

7.2.5 Adequacy of Routine Clinical Testing

The routine clinical laboratory and ECG testing were adequate. Measurements of lab parameters expected to be affected by a RAAS inhibitor, e.g., renal function and serum electrolytes, were frequent enough to detect significant problems, liver enzymes and creatine kinase were adequate for detecting liver toxicity or rhabdomyolysis, and the through QTc study addressed potential ECG effects satisfactorily. The one aspect of the clinical monitoring that was less than ideal was the collection of information on adverse effects—see Section 7.2.7.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

These are my preliminary evaluations based on my own review of the sponsor's clinical pharmacology summaries. I have not yet reviewed a copy of the FDA clinical pharmacologist's review.

While I found most aspects of the metabolic, clearance, and interaction workup by the sponsor to be adequate, I did identify several deficiencies or interpretation with which I disagree. In particular, the sponsor dismisses renal excretion and metabolism as unimportant because each constitutes only a small percentage of the (ingested) dose. What the sponsor overlooks is that the importance of the contribution of renal excretion and metabolism must be judged based on the percentage of the bioavailable (absorbed, not ingested) drug. Because only about 2.6% of an ingested dose is absorbed, even low percentages excreted or metabolized are significant. For example, the sponsor dismisses renal excretion because it is only 0.6% of the (ingested) dose. However, 0.6% represents 23% of the absorbed dose and a study in renal impairment showed that exposure was increased 1.5-1.9 fold. Metabolism may also be important, constituting 54% of the absorbed dose (although some of the metabolites may be formed in the gut by microbial degradation). It is unfortunate that the sponsor has not documented the activities of the major metabolites.

One interaction was not characterized sufficiently: the interaction with food. Aliskiren absorption is reduced substantially (62-71%) by a high fat meal. Despite this substantial food effect, all later clinical trial protocols were silent regarding the timing of administration relative to breakfast. The sponsor did not study whether blood pressure reductions varied with consistently different timings relative to meals (i.e., consistent fed vs. consistent fasted administration), whether a bedtime administration might be preferable, or whether blood pressure control for an individual varies with varying administration relative to meals.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The evaluation for potential adverse events was adequate with the following limitations:

- While the stroke rates in the development program are not unduly concerning and appear consistent with rates in a hypertensive population, we would like to see antihypertensives preventing most strokes. Ideally a stroke outcome study would be useful to compare stroke rates with aliskiren to those with other antihypertensives, e.g., ARBs or ACEIs. However, outcome studies have not been required for approval of antihypertensives.
- Potential carcinogenesis issues also are impossible to address in the usual drug development program. For aliskiren the on-going human colonic biopsy study is the most appropriate next step for determining whether aliskiren does have any carcinogenesis potential.

- The aliskiren safety data base does have one other limitation regarding non-serious AEs: Other than for SAEs, minimal information was collected on AEs. Examples of this minimalist approach are that we know that one patient suffered an “ISCHAEMIA ACCIDENT” and another had a “TEMPORARY RT PERIPHERAL VISION LOSS” but little else. This lack of information on AEs other than SAEs makes the assessment of minor strokes, TIAs, angioedema, and other AEs difficult.

7.2.8 Assessment of Quality and Completeness of Data

Please see Section 4.4 for a description of the DSI site audits. While one of the three sites audited had misrecorded BP measurements and another had give study drug at a visit when the protocol specified otherwise, DSI did not find any disqualifying problems at the sites.

I did not identify any problems with major discrepancies among the CRFs and Medwatch forms, SAS data sets, and study reports. Minor discrepancies were rare, e.g., one patient had different ages recorded on various forms. My one concern with data completeness is that recording of information on AEs other than those classified as SAEs was limited as discussed in Section 7.2.7.

7.2.9 Additional Submissions, Including Safety Update

I incorporated the data from the 120-day safety update into my discussions of specific adverse events.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Aliskiren is a RAAS inhibitor that appears to share many of the AEs of other RAAS inhibitors in addition to one common predictable and one potential problem plus some other rare AEs. The predictable problem is diarrhea at high dosages. While diarrhea is not a substantial problem leading to discontinuations at the proposed to-be-marketed dosages, its incidence is increased about two-fold at the highest proposed dosage (300 mg) in the general population and may also be increased two-fold at the lowest proposed dosage (150 mg) in some subgroups, e.g., women, the elderly. The potential problem is whether aliskiren GI effects can lead to hyperplasia as in the rat studies and whether, if hyperplasia is induced, GI cancer rates will increase.

Aliskiren appears to share these AEs with other RAAS inhibitors:

- Increases in serum potassium and slight or transient decreases in renal function - Frank hyperkalemia only appears to be a problem in special populations, e.g., diabetics.
- Cough – Cough rates may be slightly increased with aliskiren compared to placebo, but they do appear lower (one half to one third) those seen with ACEIs.
- Angioedema – Several cases associated with aliskiren use were reported in the development program, including two with suggestions of inspiratory compromise. My

estimates of the rates per person exposure year are comparable to those seen with ACEIs. However, the true rate of angioedema in the development program is difficult to estimate because of limited information on AEs that are not classified as SAEs.

- Rhabdomyolysis – No severe cases with renal dysfunction were reported in the development program. However, some suggestive CK increases were reported particularly in patients of Asian racial background. Delineation of this problem is also hindered by limited information on AEs that are not classified as SAEs.
- Slight decreases in hemoglobin and related parameters – While this effect, also seen with both ACEIs and ARBs, is supposed to be rarely of clinical significance, the large aliskiren development program and the large LIFE study with losartan suggest that it may result in small increases in clinical events such as reported anemia AEs or hospitalizations for anemia.

Aliskiren has these additional AEs:

- Hyperuricemia, gout, and renal stones – Aliskiren, like HCTZ, increases serum uric acid levels, although the increases are lower with aliskiren. Both drugs may increase rates of gout and renal stones similarly.
- Rash – Aliskiren has about a three-fold higher rash rate than placebo, with rashes being reported in about 1% of aliskiren patients.
- Seizures – The two cases of unexplained tonic-clonic seizures in aliskiren patients are concerning.

Overall I judge this AE profile for aliskiren to be acceptable for an antihypertensive. The one issue for which I would most like to see additional data is potential carcinogenesis. The ongoing colonic biopsy study should provide useful information on this issue.

7.4 General Methodology

7.4.1 Pooling Data across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

I summarize individual study data in the Appendices, Section 10.1, and pooled data in the ISS, Section 7.

7.4.1.2 Combining data

I combined data in two ways: (1) simple rates, by pooling the counts of patients with events in the numerators and counts of patients in the denominators; (2) rates per person exposure years (PEYs), by pooling the counts of patients with events in the numerators and the person exposure years in the denominators. I usually examined pooled rates for the aliskiren monotherapy arms

in the placebo-controlled trials and in all controlled trials. I also compared these rates to those for any aliskiren use vs. no aliskiren use and to rates for specific active control groups, e.g., ACEI control groups, HCTZ control groups.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

I explored dose-dependency of all AEs by calculating rates for each dosage in the aliskiren monotherapy arms.

