

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-985

MEDICAL REVIEW(S)

Memorandum

From: Office Director's Overview
Date: March 5, 2007
Subject: NDA 21-985, Tekturna (aliskiren)
Sponsor, Novartis

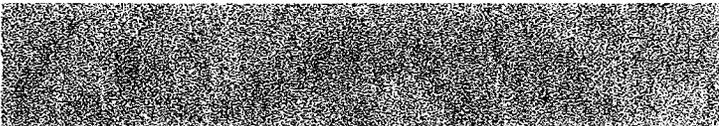
I. Introduction

Aliskiren is the first renin antagonist antihypertensive, joining angiotensin converting enzyme inhibitors (ACEI's), direct angiotensin receptor blockers (ARB's), and beta blockers (part of whose effect involves the renin-angiotensin system) as drugs that have their effect by inhibiting the renin-angiotensin-aldosterone system (RAAS). The drugs are, as a class, well-tolerated, although all can on occasion cause excessive falls in blood pressure, and hyperkalemia. The ACEI's and ARB's cause, if used in the second and third trimesters, fetal renal and other abnormalities, and should not be used at that time; aliskiren will bear a similar warning. ACEI's cause a significant rate of cough (more than 5%), thought related to inhibition of bradykininase, and a lower, but troublesome, rate of significant angioedema of the head and neck. ARBs and beta blockers do not do this and there is uncertainty as to whether, and to what extent, aliskiren carries this risk. This is discussed further below. Cough is clearly less common with aliskiren than with ACEI's. Diarrhea is clearly caused by aliskiren, but at a low rate at the 300mg maximum recommended dose.

II. Additive effects with other drugs

The effectiveness of aliskiren was evaluated at doses from 75-600mg once daily with useful effects at 150-600mg, but no consistently greater effect of 600mg than 300mg. The 6 placebo-controlled trials results including the zero diuretic arms of an HCTZ/aliskiren combination study; are shown in labeling, with 300mg giving a seated BP of 5-11/3-7.5 (5 of the 6 give 8-11/3.5-7.5), typical of the RAAS drugs. (Actually, a 7th trial testing the valsartan-aliskiren combination could have been included and showed a similar effect).

Although mechanistically one would not expect renin inhibitors, ACEI's, and ARB's, used at maximum effective doses, to have additive effects, this has not always been the case in



hypertension or in heart failure (another major use of ACEI's). Thus candesartan has been shown to have added benefit in people on maximum doses of ACEI's (the CHARM added study, reflected in current labeling for candesartan). Aliskiren has been shown to have an added blood pressure effect when used with valsartan (an ARB). As responses here do not seem wholly predictable (valsartan did not seem to have an added effect with full doses of ACEI's), we are asking for studies of the combinations. Thus aliskiren labeling will note the lack of information on use with full doses of ACEI's. (We presume all RAAS inhibitors will have added effects when used with sub-maximal doses of any of the RAAS drugs, including members of the same class). Like all RAAS inhibitors, aliskiren has additive effects with diuretics. One would expect such an effect with dihydropyridine CCB's but this has not been adequately studied.

III. Major Safety Issues

The principal safety concern with aliskiren was a finding in mice and rats of rapidly occurring lower-intestinal epithelial hyperplasia, with single cases of colonic adenoma and cecal adenocarcinoma in the rat. While single tumors are very hard to interpret, these are very rare (less than 0.1%) in the rat strain studied. A human colonic biopsy study in 30 normal volunteers after 8 weeks of 300mg/day showed no evidence (no cases) of colonic mucosal hyperplasia, long enough to have seen the effect observed in the rat, and providing a very high degree of assurance that aliskiren will not cause hyperplasia or tumors. The drug is not mutagenic. See Dr. Marciniak's detailed review of 2/26/07. The sponsor has agreed to examine this further in a planned sizable long-term outcome study. (See Dr. Stockbridge's memo for details).

IV. DSI review

DSI found minor problems at several sites and more important violations at one site regarding BP effect, but these clearly cannot effect a 6000+ patient database with at least 7 (5 placebo, 2 combination studies) studies showing effectiveness.

V. Clinical Pharmacology; dose interval

As Dr. Stockbridge notes, aliskiren is minimally bioavailable (about 2.5-3%) and its bioavailability is modestly affected by many factors, reduced by a fatty meal, increased by CYP 450 3A 4 inhibitors, but given documented effectiveness over at least a 4 fold range (150-600mg) and reasonable tolerability over this range, these differences seem unlikely to be a problem. It is also notable that in one randomized withdrawal study after 11 months on drug effects persisted for 1-2 weeks, suggesting that acute blood levels and acute PRA inhibition are not the source of the blood pressure effect. Moreover, PRA after a 300mg dose returns to pre-treatment levels by about 10 hours, suggesting some dissociation of pharmacologic and anti-hypertensive effect (see Marciniak 12/5/06 review, p 38). Somewhat against a prolonged effect however, is variable evidence on trough/peak ratio, which is not the near 100% one would expect for a drug with a 2 week persisting antihypertensive effect.

I also note that a placebo controlled discontinuation in study 2308, after 8 weeks of Rx, showed a considerable loss of effect after just a few days (Marciniak 12/5/06 review, p 43, 45). The sponsor has agreed to explore the effect of daily dose interval further, either by comparing once daily and daily dosing, or some other way.

VI. ACEI-type effects

A renin inhibitor would not be expected to produce the cough and angioedema characteristic of ACEI's. For ACEI package inserts that give rates, angioedema is reported as about 0.1% to 0.2% (quinapril, ramipril, trandolapril) to 0.4-0.5% (benazepril, moexipril), or, all in all, about 1-4/1000. In the aliskiren database there were 4 cases, 2-3 with respiratory symptoms, (see Marciniak 12/5/06, p 69) for a rate of about 0.06%, roughly 1/2 to 1/6-8 the rate reported for most ACEI's. The rate thus seems somewhat lower than with ACEI's but there are difficulties with such an indirect comparison. First, cross-study comparisons are difficult; as is with such one cannot be sure the search for, or definition of events is the same. Second, edema involving the face, hands, or whole body was fairly common in both aliskiren, placebo, and active control (HCTZ) groups, about 0.4-0.5%, making differential diagnosis critical. Again, it is very difficult to be sure this was done.

Cough occurred at a pooled rate on placebo of 0.6%, compared with 1.1% for any dose (or 300mg) of aliskiren. Whether this is a real difference is hard to say. Rates with ACEI's in comparative studies were clearly higher (1.7% to 4.7%), generally about 3 times the aliskiren rate (Marciniak review of 12/5/06, p 74-75).

VII. Disagreements

There were no disagreements among reviewers and supervisors as to the approval action, phase 4 commitments, or labeling.