7.4.2.2 Explorations for time dependency for adverse findings

I explored time dependency of adverse findings for the major AE, diarrhea, and displayed starting days for most AEs in the individual study reports. I also looked at the relationship between dose changes and stroke occurrences.

7.4.2.3 Explorations for drug-demographic interactions

I explored subgroup specific rates, when sufficient events were available in subgroups, by age, race, and gender.

7.4.2.4 Explorations for drug-disease interactions

The sponsor identified an interaction between diabetes and aliskiren for hyperkalemia. I did not identify any other drug-disease interactions.

7.4.2.5 Explorations for drug-drug interactions

I looked at AE rates particularly in the combination arms of aliskiren with HCTZ or valsartan in the individual study reports.

7.4.3 Causality Determination

I did not try to perform any causality determinations other than associations suggested by increased rates.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

I discuss dosing regimen and administration issues in the ISE, Sections 6.1.4.3 and 6.1.4.6.

8.2 Drug-Drug Interactions

I discuss BP effects with other antihypertensives in the ISE, Section 6.1.4.7. The sponsor formally studied PK interactions with some antihypertensives and other drugs commonly used in the hypertensive and diabetic populations. The sponsor also studied the effect of maximum inhibition of P-glycoprotein using the inhibitor ketoconazole. The following are the sponsor's brief summaries of these formal interaction studies:

- Co-administration of irbesartan, furosemide, digoxin, ramipril, and HCTZ with aliskiren had no effect on aliskiren steady-state pharmacokinetics (Study 2209, Study 2211, Study 2214, Study 2221, and Study 2228).

- Co-administration of aliskiren did not affect the steady-state pharmacokinetics of digoxin, valsartan, amlodipine, metformin, ramipril or its active metabolite ramiprilat and hydrochlorothiazide (Study 2214, Study 2216, Study 2218, Study 2220, Study 2221 and Study 2228).
- Co-administration of valsartan or metformin resulted in a 25-30% reduction in aliskiren steady-state AUC and C_{max} (Study 2216 and Study 2220). Co-administration of amlodipine resulted in a 29% increase in aliskiren steady-state AUC (Study 2218).
- Co-administration of aliskiren and furosemide does not alter the pharmacokinetics of aliskiren but decreases the AUC and C_{max} of furosemide (28% and 49%, respectively) (Study 2211). The sponsor recommends that the effects of furosemide be monitored and the dose adjusted, if necessary, when initiating treatment with aliskiren.
- Ketoconazole, a potent P-glycoprotein and CYP3A4 inhibitor, increases exposure to aliskiren 300 mg by 1.8-fold (Study 2334). The sponsor hypothesizes that this is primarily due to the inhibition of P-glycoprotein by ketoconazole since aliskiren is minimally metabolized (<1.4% of dose) (Study 2223) and hepatic impairment had no effect on the pharmacokinetics of aliskiren (Study 2210).

Please see the FDA clinical pharmacology review for a more critical review of the drug interactions studies.

COMMENT: The sponsor is erroneously concluding that metabolism is unimportant because "aliskiren is minimally metabolized (<1.4% of dose)". The correct interpretation is that 1.4% is 54% of the absorbed dose, so metabolism may be important. However, the sponsor did perform an extensive battery of drug interaction studies as listed above that do not suggest major problems with drug interactions for aliskiren. Dosage adjustments of aliskiren are not needed except for halving the dose when administering with non-topical ketoconazole. The sponsor's recommendation for monitoring for effects of furosemide and adjusting dosage of furosemide co-administered with aliskiren is reasonable.

8.3 Special Populations

I address the efficacy findings and recommendations regarding demographic subgroups in Section 6.1.4.5. My conclusions from that section are the following:

- Blacks show a reduced response to aliskiren.
- Asians show an enhanced response particularly at the lower doses, i.e., 75 mg.
- The elderly (age ≥ 65) also show a reasonable response to 75 mg.
- There do not appear to be significant differences in response by gender.

The sponsor did not identify any variations in adverse events by demographic subgroups other than females in all groups reported slightly higher rates of AEs than males. The sponsor also noted that Asian patients were reported to have orthostatic BP change at every time point with a tendency for this to be dose related. The sponsor hypothesized that these observations were in part due to a different methodology for assessing orthostatic blood pressure change in Study 1201 conducted in Japan. In Study 1201 the position change was from supine to standing, compared to sitting to standing for all other studies.

I examined variations in demographic subgroups with my reviews of adverse events in the ISS and in the individual study reports. The association that I found was that events of myositis or elevated CKs occurred predominantly in Asians. In specifically reviewing AE rates by demographic, I found these two additional associations: Rash and dyspepsia were reported more frequently by females with aliskiren, particularly at doses < 600 mg.

The sponsor's specific evaluation of aliskiren in renally-impaired and hepatically impaired patients was limited to PK studies. Compared to matched healthy volunteers with normal renal function, steady state exposures to aliskiren (C_{max} and AUC) were greater (~1.5 to 1.9-fold) in subjects with mild to moderate renal impairment (creatinine clearance 30-80 mL/min). In patients with hepatic impairment (Child-Pugh score of 5 to 15), there were no differences in the pharmacokinetics of aliskiren (AUC and C_{max}) compared to matched healthy volunteers in a single dose study. The sponsor concludes that dosage adjustment is not needed in either patient subgroup.

Four pregnancies occurred during the aliskiren trials in aliskiren patients. I summarize the results of those pregnancies, and the sponsor's proposal for labeling, in Section 7.1.14.

COMMENT:

The variations in AEs by demographic factors are not striking—I suspect that the higher frequencies of rashes and dyspepsia in females are due to a higher likelihood of reporting of these symptoms as AEs by females. The sponsor's proposal to include a black box warning regarding pregnancy like those in the labels for ACEIs and ARBs is reasonable.

8.4 Pediatrics

The sponsor has not conducted pediatric studies. At the request of the sponsor, the Division in a letter dated August 26, 2004, granted a deferral for studying patients younger than 16 years until two years after approval for use in adults. The Division agreed that a deferral would be acceptable on the basis that more safety and efficacy data in adults are needed before it would be reasonable to issue a written request.

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8.5 Advisory Committee Meeting

Aliskiren has not been discussed at an advisory committee meeting nor is one planned for it.

8.6 Literature Review

I did Pubmed searches for "aliskiren" and "renin inhibitors" and also examined related references for pertinent references identified by these primary searches. I did not identify any aliskiren studies not submitted with the NDA. One relevant observation in some of the published studies examining the relationship between RAAS intermediates and blood pressure is that the blood pressure reductions with renin inhibitors may persist longer than the reductions in renin (Luther, Glassman et al. 1991) or angiotensin II (Schalekamp, Derkx et al. 1992) (van den Meiracker, Admiraal et al. 1990). While dissociation between angiotensin II and blood pressure reductions have also been observed in some studies of ACE inhibitors, the authors of these older papers expressed uncertainty about whether the dissociation was real or an artifact of the assays.