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/s/

Robert Temple
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MEDICAL OFFICER



DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Divisional Memorandum

NDA: 21-985 (aliskarin for hypertension)

Sponsor: Novartis

Review date: 28 February 2007

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

Distribution: NDA 21-985

DCaRP/David/Jagadeesh/Marciniak

OB/Liu

ONDC/Ysern

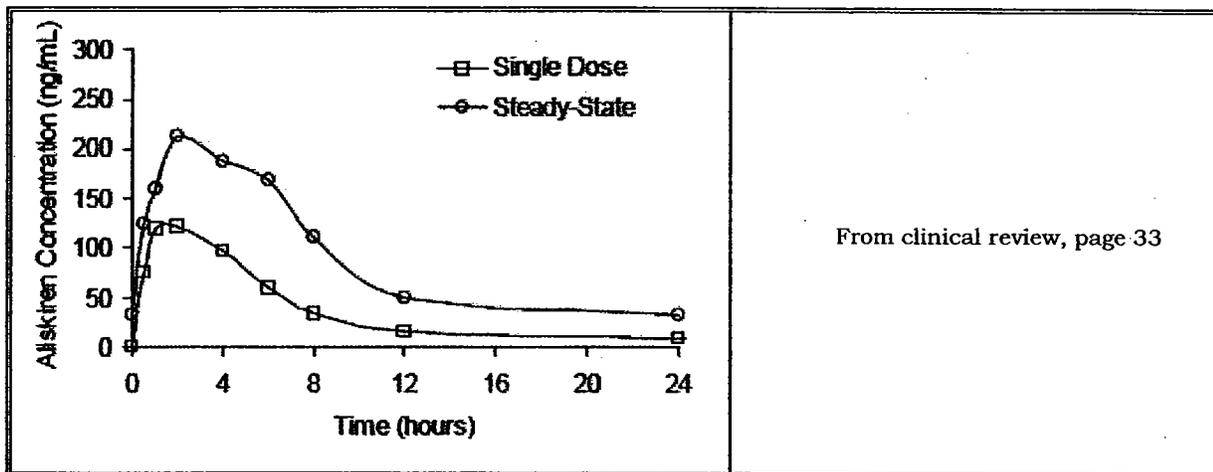
OCP/Valazquez/Madabushi/Garnett

This memo lays out the Division's recommendations regarding the approval of aliskiren. If approved, aliskiren would be the first renin inhibitor for hypertension.

NDA 21-985 had primary reviews by Dr. Ysern (CMC; 1 November 2006 and 21 December 2006), Dr. Jagadeesh (pharmacology; 28 September 2006 and 13 February 2007), Drs. Valazquez and Madabushi (clinical pharmacology and biopharmaceutics; 11 January 2007), Marciniak (medical; 7 December 2006 and 26 February 2007). There is a statistical review for carcinogenicity (Liu; 5 September 2006), but no statistical review of the clinical studies. QT effects were assessed by Drs. Garnett (pharmacometrics) and Targum (clinical).

Three issues arise from the pharmacology review. First, although there are compelling data for renin inhibition, there are no good data relating to other pharmacological activities, even those affecting the renin-angiotensin system. Second, the primary toxicity appears to be GI irritation, mostly in the lower GI tract, characterized by hyperplasia of the mucosal epithelium, erosions, and ulcerations. Third, possibly related to GI effects, there were precancerous effects in the mouse—focal atypical hyperplasia in 8% of mice on drug and 0% on controls—and two tumors in the rat 2-year study, one colonic adenoma and one cecal adenocarcinoma (a rate of 4% for tumors considered rare— <0.1% —as a background event. None of these findings were statistically significant. A subsequent study of the effects of aliskiren on GI permeability in rat and human colonic epithelia suggests that rats are more sensitive to aliskiren.

Absolute bioavailability of aliskiren is about 3%. Plasma levels rise less than proportionally with dose. The T_{max} is 2 h, and the elimination half-life is about 40 h (accounting for 5-7 days of repeat daily dosing to achieve quasi-steady state at around twice the single-dose exposure). At quasi-steady-state, plasma levels are about 5-fold higher at C_{max} than they are at C_{min}.

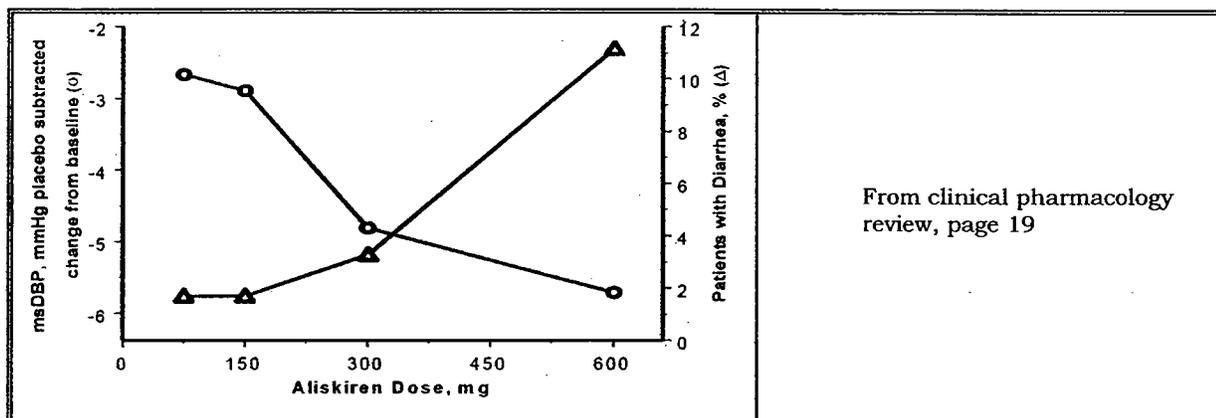


From clinical review, page 33

A high-fat meal reduces C_{max} by 85% and AUC by a lesser amount. If that does not matter (and it did not affect the instructions for use in clinical trials), then a host of lesser and less well characterized effects cannot matter much either—age, questionable effects of renal impairment, and drug-drug interactions (most prominently ketoconazole). When meals and other factors are controlled, intra-subject variability is only about 20%.

Effectiveness and the rate of diarrhea increase in tandem with dose, as shown in the figure below. Although the rate is high, diarrhea was seldom a cause for study drug discontinuation. Nevertheless, both exposure-blood pressure and exposure-diarrhea analyses support dosing 150 and 300 mg.

The data with 300 mg, ABPM data after 8 weeks, and randomized withdrawal data support once-daily dosing, but the wide variation in plasma levels through the interdosing interval suggest that twice-daily dosing should have been studied.



From clinical pharmacology review, page 19

There is little hysteresis in the relationship between plasma levels of aliskirena and plasma renin activity, at least at steady-state, but I see no similar analysis for blood pressure.

Use of aliskiren with amlodipine and valsartan appeared to show incremental benefits attributable to each drug. Appropriate studies have not been performed with high doses of an ACE inhibitor, so use with an ACE inhibitor would be quite speculative.

QTcF is little affected by aliskiren.

The possible relationship among GI irritation, colonic epithelial hyperplasia, and the several reported GI tumors in the pre-clinical studies led the sponsor to conduct a special 8-week, high-dose colonoscopy study in normal volunteers looking for hyperplasia. The sponsor's blinded reading of the biopsy data found no differences between study drug and placebo. The Division's review also included a blinded review of slides by Dr. Williams and was entirely consistent with the sponsor's findings. Some immunohistological data are still outstanding from this study, but the interpretation of those data will not be straightforward, and not having those data should not impede approval. In this decision, our consultants in Oncology are agreed.

The full set of post-marketing commitments upon which the sponsor and the Agency have agreed are as follows:

To establish an assay method and acceptance criterion for —SPPIOO Assay method and assay specification will be introduced into the testing monograph No. RM-5000702 for — post approval by March 2007. The revised testing monograph will be submitted to FDA in the first NDA Annual Report.

To re-evaluate the specifications for the — when further data are available from the additional manufacturing sites. Novartis expects to have this data evaluation completed by June 2007. The study results should be submitted by August 2007.

To submit the results of the cellular markers of proliferation and apoptosis from Study 2103 as soon as they are available, but no later than September 2007.

To include intestinal procedures and neoplasms and angioedema as events of special interest in your proposed ALTITUDE trial as detailed in the special protocol assessment letter. The revised protocol, including case report forms, should be submitted no later than September 2007.

To incorporate a colonoscopy substudy into your proposed long-term outcome study. The colonoscopy substudy should include colonoscopies performed at baseline and after drug treatment for 12 months or longer. This study should be powered to rule out a doubling in the rate of cancerous or precancerous lesions. You should discuss this substudy with the Agency and submit the protocol no later than September 2007. The substudy should be completed no later than February 2009. The study results should be submitted by May 2009.

You should provide evidence that it is not likely to be clinically useful to give aliskiren in a twice-daily dosing regimen to patients whose blood pressure is not controlled on the highest recommended dose given once daily. These data could come from a study comparing once- and twice-daily dosing, but the Division would consider alternative strategies to address this issue. You and the Division should reach an agreement by June 2007 on the strategy to address this deficiency. If a study is required, that study should be completed and reported by February 2009

Clinical and manufacturing inspections were adequate. Financial disclosure was adequate. Pediatric studies have been deferred. The tradename Tekturna raises no concerns.

I support approval of aliskiren for the treatment of hypertension.

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/s/

Norman Stockbridge
2/28/2007 03:04:55 PM
MEDICAL OFFICER

CLINICAL REVIEW ADDENDUM

Application Type NDA 21-985
Submission Number 000
Submission Code 1S

Letter Date 02/10/06
Stamp Date 02/13/06
PDUFA Goal Date 03/13/07

Reviewer Name Thomas A. Marciniak, M.D.
Review Completion Date 02/26/07

Established Name aliskiren
(Proposed) Trade Name Tekturna
Therapeutic Class anti-hypertensive
Applicant Novartis

Priority Designation S

Formulation tablets
Dosing Regimen once daily
Indication treatment of hypertension
Intended Population hypertensive adults

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

From a clinical perspective I recommend approval of aliskiren for the treatment of hypertension in adults. The one issue outstanding from my review of the original NDA submission was whether there was substantial evidence conforming that aliskiren does not cause colonic mucosal hyperplasia in humans as it does in rodents. In this addendum I review the results of a colonoscopy biopsy study in humans that was negative, i.e., there was no evidence of colonic mucosal hyperplasia after exposure to aliskiren 300 mg daily, the maximum recommended human dosage, for eight weeks. In rodents hyperplasia was detected after exposure for a few weeks. This human colonic biopsy study is reassuring that aliskiren does not cause hyperplasia in humans.

In this addendum I also review the results of a second aliskiren/valsartan combination study. This study shows that the combination of aliskiren and valsartan, each at the maximum recommended dosage, provides incremental reductions in blood pressure over that produced by the corresponding monotherapies. These results are relevant to the labeling of aliskiren monotherapy for use alone or in combination with other antihypertensives because an initial study of the combination failed to show an incremental benefit. This study included reasonable numbers of blacks and demonstrated blood pressure reductions with the monotherapy in blacks. All of the findings from this study will be incorporated into the labeling and will help clinicians in understanding how to use this drug.

1.2 Recommendation on Postmarketing Actions

The sponsor is planning large outcome trials in heart failure and in high risk coronary artery disease patients. I recommend that the sponsor incorporate specific questions regarding the occurrences of colonoscopies, colonic polyps, intestinal cancers, or other intestinal pathology in these patients. The sponsor should collect colonoscopy reports and reports of intestinal surgery in these patients.

2 INTRODUCTION AND BACKGROUND

This review is an addendum to my clinical review for the initial NDA submission for aliskiren. Aliskiren (SPP100, Tekturna) is an orally active renin inhibitor, the first of its class submitted for approval. The initial indication for aliskiren is the treatment of hypertension in adults. During the review of the initial NDA submission we identified a potential problem: Aliskiren causes diarrhea and colonic mucosal hyperplasia in rodents. In humans aliskiren causes diarrhea, particularly at dosages slightly higher than the proposed to-be-marketed dosages. The sponsor submitted late in the review cycle the results of a colonic biopsy study in humans. We considered the submission of this study to be a major amendment and extended the PDUFA goal date by three months. This review critiques the human colonic biopsy study.

The sponsor also submitted recently the full study report for Study 2327 of aliskiren in combination with valsartan. Because an earlier aliskiren/valsartan combination study (Study 2203) failed to show an additive anti-hypertensive effect of the two drugs in combination, Study 2327 is highly relevant to labeling of aliskiren in combination with other agents. In addition, Study 2327 includes reasonable representation of blacks, so it is also highly relevant to labeling of aliskiren for use in blacks. This review also critiques Study 2327.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The sources of clinical data are the NDA submissions since my review of the initial NDA submission. I have listed all the later NDA submissions in Table 1.

Table 1: NDA Submissions Since Initial NDA Review

Date	Description	This Review
2006-11-21	Treatment start and end dates in SAS files	
2006-11-29	Response to question on hygroscopic tablets & stability	
2006-11-30	Dose-response modeling in elderly	
2006-12-01	More dose-response modeling	
2006-12-04	Study 2103 report of human colonic biopsy study	x
2006-12-08	CRFs & explanation of histologic methods for Study 2103	x
2006-12-14	Study 2103 responses	x
2006-12-20	Code break cards	x
2007-01-12	Study 2327 final report	x
2007-01-26	Carton & container labels	

Because some of the later submissions are not relevant to my clinical review and others cover issues that I have addressed in my initial review, I indicate in the last column the submissions that this review covers.

4.2 Tables of Clinical Studies

I have listed the two studies critiqued in this review in Table 2.

Table 2: Clinical Studies Critiqued in this Review

#	N	Wks	Aliskiren/Coadmin	Control	Comment
2103	30 (20 aliskiren)	8	300	Placebo	Colonic biopsy study in healthy volunteers
2327	1797 (4 groups)	8	150-300 ± valsartan 160-320	Placebo, valsartan 160-320	Combo with valsartan; force titrated up at 4 wks

4.3 Review Strategy

The critical issue for approval is the review of the colonic biopsy study, Study 2103. In addition to reviewing the sponsor's presentations of the results and reviewing the photomicrographs, I also enlisted the aid of one of the Division clinical reviewers, who is a pathologist, to check the biopsy slides that I requested the sponsor to submit. For the other study (Study 2327, the valsartan combination study), I focused on the questions of whether valsartan and aliskiren are both contributory in combination and whether the effects in blacks are similar to those in whites. I had already incorporated the safety data from Study 2327 into my integrated safety review of the initial NDA submission, so I only comment briefly on some safety findings from it.