8.7 Postmarketing Risk Management Plan

The sponsor did not submit a postmarketing risk management plan.

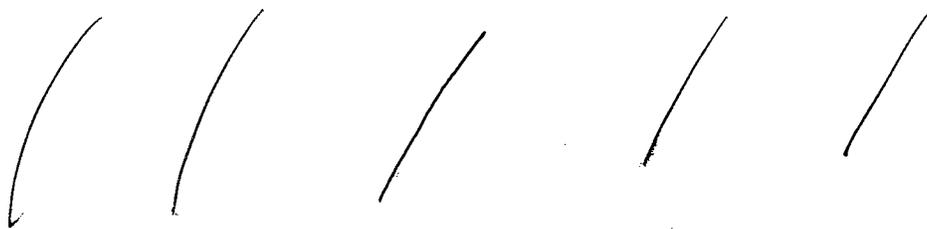
8.8 Other Relevant Materials

I did not identify any other relevant materials other than the NDA submissions and the literature review.

9 OVERALL ASSESSMENT

9.1 Conclusions

Aliskiren appears to be an effective antihypertensive agent. While it clearly works, I do have some disagreements with the sponsor regarding its proposed use. My differences from the sponsor's evaluations are the following:



- Aliskiren shows reduced efficacy in blacks. This limitation should be included in the label.
- There is inadequate evidence to recommend aliskiren administration with full doses of ACEIs. There is also uncertainty regarding use with ARBs and beta blockers.

For understanding better how to use aliskiren, I would also like to see more data regarding effects throughout the interdosing interval and effects upon BP with varying timings of administration relative to breakfast.

Aliskiren appears to have an acceptable adverse event profile for an antihypertensive. However, I do have some disagreements with the sponsor regarding its safety. My differences from the sponsor's evaluations are the following:

- The major safety question regarding aliskiren is whether its GI toxicity can lead to serious sequelae, i.e., GI cancer. There is no practical way in a drug development program, even this large one, to resolve this question with an outcome study. An ongoing colonic biopsy study should be helpful; a real question is whether to wait for its results before approval.
- I do not find that aliskiren has a placebo-like AE profile. It has the following AEs, none of which prohibit approval:
 - While the GI toxicity (primarily diarrhea) only rarely led to discontinuation at the proposed to-be-marketed doses, it is increased even at the lower doses in some subgroups, i.e., the elderly. However, the major problem with the GI toxicity is the fear of cancer mentioned above.
 - Aliskiren appears similar to other RAAS inhibitors in increasing serum potassium and decreasing renal function slightly, increasing cough rates (although not as much as ACEIs), causing rare cases of angioedema, and decreasing hemoglobin. It may also be associated with CK rises and rare occurrences of myositis or rhabdomyolysis.
 - It has about a three-fold higher rash rate than placebo, with rashes being reported in about 1% of aliskiren patients.
 - It, like HCTZ, increases serum uric acid levels, although the increases are lower with aliskiren. Both drugs may increase rates of gout and renal stones similarly.
 - It was associated with rare cases of grand mal seizures.

9.2 Recommendation on Regulatory Action

From a clinical perspective I recommend that aliskiren is approvable for the treatment of hypertension pending the resolution of the two issues described below. Aliskiren demonstrated antihypertensive efficacy in five randomized, double-blind, placebo-controlled trials as well as in other active-controlled studies. It has demonstrated long-term maintenance of efficacy in double-blind, placebo-controlled, randomized withdrawal after treatment maintained for up to eleven months. Its adverse event profile is similar to other renin-angiotensin-aldosterone system (RAAS) inhibitors approved as antihypertensives. Its one clear dose-related toxicity, diarrhea, is

tolerable at the proposed to-be-marketed dosages. The issues that require resolution are the following:

1. Aliskiren causes diarrhea and colonic mucosal hyperplasia in rodents at colonic content drug levels not substantially different than those observed in humans. Marmosets, the one primate species tested in nonclinical studies, experienced diarrhea but did not develop colonic mucosal hyperplasia. Rodents may be more susceptible to gastrointestinal toxicity than primates. The sponsor is performing a colonic biopsy study in normal volunteers that should resolve whether colonic mucosal hyperplasia is seen in humans at the highest proposed to-be-marketed dosage. Approval depends upon this study being negative.
2. The sponsor is proposing the 150 and 300 mg tablets to be marketed in the U.S. However, blood pressure reductions in the elderly (age ≥ 65) were reasonable at the 75 mg daily dosage and diarrhea rates showed increases in the elderly as low as the 150 mg daily dosage.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

Aliskiren does not have any unusual risks for which a postmarketing risk management plan would be useful. Other than the GI toxicity at higher dosages, aliskiren adverse effects are similar to those seen with other RAAS inhibitors and other antihypertensives.

9.3.2 Required Phase 4 Commitments

I do not recommend any phase 4 commitments at this time.

9.3.3 Other Phase 4 Requests

I do not recommend any other phase 4 requests at this time.

9.4 Labeling Review

The original trade name proposed by the sponsor, Rasilez, was rejected by the Division of Medication Errors and Technical Support as being too similar to names used for some other drugs. The sponsor elected to use an alternative name, Tekturna.

I have many disagreements with the sponsor's proposed label. My major areas of disagreement are regarding

 Please see the line-by-line label review in Section 10.2 for the details.

9.5 Comments to Applicant

The comments to be communicated to the sponsor are the following:

1. The GI mucosal hyperplasia in rodents and the dose-related GI adverse events in humans, i.e., diarrhea, remain concerning. The complete results and data for the human colonic biopsy study should be submitted as soon as available.
2. We have many recommendations regarding the label for aliskiren for the treatment of hypertension. We will discuss these recommendations with you.

**APPEARS THIS WAY
ON ORIGINAL**

10 APPENDICES

10.1 Review of Individual Study Reports

10.1.1 Study 04 HTN DR - A dose-ranging study of the effects of SPP100 on 24-hour ambulatory blood pressure following once a day administration of 37.5, 75, 150 or 300 mg for 4 weeks compared to losartan at 100 mg in patients with mild to moderate hypertension

10.1.1.1 Background

This study was one of the first proof-of-concept studies conducted by the prior sponsor, Speedel. The submission does not include CRFs or SAS data sets for this study.

10.1.1.2 Design and Conduct

This randomized, double-blind, active-controlled, parallel group study was conducted at six sites in Ireland under GCP from August 2000 to September 2001. Adult hypertensives with mild-to-moderate hypertension (average daytime SBP ≥ 140 by ABPM) were randomized to one of five treatment groups: losartan 100 mg or aliskiren 37.5, 75, 150 or 300 mg (in a formulation different than the to-be-marketed formulation.) The duration of treatment was four weeks with an additional 1-3 week follow-up after the last dose. The primary efficacy endpoint was change in daytime SBP by ABPM at four weeks; cuff measurements were also taken. Day-time was defined as the hours between 09:00 and 21:00 hours (excluding the initial period of one hour after the monitor was applied). Night-time was defined as 01:00 to 06:00. The primary analysis defined in the statistical analysis plan dated September 24, 2001, was an ANCOVA excluding the losartan group with aliskiren dose and baseline BP as covariates and center and naïve to therapy as cofactors.