4.4 Data Quality and Integrity

I evaluated the data quality and integrity of Study 2103 by obtaining and reviewing both the source records for the colonoscopies, i.e., the colonoscopy reports and the endoscopic photos taken during them, and the biopsy slides. For evaluating the quality of Study 2327 I reviewed the case report forms and SAS data sets as well as the details of the protocol—probably in order not to repeat the failure of the previous study, the sponsor incorporated some protocol changes that should have enhanced the reliability of the study. I did not request DSI audits on these studies because of the limited time available for audit and the lack of any problem suggesting that audits would be worthwhile.

4.5 Compliance with Good Clinical Practices

Each study report states that the study adhered to Good Clinical Practices.

4.6 Financial Disclosures

For Study —, the submission includes financial disclosure summaries for all of the investigators. A — at one site reported receiving speaker fees in excess of \$25,000 from the sponsor. However, that site did not randomize any patients in the study. Financial disclosures were not provided for Study —, nor did I specifically request them as I did for Study —.

COMMENT: The financial disclosures for Study — are clean. While I have not seen the financial disclosures for Study — the documentation on the conduct of the study is excellent and does not suggest any biases and I am depending upon our own review of the biopsy slides, the critical issue for the study, to avoid any biases from financial influences.

6 INTEGRATED REVIEW OF EFFICACY

The source of new efficacy data for this review addendum is Study 2327, a study of aliskiren and valsartan alone and in combination. In addition to providing data highly relevant to the issue of using aliskiren in combination with angiotensin receptor blockers (ARBs) like valsartan, this study also included reasonable numbers of black patients. Hence it is also highly relevant to the use of aliskiren in blacks.

Study 2327 was entitled “An 8-week randomized, double-blind, parallel group, multi-center, placebo and active controlled dose escalation study to evaluate the efficacy and safety of aliskiren (150 mg and 300 mg) administered alone and in combination with valsartan (160 mg and 320 mg) in patients with hypertension.” It was an international, four-arm (the two monotherapies, the combination, and placebo) study with a forced doubling of initial doses at four weeks and evaluations at four and eight weeks. It enrolled the usual patients with mild-to-moderate essential hypertension (office cuff DBP 95-109) with mean 8-hour ABPM DBP \geq 90 as an inclusion criterion. It studied the proposed to-be-marketed doses of aliskiren (150 and 300 mg) and the highest labeled dose of valsartan and half of that dosage (320 and 160 mg). The study plan is shown in Figure 1.

Figure 1: Sponsor’s Study 2327 Plan

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

¹ If the patient was required to be tapered off the current anti-hypertensive medication then the tapering was to occur at Visit 1. The patient was to be washed out of their anti-hypertensive medication for at least 1 week prior to Visit 2.
² For currently untreated patients Visit 1 and Visit 2 were combined into one Visit.
³ Visit 5 consisted of 2 days. Randomization occurred on the second day of Visit 5.
⁴ Titration occurred at Day 29 (Visit 7) of double-blind treatment.
⁵ Duration refers to the time between current visit and next Visit.
⁶ If the placebo run-in period was extended for 1 week to meet randomization criteria then, Visit 1 became Day -42 (if the duration between Visit 1 and Visit 2 was 2 weeks), Visit 2 became Day -28, Visit 3 became Day -14 and Visit 4 became Day -7.

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

ABPM at visit 5, with the goal of 400 patients (100 per treatment arm) completing both 24-hour ABPM evaluations (at visits 5 and 9).

In the end 1797 patients were randomized; 459 patients were randomized to placebo; 437 patients to the aliskiren group, 455 to the valsartan group, and 446 to the aliskiren/valsartan group. Of the randomized patients, 89% (1601) completed the double-blind treatment phase. Rates of premature discontinuation were lowest in the combination group (8.3%), and highest in the placebo group (13.7%). The increased rate of discontinuation in the placebo group was accounted for by an increase in patients who discontinued due to unsatisfactory therapeutic effect. Few patients discontinued due to adverse events; the incidence was lower in the combination group (7 patients, 1.6%) compared with placebo (10 patients, 2.2%), aliskiren monotherapy (11 patients, 2.5%), or valsartan monotherapy (11 patients, 2.4%).

The mean age was 52 with 12.5% 65 or older. Males comprised 61% of the study population. Regarding race, 75% were white and 16% black. The average baseline BP was about 154/100. Baseline characteristics were reasonably balanced among the four randomization groups.

The sponsor's analysis of the primary endpoint (DBP) is shown in Table 3 and of the secondary endpoint (SBP) in Table 4.

Table 3: Sponsor's Change from Baseline in DBP at Week 8 in Study 2327 (Aliskiren 300 mg and Valsartan 320 mg)

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

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

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

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

* Indicates statistical significance at 0.05 level

Table 4: Sponsor's Change from Baseline in SBP at Week 8 in Study 2327 (Aliskiren 300 mg and Valsartan 320 mg)

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

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

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

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

* Indicates statistical significance at 0.05 level.

Source: PT-Table 14.2-2.1b

COMMENT: These results show reasonable reductions in both DBP and SBP for the monotherapies compared to placebo and reasonable increments, about 4.2-4.4/2.5-3.2, with the combination over the maximum recommended dosages of the monotherapies. The placebo effect in this study (about 5/4) is comparable to what typically see in other antihypertensive development programs and substantially less than that seen in the failed aliskiren/valsartan combination Study 2203.

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Table 5: Sponsor's Change from Baseline in DBP at Week 4 in Study 2327 (Aliskiren 150 mg and Valsartan 160 mg)

Treatment Group	N	LSM change from baseline(SE)	
Placebo	455	-4.80 (0.36)	
Aliskiren	430	-7.46 (0.37)	
Valsartan	453	-8.68 (0.36)	
Aliskiren/Valsartan	438	-10.50 (0.37)	
Pairwise Comparison	LS M difference in change from baseline (SE)	95% CI for LSM difference	P-Value+
Aliskiren vs. Placebo	-2.66 (0.51)	(-3.66, -1.66)	<.0001*
Valsartan vs. Placebo	-3.88 (0.50)	(-4.87, -2.89)	<.0001*
Aliskiren/Valsartan vs. Placebo	-5.70 (0.51)	(-6.69, -4.70)	<.0001*
Aliskiren/Valsartan vs. Aliskiren	-3.04 (0.51)	(-4.05, -2.03)	<.0001*
Aliskiren/Valsartan vs. Valsartan	-1.82 (0.51)	(-2.82, -0.82)	0.0004*

SE=Standard Error; LSM=Least Squares Mean; CI=Confidence Interval
 Least square means, confidence intervals, and p-values were from an ANCOVA model containing treatment, region, and baseline.

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

* Indicates statistical significance at 0.05 level

Table 6: Sponsor's Change from Baseline in SBP at Week 4 in Study 2327 (Aliskiren 150 mg and Valsartan 160 mg)

Treatment Group	N	LSM change from baseline(SE)	
Placebo	455	-5.24 (0.58)	
Aliskiren	430	-10.69 (0.60)	
Valsartan	453	-10.85 (0.58)	
Aliskiren/Valsartan	438	-15.29 (0.59)	
Pairwise Comparison	LS M difference in change from baseline (SE)	95% CI for LSM difference	P-Value+
Aliskiren vs. Placebo	-5.44 (0.83)	(-7.07, -3.82)	<.0001*
Valsartan vs. Placebo	-5.61 (0.82)	(-7.21, -4.01)	<.0001*
Aliskiren/Valsartan vs. Placebo	-10.05 (0.82)	(-11.66, -8.43)	<.0001*
Aliskiren/Valsartan vs. Aliskiren	-4.60 (0.84)	(-6.24, -2.96)	<.0001*
Aliskiren/Valsartan vs. Valsartan	-4.44 (0.83)	(-6.06, -2.82)	<.0001*

SE=Standard Error; LSM=Least Squares Mean; CI=Confidence Interval
 Least square means, confidence intervals, and p-values were from an ANCOVA model containing treatment, region, and baseline.

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

* Indicates statistical significance at 0.05 level

COMMENT: The increment of the combination over valsartan monotherapy for DBP is not large (1.8) but it is statistically significant. The incremental reductions with the combination over the monotherapies are reasonable.

I show the changes from baseline in ambulatory DBP by hour in Figure 2 and for SBP in Figure 3.

Figure 2: Reviewer's Changes from Baseline in Ambulatory DBP by Hour

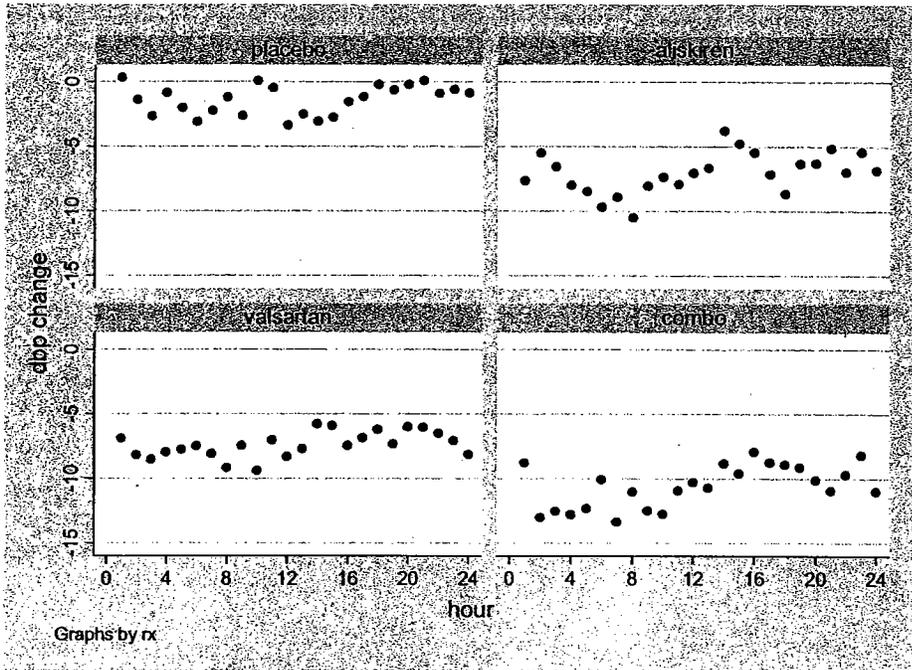
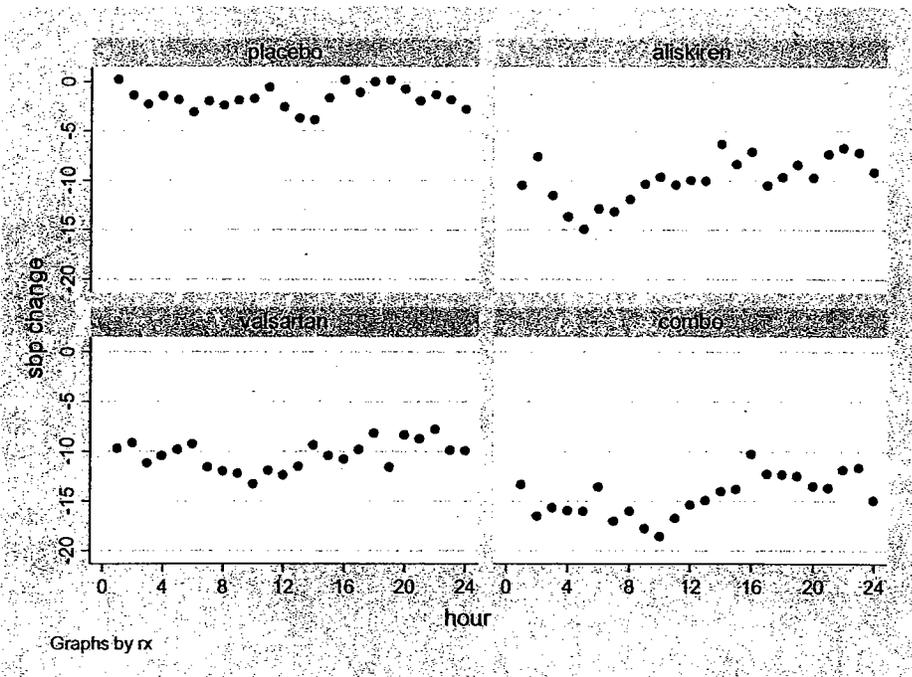


Figure 3: Reviewer's Changes from Baseline in Ambulatory SBP by Hour



COMMENT: I have the following observations about the ABPM results:

- In this study there does appear to be a small placebo effect. The placebo changes from baseline are virtually all between 0 and -4 mm Hg. Note that in this study a mean DBP > 90 for the first 8 hours of baseline ABPM recording was an entry criterion.*
- The trough (smallest BP reductions) do not appear to occur at 24 hours. While this could be an interaction with diurnal variation, I wonder whether it could be an artifact of measurement: If patients were relatively inactive or resting prior to the removal of the ABPM device, then their BP may be lower at that time than with usual activity. We probably shouldn't use the BP at 24 hours as the trough value in assessing trough-to-peak ratios or, alternatively, ABPM recordings should routinely run to 26 or 28 hours.*
- Aliskiren shows more random variability than valsartan. Aliskiren also appears to show a much more pronounced peak effect than valsartan.*
- The combination shows incremental BP reductions. The variability is intermediate between those of the individual drugs.*

The BP reductions did not vary substantially or consistently by gender or age less than or greater than 65. The reductions were substantially less in blacks as shown in Table 7.

Table 7: Reviewer's Mean Placebo-Subtracted Changes from Baseline in BP by Race

	Half Dose at 4 weeks				Full Dose at 8 weeks			
	White		Black		White		Black	
	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP
Aliskiren	-6.4	-2.9	-4.2	-1.9	-8.8	-5.0	-6.3	-4.0
Valsartan	-6.3	-4.3	-4.4	-3.0	-9.1	-6.0	-4.7	-4.4
Combo	-11.0	-6.5	-4.7	-3.3	-13.6	-8.7	-6.6	-6.1

For the placebo subtractions for Table 7 I used the race-specific mean changes from baseline in the placebo group. There were two few numbers in racial groups other than blacks and whites to generate reliable estimates.