The originally planned sample size of 300 was reduced to 200 based on an observed SD of 11 mm Hg for the first 109 patients compared to an estimated SD of 15 used for the original sample size calculations. Ultimately 226 patients were randomized, with dispositions as shown in Figure 20. Including the dropouts, 29 patients were excluded from the ITT population, primarily because of missing ABPM measurements. The study population had a modest majority of males (66%) and a mean age of 52. Race is not mentioned in the study report but is presumably all or predominantly white because of the location of the study.

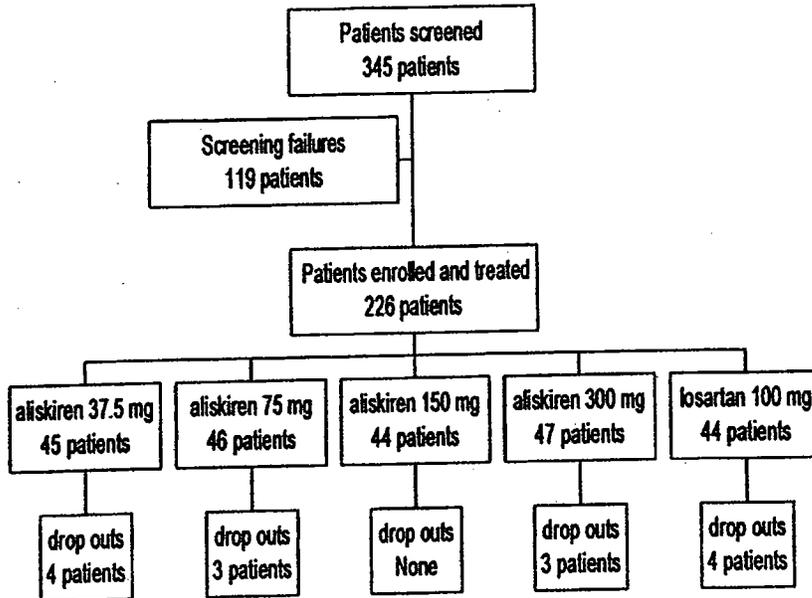


Figure 20: Disposition of Patients in Study 04 HTN DR

10.1.1.3 Efficacy Summary

Changes in the primary efficacy variable, mean daytime SBP, are shown in Table 60. Aliskiren dosage as a covariate in an ANCOVA was highly significant per the sponsor’s primary analysis (P = 0.0002). Changes in mean daytime DBP are shown in Table 61, changes in nighttime BP are shown in Table 62, and changes in trough seated cuff BP are shown in Table 63.

Table 60: Changes in Mean Daytime SBP in Study 04 HTN DR

	Aliskiren 37.5 mg n=39		Aliskiren 75 mg n=41		Aliskiren 150 mg n=41		Aliskiren 300 mg n=40		Losartan 100 mg n=36	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Baseline (mmHg)	153.8	13.1	153.9	11.0	156.2	10.5	152.6	9.7	152.6	10.5
End of study (mmHg)	153.4	15.4	148.6	13.3	148.2	15.1	141.7	12.9	141.7	12.5
Difference (mmHg)	-0.4	11.7	-5.3	11.3	-8.0	11.0	-11.0	11.0	-10.9	13.8

Table 61: Changes in Mean Daytime DBP in Study 04 HTN DR

	Aliskiren 37.5 mg n=39		Aliskiren 75 mg n=41		Aliskiren 150 mg n=41		Aliskiren 300 mg n=40		Losartan 100 mg n=36	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Baseline (mmHg)	93.3	12.3	94.5	9.9	96.5	8.4	93.5	8.9	91.1	9.0
End of study (mmHg)	93.7	13.9	91.5	10.6	91.7	10.1	86.3	9.4	85.4	10.0
Difference (mmHg)	0.4	8.7	-3.0	5.6	-4.8	6.4	-7.2	8.0	-5.7	8.9

Table 62: Changes in Mean Nighttime BP in Study 04 HTN DR

	Aliskiren 37.5 mg n=39		Aliskiren 75 mg n=41		Aliskiren 150 mg n=41		Aliskiren 300 mg n=40		Losartan 100 mg n=36	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
NASBP										
Baseline (mmHg)	130.1	17.9	131.9	16.4	132.6	14.9	132.4	13.6	135.1	12.9
End of study (mmHg)	131.0	18.5	128.0	15.0	126.5	13.4	122.5	15.5	125.0	11.4
Difference (mmHg)	0.9	16.2	-3.9	11.7	-6.1	12.1	-9.9	13.8	-10.1	14.4
NADBP										
Baseline (mmHg)	74.5	11.4	77.6	11.7	78.0	11.5	77.6	9.4	78.6	12.1
End of study (mmHg)	75.8	12.1	74.7	10.4	73.7	10.0	70.8	9.2	72.6	11.2
Difference (mmHg)	1.3	7.1	-2.9	7.1	-4.3	7.7	-6.7	8.2	-6.0	8.9

Table 63: Changes in Trough Seated Cuff BP in Study 04 HTN DR

	Aliskiren 37.5 mg n=39		Aliskiren 75 mg n=41		Aliskiren 150 mg n=41		Aliskiren 300 mg n=40		Losartan 100 mg n=36	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
SiSBP										
Baseline (mmHg)	156.8	18.9	158.2	19.4	159.5	18.5	157.6	16.8	159.0	15.5
End of study (mmHg)	152.4	18.6	154.2	21.1	149.6	21.3	145.8	18.4	147.6	18.2
Difference (mmHg)	-4.3	17.8	-4.1	16.9	-10.0	17.0	-11.8	14.9	-11.4	19.2
SiDBP										
Baseline (mmHg)	92.7	11.4	93.4	11.4	93.3	9.9	94.1	11.1	95.0	8.1
End of study (mmHg)	90.8	12.6	93.3	12.2	91.1	12.6	88.4	11.9	89.6	12.5
Difference (mmHg)	-1.9	10.5	-0.2	12.4	-2.2	10.0	-5.7	11.0	-5.5	10.7

COMMENT: These results appear to show a consistent, dose-related reduction in ambulatory BP for the daytime and nighttime periods. The effects at 300 mg are roughly comparable to losartan 100 mg and arguably slightly greater. The cuff changes don't show a dose response as clearly but the 300 mg dosage is distinguished from the lower dosages.

10.1.1.4 Safety Summary

Exposure was similar in all groups and averaged 31 days. One patient in the losartan group died of a ruptured iliac aneurysm. In addition to the death two patients experienced SAEs, both in the 300 mg group: one patient had chest tightness and one patient had collapse and hypotension. Nine patients were withdrawn from the study because of adverse events, two patients in the aliskiren 37.5 mg group, three patients in the aliskiren 75 mg group, two patients in the aliskiren 300 mg group and two patients in the losartan 100 mg group. In addition to the SAEs, aliskiren patients discontinued for abdominal pain, dyspepsia, fatigue, headache, and increased BP.