COMMENT: Both aliskiren and valsartan were substantially less effective in blacks than in whites. It is not clear that the combination is more effective than monotherapy in blacks. Only the DBP value at full dose appears to show incremental reduction, but it is the value least consistent with the other values.

7 INTEGRATED REVIEW OF SAFETY

The major new safety data that I critique in this review addendum are from the human colonoscopic biopsy study, Study 2103. I reviewed the majority of the safety data from the second aliskiren/valsartan combination study, Study 2327, in my review of the initial NDA

submission. There are some safety issues raised by events from Study 2327 that are worthy of separate comment:

- Study 2327 reported the second case of isolated seizures following aliskiren administration. I included this case in my integrated summary of safety in my review of the initial NDA submission. Whether the two cases of seizures represent random occurrences or a definite adverse effect of aliskiren remains to be determined—the large outcome trials should help answer this question.
- Two cases of renal cell carcinoma were reported in patients participating in this study. One (aliskiren group) exhibited symptoms (anemia, hematuria) during the eight weeks of active treatment but was not diagnosed until 44 days after study completion and the other (placebo group) exhibited symptoms 20 days after study completion. Because one case was in the placebo group as well as one case in the aliskiren group and the treatment period was too short for the *de novo* development of a solid tumor, these cases do not implicate aliskiren. However, it is disconcerting that these cases were not discussed in the body of the study report (narratives for these events were included). These cases also have relevance to general questions of whether renal cell carcinoma is more frequent in hypertensives than in the general population or whether some antihypertensives, e.g., thiazides, are associated with its development, but those questions are not relevant to aliskiren approval.
- There was not any clear pattern of interactions on adverse event rates except perhaps that diarrhea was reported least frequently in the combination group (0.9%) and most frequently in the aliskiren monotherapy group (2.3%) and intermediate in the valsartan monotherapy group (1.5%). This pattern was not observed in the earlier aliskiren/valsartan combination Study 2203, in which the highest rate of diarrhea was seen in the combination group and the rate in the valsartan group was lower than in the placebo group. There are suggestions of potential interactions from the lab data as shown in Table 8 and Table 9.

Table 8: Reviewer’s Mean Percent Change from Baseline in Selected Lab Values

	Placebo	Aliskiren	Valsartan	Combo
Hemoglobin	0.2%	-0.5%	-0.9%	-2.0%
Potassium	-0.8%	1.8%	1.2%	2.3%
Urea	3.4%	3.9%	7.0%	7.7%
Uric acid	1.4%	3.7%	1.5%	3.9%

Table 9: Sponsor’s Lab Values [Selected] with Notable Changes at Any Tune

	Placebo	Aliskiren	Valsartan	Combo
Hemoglobin >20% decrease	0.0%	0.0%	0.0%	1.0%
Potassium >20% increase	6.7%	9.1%	7.0%	12.0%
Creatinine >50% increase	0.7%	1.4%	2.0%	3.1%

	Placebo	Aliskiren	Valsartan	Combo
Urea >50% increase	8.5%	11.0%	15.7%	18.1%
Uric acid >50% increase	0.9%	1.5%	0.7%	1.7%

COMMENT: There does appear to be additivity (or greater) of negative effects of aliskiren and valsartan upon hemoglobin. There was one AE of anemia reported in each of the treatment groups and one in the placebo group. For potassium, urea, and uric acid there appears to be some incremental effect of the combination but not complete additivity. The mean changes are consistent with the notable changes observed at any time. These effects and the relationships to AEs will be examined in greater detail when the aliskiren/valsartan combination NDA is submitted.

Study 2103 was entitled "Double-blind, placebo-controlled, randomized, parallel group, multi-center study to assess the effects on the colon mucosa of a daily dose of aliskiren 300mg administered orally for 8 weeks in healthy volunteers." The study design was relatively simple: randomize 30 healthy volunteers 2:1 to treatment with aliskiren 300 mg daily or placebo for eight weeks; perform a colonoscopy pre-treatment and at eight weeks with multiple biopsies throughout the rectum, colon, and terminal ileum (if reached). The protocol states the primary objective as "To determine the occurrence of epithelial hyperplasia in mucosal biopsy sections obtained from the colon using a validated histological grading scale in subjects treated with aliskiren 300 mg daily for 8 weeks compared to subjects treated with placebo." Secondary endpoints included examining biopsies for inflammation and dysplasia as well as observing mucosal abnormalities during colonoscopy and obtaining mucosal and fecal aliskiren levels. Exploratory endpoints included immunohistological tests evaluate markers of colon cell proliferation (Ki 67, PCNA) and apoptosis (bcl-2) and of response to inflammation.(e.g. myeloperoxidase for leukocytes). Three US study centers enrolled subjects, with the first subject dosed August 3, 2006, and the last subject completing November 30, 2006.

The original protocol, dated May 31, 2006, had a few procedural peculiarities: It referenced the two arms as "Treatment A (Test)" and "Treatment B (Reference)" without an explanation of why these designations were needed. It specified that "the bioanalyst will receive a copy of the randomization schedule to facilitate analysis of the pharmacokinetic samples. The bioanalyst will provide the samples' concentration data to the team under blinded conditions." The original protocol was amended several times. The third amendment, dated August 9, 2006, changed the study biostatistician and the assignment of randomization numbers so that all centers used the same randomization number sequence rather than assigning a separate block of randomization numbers to each center. Despite that amendment, study medications and sealed envelopes with the code breaks were shipped to centers at different times and in erratic groupings: 5101-5110, 5111-5116, 5117-5122, 5123-5125, 5126-5130, and 6126-6130. I requested, and the sponsor submitted, the sealed envelopes with the code breaks provided to the centers. The sealed, unopened envelopes were labeled with the study numbers listed previously and the sponsor's address but were not labeled with the names of the centers. The scratchoffs on the enclosed sheets were completely opaque and completely concealed the treatment identities.

COMMENT: The protocol and procedures appear to have minor irregularities: There does not appear to be any justification for referring to the two arms as Treatment A and Treatment B in the protocol. There does not appear to be a need for providing sample concentration data to the team under blinded conditions. The approach to assigning randomization numbers appears to be overly complicated, although it was conservative on use of study drug supply. Conversely, not labeling the code break envelopes with the center and having the center verify receipt of them on the envelope is oversimplified and makes it impossible to audit the authenticity of the codebreaks. However, while I can not verify that the randomization was conducted properly and that randomization lists were properly protected, neither do I have any evidence that the randomization or blinding was mishandled. This experience does reinforce my belief that the Division should routinely request sealed copies of randomization lists for critical studies when they are generated.

In the end 31 subjects were enrolled and 30 subjects completed the study. One subject was discontinued prematurely from the study due to a protocol violation (received concomitant oral prednisone and cephalexin for a pustular lesion on the face) at 10 days. The subjects had a mean age of 41.2 with a slight majority of males (55%) and 71% white and 19% black.