The narrative for the patient with collapse is the following: Due to headache and a BP of 165/100 mmHg, a 44-year old man with a history of obesity, insulin resistance syndrome, left ventricular hypertrophy, and depression was instructed to discontinue his study medication on _____ and recommence his previous medication, i.e. candesartan 10 mg od and doxazosin 4 mg od. Later that evening, the patient collapsed at home and was admitted to the CCU with hypotension: BP 100/65 mmHg. He was treated with saline infusion (iv 0.9% normal saline iv, PRN initially) and discharged home on _____ on candesartan 10 mg od and doxazosin 4 mg od. The study drug (aliskiren 300 mg in his case) was discontinued and the SAE was considered by the investigator to be possibly related to the study drug.

The narrative for the patient with chest tightness is the following: A 55-year old man with a history of hypercholesterolemia, cigarette smoking and gout presented with chest tightness on _____ and was admitted. The ECG on _____ showed new (<2mm) Q wave and inferior and lateral ischemia. The investigator rated this event to be unlikely related to the study drug, which was aliskiren 300 mg. Following this event, the patient was withdrawn from the study.

Other AEs were not remarkable except for some suggestion of a dose-response in GI AEs, reaching about 13% at 300 mg. However, the losartan group also had a 11% GI AE rate. Lab changes were unremarkable except for increased ALTs (<2x) at study end: five at 75, six at 150, nine at 300, and six with losartan. ECG changes as reported by the sponsor were also unremarkable, although the following was noted: During the study the following ECG anomalies were noted: 4 patients had a 1st degree atrioventricular block, 4 patients had right bundle branch block, 2 patients had left bundle branch block, one patient each with ventricular premature beats >3/min or a heart block not otherwise specified respectively, and 4 patients with known history of angina showed ST segment depression.

COMMENT: This small study does not suggest any major toxicity problems. The dose responses on GI toxicity and possibly on ALTs suggest scrutinizing these adverse events in the data base as a whole. The ECG blocks would also be worrisome if they show a dose response.

10.1.1.5 Conclusions

This study does suggest that aliskiren has an antihypertensive effect. It raises some questions about safety issues to explore but does not confirm any major problems. These conclusions are limited by the fact that the submission does not provide the raw data for this study.

10.1.2 Study 03 HTN - The effects of the renin inhibitor SPP 100 on 24-hour ambulatory blood pressure following once-a-day administration of 75 and 150 mg for 4 weeks each in patients with mild to moderate hypertension

10.1.2.1 Background

This study was the pilot, first proof-of-concept studies conducted by the prior sponsor, Speedel. The submission does not include CRFs or SAS data sets for this study.

10.1.2.2 Design and Conduct

The study was open label and sequential with respect to dose escalation for safety reasons. The initial protocol was to enroll 60 patients with an active comparator arm. The protocol was amended to become a pilot study including 10 patients with SPP 100 75 mg during 4 weeks followed by a forced titration to SPP 100 150 mg during another 4 weeks in an open manner. The primary endpoint was change in daytime SBP by ABPM analyzed descriptively. Nine patients were recruited, eight were treated and seven were analyzed.

10.1.2.3 Efficacy Summary

The average daytime systolic blood pressure decreased by approximately -4 and -7 mm Hg after 75 mg and 150 mg of Aliskiren, respectively. The average nighttime SBP was decreased by approximately -3 and -6 mm Hg after 75 mg and 150 mg of Aliskiren, respectively. The daytime DBP was decreased by -4 and -6 mm Hg and the night time DBP approximately -1 and -4 mm Hg.

COMMENT: In this small study the point estimates for BP reductions are greater for aliskiren 150 mg than for 75 mg.

10.1.2.4 Safety Summary

One patient dropped out because of headaches, also noted prior to starting the study. Two other patients also reported headaches. There were not deaths or SAEs.

COMMENT: This study is too small to inform safety.

10.1.2.5 Conclusions

The report interprets the results as suggesting a dose response. The study is appropriately a pilot study justifying the further studies.

10.1.3 Study 2201 - A multicenter, randomized, double-blind, placebo-controlled, parallel-group study comparing aliskiren 150 mg, 300 mg, and 600 mg to placebo and irbesartan 150 mg in patients with mild-to-moderate essential hypertension

10.1.3.1 Background

The sponsor describes this study as a dose selection study. It is, however, a large, multiple dosage, placebo-controlled that should provide primary evidence of efficacy. The formulation used was different than the to-be-marketed formulation.

10.1.3.2 Initial Protocol

The one protocol provided is dated November 6, 2002.

10.1.3.3 Protocol Amendments

There were no protocol amendments.

10.1.3.4 Sites and Investigators

There were 56 centers: 41 in the US, 14 in Germany, and 1 in Belgium.

10.1.3.5 Study Dates

The first patient was enrolled March 18, 2003, and the last patient completed on October 20, 2003.

10.1.3.6 Study Design

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

10.1.3.7 Objectives

The primary objective of this study was to determine the blood pressure lowering effects of aliskiren 150, 300, and 600 mg compared to placebo in patients with mild-to-moderate essential hypertension. The secondary objectives were to determine: (1) the dose response relationship of the blood pressure lowering effects of aliskiren 150, 300, and 600 mg in patients with mild-to-moderate essential hypertension, (2) the trough-to-peak antihypertensive effect of aliskiren, and (3) the efficacy, safety and tolerability of aliskiren compared to irbesartan and placebo.

10.1.3.8 Number of Subjects, Randomization, and Blinding

The planned number of subjects was 620. Randomization was by interactive voice response system (IVRS)—stratification or blocking is not stated. Blinding was accomplished by using identical appearing capsules for all study drugs. If necessary, unblinding was to be accomplished by IVRS.

10.1.3.9 Inclusion and Exclusion Criteria

The inclusion criteria were the following: male or female age ≥ 18 ; if fertile female using effective contraception; DBP 90-109 at visit 1 and 95-109 at visit 2; DBP difference between visits 1 and 2 ≤ 10 ; and informed consent.

The exclusion criteria were the following: DBP > 109 or SBP > 179 ; inability to stop prior antihypertensives; secondary hypertension; grade III-IV retinopathy; history of hypertensive encephalopathy or stroke; TIA within 12 months; history of significant cardiac disorder (e.g., HF or MI within 12 months, unstable angina, arrhythmias); diabetes with HbA1c $> 8\%$; ARB hypersensitivity; volume depletion; any condition altering ADME; malignancy within 5 years; life-threatening disease; drug or alcohol abuse within 12 months; pregnant or nursing; any condition per investigator producing higher risk; noncompliance; any condition jeopardizing safety or efficacy; other study within one month; and directly involved in study.

10.1.3.10 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 five treatment groups: aliskiren 150, 300, or 600 mg; irbesartan 150 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 after the last dose of study medication. In addition, at selected centers, blood pressure measurements were obtained at visit 4 and visit 6 prior to dosing and again at 2, 4, and 6 hours after dosing for the assessment of trough to-peak antihypertensive effect. A diagram of the study plan is presented in Figure 21.

Figure 21: Study 2201 Plan

Washout	Single-blind run-in	Double-blind treatment					Drug withdrawal
2 weeks	2-4 weeks	8 weeks					4 days
Visit 0	1	2	3	4	5	6	7
Week -6 to -4	-4 to 0	0	2	4	6	8	8.5
		↓ Randomization					
		Aliskiren 150 mg o.d					
		Aliskiren 300 mg o.d					
		Aliskiren 600 mg o.d.					
		Irbesartan 150 mg o.d.					
		Placebo o.d.					

Blood pressures were measured in triplicate using standard sphygmomanometers after the patient had been sitting for five minutes and again after standing for two minutes. Safety assessments consisted of monitoring and recording all AEs and pregnancies; hematology, blood chemistry and urine (performed at the central laboratory) and ECGs at beginning and end; and regular assessments of physical condition, height and body weight.

10.1.3.11 Treatment

10.1.3.12 Dosage and Administration

All dosing was orally (two capsules) at about 8:00 a.m.

10.1.3.13 Duration and Adjustment of Therapy

Duration of treatment was eight weeks followed by a four-day withdrawal. No adjustments were done.

10.1.3.14 Concomitant Therapy

Other antihypertensives were prohibited.

10.1.3.15 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. It proposed safety assessments as follows: "Safety assessments will consist of monitoring and recording all adverse events (AEs) and serious adverse events (SAEs), the regular monitoring of hematology, blood chemistry and urine values, regular measurement of vital signs and the performance of

physical examinations and ECGs.”

10.1.3.16 Statistical Considerations

10.1.3.17 Sample Size Calculations

A sample size of 620 patients was estimated based on these assumptions: 90% power, 4 mm Hg difference of at least one aliskiren group from placebo, 8 mm Hg standard deviation, dropout rate of 15%, and Dunnett’s procedure to adjust for the multiple comparisons.

10.1.3.18 Analysis Cohorts and Missing Data

The planned primary analysis cohort was modified ITT—randomized patients who had at least one post-baseline measurement. Missing data were to be handled by LOCF.

10.1.3.19 Pre-specified Analyses

The primary analysis stated in the protocol was a two-way analysis-of-covariance model (ANCOVA) with treatment and region as factors and baseline as a covariate. To assess the primary objective, the null hypothesis of no treatment difference among the three aliskiren doses (150, 300, and 600 mg) and placebo was to be tested versus the alternative hypothesis that at least one aliskiren dose has a treatment effect different from placebo. If the global test results were significant, pairwise comparisons of each dosage level with placebo were to be done using Dunnett’s procedure to adjust for the multiple comparisons.

10.1.3.20 Results

10.1.3.21 Study Implementation

There were no problems reported with study implementation.

10.1.3.22 Disposition of Subjects

A total of 793 patients were enrolled into the single-blind phase of this study. Of these, 652 patients were randomized, and 141 were screening failures. The most common reasons for discontinuation from the single-blind phase were failure to meet blood pressure criteria (69), withdrawal of consent (19) and abnormal test procedure results (15). The disposition of the randomized patients is shown in Table 64.

Table 64: Sponsor's Disposition of Patients in Study 2201

Disposition	Placebo	Aliskiren 150 mg	Aliskiren 300 mg	Aliskiren 600 mg	Irbesartan 150 mg	Total
	N=131 n (%)	N=127 n (%)	N=130 n (%)	N=130 n (%)	N=134 n (%)	N=652 n (%)
Randomized	131 (100.0)	127 (100.0)	130 (100.0)	130 (100.0)	134 (100.0)	652 (100.0)
Completed	109 (83.2)	115 (90.6)	119 (91.5)	120 (92.3)	123 (91.8)	586 (89.9)
Discontinued	22 (16.8)	12 (9.4)	11 (8.5)	10 (7.7)	11 (8.2)	66 (10.1)
Reason for discontinuation						
Adverse event(s)	3 (2.3)	5 (3.9)	4 (3.1)	3 (2.3)	3 (2.2)	18 (2.8)
Abnormal laboratory value(s)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)*	0 (0.0)	1 (0.2)
Unsatisfactory therapeutic effect	10 (7.6)	2 (1.6)	5 (3.8)	1 (0.8)	3 (2.2)	21 (3.2)
Protocol violation	3 (2.3)	1 (0.8)	1 (0.8)	2 (1.5)	0 (0.0)	7 (1.1)
Patient withdrew consent	5 (3.8)	2 (1.6)	0 (0.0)	2 (1.5)	3 (2.2)	12 (1.8)
Lost to follow-up	1 (0.8)	2 (1.6)	1 (0.8)	0 (0.0)	2 (1.5)	6 (0.9)
Other	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.2)

COMMENT: The dropout rates are acceptable. The higher dropout in the placebo group is accounted for by the unsatisfactory therapeutic effect, withdrawing consent, and protocol violations.

10.1.3.23 Subject Demographics and Baseline Characteristics
 Demographics and other selected baseline characteristics are shown in Table 65.

Table 65: Reviewer's Baseline Characteristics in Study 2201

	Placebo	Aliskiren			Irbesartan	Total
		150	300	600		
Male %	49	58	42	53	49	50
Black %	18	15	12	20	22	17
Other race %	7	8	8	3	4	6
Median age	57	56	55	55	57	56
Age ≥65 %	24	25	19	20	25	23
Median BMI	30	30	29	30	30	30
Median SBP	152	151	152	153	153	151
Median	98	98	98	98	98	98

DBP						
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The majority of blacks were female (64%) while about half of whites were female (48%).

COMMENT: Note that aliskiren 300 mg group has a lower percentage of blacks. Otherwise the demographic and baseline factors are well balanced among the groups.

10.1.3.24 Conduct

10.1.3.25 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. The sponsor describes an audit approach but does not provide details on audits, if any.

10.1.3.26 Protocol Changes and Violations

There were no protocol changes. Overall 93 patients were excluded from a per-protocol analysis due to protocol deviations. The major reason for excluding patients from the per-protocol analysis was failure to complete the final assessment (66). Other reasons for exclusion from the per-protocol analysis were use of excluded medications (13), failure to meet blood pressure criteria (6), compliance with study medication (5), excluded surgical history (2) and therapy duration (1).

10.1.3.27 Dosing

10.1.3.28 Study Drug

This study used a formulation different from the to-be-marketed formulation. Dosing was once daily. The sponsor did not report any problems with study drug dosing. The sponsor did not provide compliance statistics.

10.1.3.29 Concomitant Therapy

Overall, 52% of the patients took concomitant medications that started prior to start of double-blind randomization and continued during the study, but the use of individual medications was low. The most frequently used medication was acetylsalicylic acid (9%). Approximately one quarter of the patients started taking concomitant medications during the double-blind treatment period, and the most frequently used medication was ibuprofen (4% overall). Only 5% of the patients started taking concomitant medications during the withdrawal period, and the most frequently used medication was hydrochlorothiazide (1%).