The primary endpoint for this study was a hyperplasia score developed by the sponsor. While the original protocol specified the objective to use a "validated histological grading scale" as mentioned above, the sponsor did not provide any references or other material validating the score used. The hyperplasia score and a related mitosis score are given in Table 10.

Table 10: Sponsor's Hyperplasia and Mitosis Scores

Hyperplasia Score (crypt length / mucosal disorganization)	
0	No increase in crypt length (< 0.5 mm)
1	Increase of crypt length (≥ 0.5 mm), without loss of goblet cells or appearance of nuclear crowding
2	Increased crypt length (≥ 0.5 mm) plus loss goblet cells or appearance of nuclear crowding
3	Increased crypt length (≥ 0.5 mm) plus loss of goblet cells and appearance of nuclear crowding as well as superficial serrations, crypt budding, or bifurcations

Mitosis Score (mitotic count)	
0	≤ 2 mitotic figures in basal 1/2 of 5 consecutive crypts
1	3-4 mitotic figures in basal 1/2 of 5 consecutive crypts
2	Any mitotic figure in superficial 1/2 of 5 consecutive crypts
3	≥ 5 Mitotic figures in 5 consecutive crypts

The sponsor's description of the scoring is the following: "Slides for analysis of hyperplasia and mitotic count were prepared at the core pathology laboratory /

To ensure adequate blinding, the slides were relabeled with log-in numbers that originated at the medical center and were unrelated to Novartis subject randomization numbers. Two independent expert GI pathologists (from detailed in External Personnel section, above) blinded to treatment allocation and colonoscopy sequence, scored slides based on the criteria in [Table 10]. The second pathologist scored the entire set of slides from the caecum and descending colon and 50% of slides from the ascending colon and rectum that had been randomly selected."

The sponsor's summary of the hyperplasia scoring is the following: "At baseline, no subject in either treatment group demonstrated evidence of hyperplasia (score ≥ 2) in any of the 4 regions examined (caecum, ascending colon, descending colon and rectum). There were no subjects in the aliskiren treated group that developed hyperplasia. Only 2 subjects in the aliskiren treated group had a hyperplasia score of 1, both at baseline with post-treatment values of 0. Only one subject (5118) in the placebo group was observed to exhibit hyperplasia in the rectum following treatment (pre-treatment score = 0 and posttreatment score = 3)."

The sponsor's summary of the mitosis scoring was similarly negative: "Baseline values for mitosis scores were comparable between treatment groups. No subject in either group demonstrated an increase in mitotic activity following treatment (increase in baseline score of 0 or 1 to a post-treatment value of 2 or 3) in any of the 4 regions examined (caecum, ascending colon, descending colon and rectum). In both groups, a few subjects showed a decrease in post-treatment mitosis score compared to baseline; however, there were no statistically significant differences in either group."

Because the sponsor's scoring was based on unvalidated scales, I performed the following screening to determine whether any additional formal scoring of the biopsies appeared necessary. The sponsor submitted the colonoscopy reports, including endoscopic photographs, and photomicrographs of representative sections from all biopsies. I reviewed all the colonoscopy reports and confirmed that the descriptions of the minimal macroscopic findings from the colonoscopies were described accurately in the study report. I also scanned all of the photomicrographs (blinded to treatment group) to evaluate whether I could detect any differences in patterns between the screening and end of treatment biopsies. (The sponsor provided the photomicrographs with the screen and end of treatment photomicrographs side-by-side, so obscuring the times of the biopsies was difficult.) I could not detect any definite differences in patterns. In particular, while I judged that the lengths of the crypts appeared identical pre and post treatment, I thought that there might be more variation in the widths of the crypts. Hence I scored all photomicrographs (remaining blinded to treatment group) according to whether I thought the crypt widths might be increased. I show the results of my scoring in Table 11.

Table 11: Reviewer's Scoring of Crypt Width Increases Blinded to Treatment Group

	Same	Increased
Placebo	5	5
Aliskiren	13	7

Blinded to treatment group I could not identify any differences in the patterns of the photomicrographs. However, because I reviewed only the photomicrographs and did not review the slides themselves and because the sponsor could have selected relatively normal appearing areas from the slides for the photomicrographs, I enlisted the aid of one of the Division clinical reviewers who is a pathologist by training to examine a randomly selected sample of the slides. I gave him the biopsy slides from ten cases (five aliskiren and five placebo) but I did not identify the treatment groups or tell him how many aliskiren and placebo cases were included in the sample. Because the sponsor had arranged the slides grouped by case with different accession numbers for the baseline and post-treatment slides, he was aware of the timings of the slides. He

reported back to me his informal grading of hyperplasia by case, which I unblinded and summarize in Table 12.

Table 12: FDA Pathologist's Grading of Hyperplasia for a Blinded Sample of Biopsies

	Hyperplasia				
	1	1+	2	2+	3
Placebo	0	1	2	0	1
Aliskiren	1	0	2	2	0

COMMENT: Neither the sponsor's evaluations of the slides nor the screenings of the photomicrographs performed by me or the review of a random sample of the slides performed by a Division pathologist suggest any differences in histopathology induced by aliskiren 300 mg daily in healthy volunteers. Both my screening and the FDA pathologist's were hypersensitive, i.e., we called things abnormal if we found any suggestion of an abnormality. I believe that hypersensitivity is the appropriate level of sensitivity for these screenings. If our screenings had hinted at any problems, we would have arranged for a second, more formal evaluation of the biopsies. The completely negative results of our screenings, consistent with the sponsor's evaluations, confirm that a second formal evaluation is not necessary.

The sponsor has not yet provided the results of the immunohistological tests (Ki67, PCNA, etc.) described in the protocol. We consulted with the Division of Oncology Drug Products regarding whether we should review the results of these tests prior to approval. They commented that these biomarkers are useful at determining cell proliferation and apoptosis rates in the research setting. In oncology clinical trials, these markers are occasionally examined as exploratory endpoints. They advised against using the tests in a decision affecting approval and against delaying approval to obtain the results.

The sponsor's summary of the aliskiren concentration data are shown in Table 13.

Table 13: Sponsor's Aliskiren Concentrations in Feces, Rectal Mucosa, and Plasma

	Feces (ng/g)	Rectal Mucosa (ng/g)	Plasma (ng/mL) (pre-dose)					Plasma (ng/mL) (post-dose)
			Day 3	Day 15	Day 36	Day 53	Day 56	
	Day 53	Day 56	Day 3	Day 15	Day 36	Day 53	Day 56	Day 56
N	20	20	21	20	20	20	20	20
Mean	2101880	62387	9.703	17.173	29.800	15.812	99.890	85.640
Std dev	1545429	78535	6.234	13.916	47.498	11.252	335.383	58.469
Minimum								
Median	2265000	38800	9.24	13.75	17.60	13.25	12.32	70.15
Maximum								

COMMENT: Note that these feces and rectal mucosa aliskiren concentrations are substantially higher (about double) than those reported previously: feces 2,265,000 vs. 1,234,000 ng/g; rectal mucosa 38,800 vs. 17,900 ng/g. The margin of safety vs. levels in the rat, if any, is halved.