10.1.3.30 Blinding

The sponsor did not report any problems with blinding or cases of unblinding.

10.1.3.31 Efficacy

10.1.3.32 Primary Endpoint

The sponsor's analysis of the primary endpoint (ANCOVA of LOCF DBP at eight weeks with treatment and region as factors and baseline as covariate) is shown in Table 66.

Table 66: Sponsor's Statistical Analysis of Change from Baseline in MSDBP (mmHg) at Endpoint (ITT population) in Study 2201

Treatment Group	N	LSM change from baseline (SE)	
Placebo	130	-6.34 (0.75)	
Aliskiren 150 mg	127	-9.28 (0.76)	
Aliskiren 300 mg	130	-11.77 (0.75)	
Aliskiren 600 mg	129	-11.50 (0.75)	
Irbesartan 150 mg	133	-8.88 (0.74)	

Pairwise Comparison	LSM difference in change from baseline (SE)	95% CI for LSM difference	P-Value
Aliskiren 150 mg vs. Placebo	-2.94 (1.04)	(-4.98, -0.90)	0.0047*
Aliskiren 300 mg vs. Placebo	-5.43 (1.03)	(-7.46, -3.40)	<.0001*
Aliskiren 600 mg vs. Placebo	-5.16 (1.03)	(-7.20, -3.13)	<.0001*
Aliskiren 150 mg vs. Irbesartan 150 mg	-0.40 (1.03)	(-2.43, 1.63)	0.6958
Aliskiren 300 mg vs. Irbesartan 150 mg	-2.89 (1.03)	(-4.91, -0.87)	0.0051*
Aliskiren 600 mg vs. Irbesartan 150 mg	-2.63 (1.03)	(-4.65, -0.61)	0.0109*
Irbesartan 150 mg vs. Placebo	-2.54 (1.03)	(-4.56, -0.52)	0.0137*

* indicates statistical significance at 0.05 level.

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

COMMENT: All aliskiren dosages reduce DBP significantly. The 600 mg dosage does not have a greater effect than the 300 mg dosage in this study.

10.1.3.33 Secondary Endpoints

The average changes in DBP by visit and group are shown in Figure 22.

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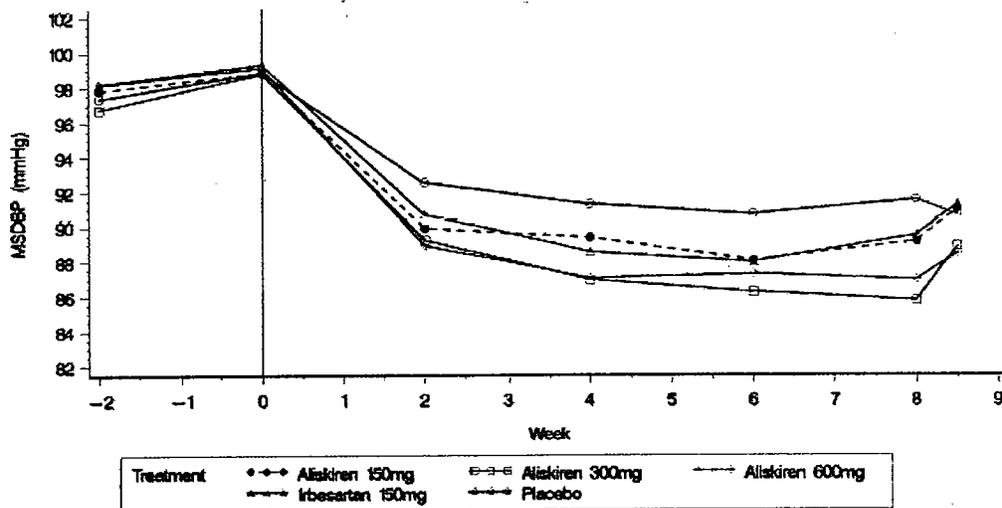


Figure 22: Sponsor's Average MSDBP by Week and Treatment (ITT Population) in Study 2201

COMMENT: As the sponsor notes, the reductions with aliskiren are well developed by the week 2 visit. Also note that the screening average DBP is lowest in the aliskiren 300 mg group.

The sponsor's analysis of the change in SBP is shown in Table 67.

Table 67: Sponsor's Statistical Analysis of Change from Baseline in MSSBP (mmHg) at Endpoint (ITT population) in Study 2201

Treatment Group	N	LSM change from baseline (SE)
Placebo	130	-5.28 (1.23)
Aliskiren 150 mg	127	-11.38 (1.25)
Aliskiren 300 mg	130	-15.76 (1.23)
Aliskiren 600 mg	129	-15.73 (1.23)
Irbesartan 150 mg	133	-12.50 (1.21)

Pairwise Comparison	LSM difference in change from baseline (SE)	95% CI for LSM difference	P-Value
Aliskiren 150 mg vs. Placebo	-6.07 (1.70)	(-9.41, -2.74)	0.0004*
Aliskiren 300 mg vs. Placebo	-10.47 (1.69)	(-13.76, -7.16)	<.0001*
Aliskiren 600 mg vs. Placebo	-10.44 (1.69)	(-13.76, -7.12)	<.0001*
Aliskiren 150 mg vs. Irbesartan 150 mg	1.14 (1.69)	(-2.18, 4.46)	0.5014
Aliskiren 300 mg vs. Irbesartan 150 mg	-3.26 (1.68)	(-6.56, 0.03)	0.0523
Aliskiren 600 mg vs. Irbesartan 150 mg	-3.23 (1.68)	(-6.53, 0.07)	0.0553
Irbesartan 150 mg vs. Placebo	-7.21 (1.68)	(-10.50, -3.91)	<.0001*

* indicates statistical significance at 0.05 level.

For SBP the aliskiren 150 mg group had the lowest screening SBP. The average changes in DBP by visit and group are shown in Figure 23.

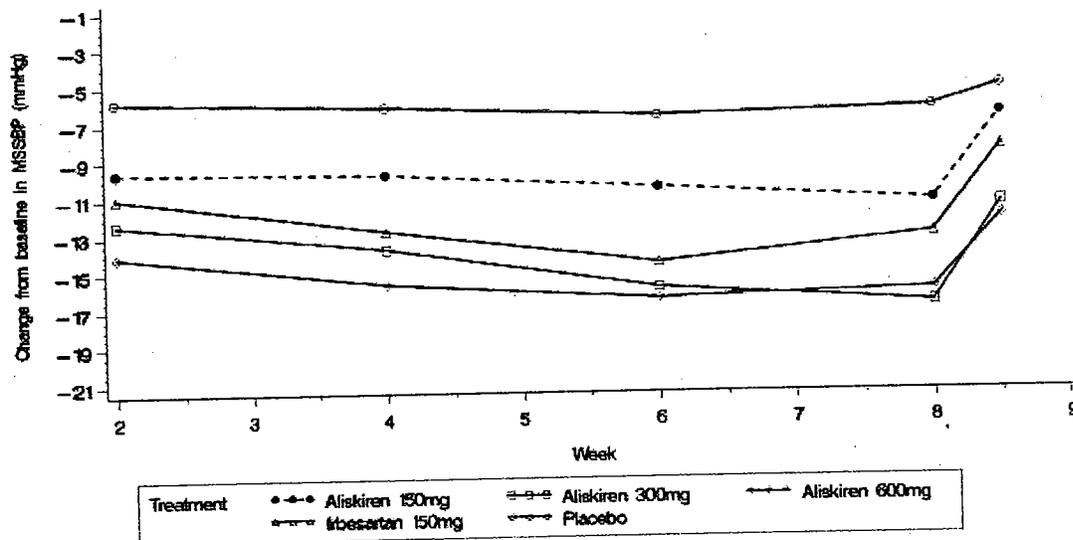


Figure 23: Sponsor's Average Change from Baseline in MSDBP by Week and Treatment (ITT Population) in Study 2201

COMMENT: The average SBP changes by week suggest that there may be a greater effect of the 600 mg dosage than the 300 mg dosage and that the effects may not be maximal by two weeks. Dropouts and LOCF may be confounding the later changes.

The sponsor's presentation of trough-to-peak ratios for DBP is shown in Table 68.

Table 68: Sponsor's Analysis of Trough-to-peak Ratios in MSDBP (mmHg) at Endpoint (ITT population) in Study 2201

Treatment Group	LSM change from baseline (SE)			
	Hour 0	Hour 2	Hour 4	Hour 6
Placebo	-6.26 (1.07)	-10.03 (1.07)	-9.15 (1.07)	-8.83 (1.09)
Aliskiren 150 mg	-8.03 (1.10)	-12.58 (1.10)	-12.45 (1.10)	-11.71 (1.10)
Aliskiren 300 mg	-11.78 (1.00)	-15.90 (1.00)	-16.08 (1.01)	-16.38 (1.01)
Aliskiren 600 mg	-12.19 (1.03)	-16.44 (1.03)	-17.87 (1.03)	-16.62 (1.03)
Irbesartan 150 mg	-9.20 (1.04)	-14.68 (1.04)	-14.90 (1.04)	-14.78 (1.04)
Treatment Group	Trough-to-Peak Ratios			
	Hour 2	Hour 4	Hour 6	
Aliskiren 150 mg	0.69	0.53	0.63	
Aliskiren 300 mg	0.94	0.80	0.74	
Aliskiren 600 mg	0.92	0.68	0.78	
Irbesartan 150 mg	0.63	0.51	0.50	

SE = Standard Error, LSM = Least Squares Mean.

I re-analyzed the data for trough-to-peak ratios in this study because, having measurements from two days (four weeks and eight weeks) at four times (0, 2, 4, and 6 hours post-dosing) each day, they should be very helpful in understanding the time course of BP reductions after aliskiren administration. The reductions in BP were greatest at the four hour time point for aliskiren. I show the DBP reductions from baseline at the 8-week visit in Table 69.

Table 69: Reviewer's Changes from Baseline in DBP at Week 8 by Hour in Study 2201

Hour:	0	2	4	6
Aliskiren 150 mg	-8.3	-12.9	-13.1	-12.1
Aliskiren 300 mg	-12.4	-16.9	-17.4	-17.3
Aliskiren 600 mg	-12.6	-16.9	-18.3	-17.8
Irbesartan 150 mg	-9.7	-15.7	-15.4	-15.2
Placebo	-7.7	-11.8	-11.2	-10.8

Note that the placebo group shows a small decrease in BP over the six hour period. The reductions in BP in each group tended to be higher at 8 weeks than at 4 weeks but, because the placebo reductions were also higher, the time-specific placebo-corrected values were similar for 4 and 8 weeks. I calculated the trough-to-peak ratios by subtracting the placebo values for each time point from the other group's values for the same time point. I then calculated the ratio of the hour 0 time-specific placebo-corrected value to the corresponding value at hour 4. I show these trough-to-peak ratios in Table 70.

Table 70: Reviewer's Trough-to-peak Ratios in Study 2201

	Week 4		Week 8	
	SBP	DBP	SBP	DBP
Aliskiren 150 mg	0.4	0.3	0.7	0.3
Aliskiren 300 mg	0.6	0.8	0.9	0.8
Aliskiren 600 mg	0.8	0.6	0.8	0.7
Irbesartan 150 mg	0.5	0.6	0.8	0.5

COMMENT: The trough-to-peak ratios for aliskiren 150 mg are inadequate except for SBP at week 8 (and this value may be confounded by an usually low placebo value at hour 0 at week 8—note that all of the ratios are high for SBP at week 8). These ratios suggest that BID dosing may be more appropriate for aliskiren.

10.1.3.34 Subgroup Analyses

10.1.3.35 Region

The primary endpoint results (change from baseline in DBP) by region (U.S. vs. Western Europe, i.e., Germany and Belgium) are shown in Table 71.

Table 71: Reviewer's Mean Change from Baseline in DBP by Region in Study 2201

	Europe	U.S.
Irbesartan	-9.8	-8.6

	Europe	U.S.
Placebo	-7.1	-6.3
150	-9.7	-9.4
300	-11.9	-12.0
600	-12.4	-11.3

COMMENT: The primary endpoint results do not appear to vary much by region.

10.1.3.36 Race

The primary endpoint results by race are shown in Table 72.

Table 72: Reviewer's Mean Change from Baseline in DBP by Race in Study 2201

	White	Black	Other
Irbesartan	-9.5	-7.6	-7.8
Placebo	-6.1	-7.2	-9.7
150	-9.9	-6.6	-10.6
300	-12.5	-8.6	-11.5
600	-12.4	-9.0	-10.2

The reductions are less in blacks for both aliskiren and irbesartan. The differences are more pronounced for SBP with aliskiren, but not with irbesartan, as shown in Table 73.

Table 73: Reviewer's Mean Change from Baseline in SBP by Race in Study 2201

	White	Black	Other
Irbesartan	-12.1	-12.8	-16.9
Placebo	-5.3	-3.8	-6.6
150	-11.4	-6.8	-12.5
300	-17.0	-7.4	-12.2
600	-16.5	-11.6	-17.7

COMMENT: Blacks appear to be less responsive to aliskiren than whites. Because the gender distribution differs for blacks and whites (see Section 10.1.3.23) and because females appear to show a greater placebo effect (see Section 10.1.3.37), I also examined BP changes by race and gender. Although not shown and within the limitations of small number (e.g., 10 or fewer black males in each treatment group and as low as 4), there does not appear to be a gender effect other than the difference in placebo responses and there does not appear to be a gender/race interaction. I examine the issue of less responsiveness of blacks further in the Integrated Review of Efficacy, Section.

10.1.3.37 Age and Gender

The primary endpoint results by age < or ≥ 65 are shown in Table 74 and by gender are shown in Table 75.