The adverse events in this study of healthy volunteers are also of interest:

- The adverse event in the subject who discontinued is described as follows: “One subject received oral prednisone and cephalexin for a pruritic, erythematous, pustular lesion on the face, a protocol violation resulting in the subject being discontinued from treatment.”
- There were six reported cases of loose stools or diarrhea in three subjects all in the aliskiren group. None of the three subjects with diarrhea discontinued study medication and all three subjects had normal post-treatment colonoscopies. Diarrhea was not associated with any consistent histopathologic change. One of the subjects experiencing diarrhea (subject 5103) was likely noncompliant with taking study medication as plasma concentrations on days 15, 36 and 53 and fecal concentration on day 53 were below the LLOQ. The descriptions of the diarrhea events are given in Table 14.

Table 14: Sponsor’s Subjects with Diarrhea

Subject number (treatment group)	Start day/ onset post-dose	Diarrhea History	
		Duration	Severity
5103 (Aliskiren)	Day 1/ 5 h 57 min	18 days	moderate
	Day 32/ 14 h 15 min	5 hours	mild
	Day 38/ 23 h 20 min	2 days 4 hours	mild
5108 (Aliskiren)	Day 7/ 16 h 20 min	4 hours	moderate
	Day 10/ 16 h 50 min	2 hours	mild
5123 (Aliskiren)	Day 15/ 24 h 15 min	30 days	mild

COMMENT: The subject discontinuing because of the pustular rash could be considered to be discontinuing for an adverse event, not a protocol violation. Oral prednisone is an unusual treatment for a pustular rash, suggesting to me that someone judged that the rash might be drug-related. This study confirms that the diarrhea with aliskiren 300 mg usually appears to be tolerable, although the rate appears approaches 10% (the two cases with multiple episodes) and possibly 15%, for any occurrences of diarrhea or loose stools.

9 OVERALL ASSESSMENT

9.1 Conclusions

The colonoscopy biopsy study in humans appears to be completely negative, i.e., there was no evidence of colonic mucosal hyperplasia after exposure to aliskiren 300 mg daily, the maximum recommended human dosage, for eight weeks. In rodents hyperplasia was detected after

exposure for a few weeks. This human colonic biopsy study is reassuring that aliskiren does not cause hyperplasia in humans.

The other study reviewed in this addendum shows that the combination of aliskiren and valsartan, each at the maximum recommended dosage, provides incremental reductions in blood pressure over that produced by the corresponding monotherapies. These results are relevant to the labeling of aliskiren monotherapy for use alone or in combination with other antihypertensives because an initial study of the combination failed to show an incremental benefit. This second study also included reasonable numbers of blacks and demonstrated blood pressure reductions with the monotherapy in blacks.

9.2 Recommendation on Regulatory Action

From a clinical perspective I recommend approval of aliskiren for the treatment of hypertension in adults.

9.3 Recommendation on Postmarketing Actions

Please see the Executive Summary for recommendations on postmarketing actions.

9.4 Labeling Review

Please see my original review for a detailed labeling review. Based on this addendum I recommend removing from the proposed label _____ and to restore the sponsor's proposed labeling that aliskiren shows reduced efficacy in blacks. These recommendations are being discussed with the sponsor in conjunction with the labeling negotiations.

9.5 Comments to Applicant

Comments are being communicated to the applicant in conjunction with the labeling negotiations.

**APPEARS THIS WAY
ON ORIGINAL**

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Thomas Marciniak
2/26/2007 08:24:08 AM
MEDICAL OFFICER

CONSULTATION REPLY

DATE: January 26, 2007

FROM: DIVISION OF ONCOLOGY DRUG PRODUCTS (HFD-150), Office of Oncology Drug Products

TO: Division of Cardiovascular and Renal Products (HFD-110)

RE: NDA #21-985

SUBJECT: Carcinogenicity potential for aliskiren

DRUG NAME: aliskiren hemifumarate

TRADE NAME: Rasilez

FORMULATION: Oral

APPROVED INDICATIONS: hypertension

SPONSOR: Novartis Pharmaceuticals Corporation

Introduction:

This consult request seeks advice on the risk of carcinogenicity with aliskiren. Aliskiren is a renin inhibitor submitted for approval for the treatment of hypertension. Aliskiren activity appears similar to other inhibitors of the renin-angiotensin-aldosterone system, particularly ACE inhibitors. According to the information provided by the Cardio-Renal Division, diarrhea has been reported as a toxicity. At the highest proposed to-be-marketed dosage (300 mg daily), diarrhea rates in humans are increased about two-fold. At 600 mg, and higher, these rates are 6-10 fold in various Phase 1 and 2 studies. The diarrhea at the to-be-marketed dosages is not a problem in itself but the Sponsor is concerned that it may be a marker for carcinogenicity, based on preclinical studies conducted in rodents and marmosets. Both species developed diarrhea with aliskiren administration while rodents (not clear for marmosets) develop colonic and small intestinal mucosal hyperplasia. With the preclinical results obtained in animals, the Cardio-Renal Division would like input from DDOP on how to address this issue:

Colonic adenoma and cecal adenocarcinoma were found in the HD (1,500 mg/kg) male rats in the 104-week carcinogenicity study. These tumors are historically rare, there could be a number of reasons why they occurred. The tumors may be due to diet, bedding, etc. The tumors was found in only 2/60 male animals and both occurred at the HD and were found not to be statistically significant. There was no dose-response relationship and occurrence was limited to only males. According the Executive Carcinogenicity Advisory Committee (eCAC), the Committee concluded that 1) the study was adequate, noting prior eCAC concurrence on doses and 2) the study was negative for drug-related neoplasms. Also, the carcinogenicity study in CBF1/Jic-Tgras H2 hemizygous mice, the focal atypical hyperplasia of the colon (a pre-neoplastic lesion) was observed in high dose animals only (1 M and 3 F). Although females had a higher incidence

compared to males, no conclusions can be determined. The Committee concluded that 1) the study was adequate, noting prior eCAC concurrence on doses; and 2) the Committee concurred that the study was negative for drug-related neoplasms.

The responsibility for assessing drug carcinogenicity lies with the eCAC. The Division of Drug Oncology Products has no special expertise or experience in this area and actually has less expertise and experience than any other Division in CDER.

CONSULTATION REPLY AND CONCLUSIONS TO THE QUESTIONS SUBMITTED:

1. The sponsor has planned special studies (Ki 67, PCNA, bcl-2) of the biopsy specimens (although the sponsor is now saying that their results will not be available prior to the new user fee goal date).
 - a. How valid and useful are these special studies? *These biomarkers are useful at determining cell proliferation and apoptosis rates in the research setting. In oncology clinical trials, these are occasionally examined as exploratory endpoints.*
 - b. Would you base a decision for non-approval on their results? *No.*
 - c. Do you recommend delaying the decision for approval until their results are known? *No.*
 - d. Do you consider one of them to be preferred? *No.*
 - e. If you consider one of more of them to be useful, can you provide references validating their usefulness? *No.*
 - f. Are there any other analyses that are preferable that can be performed on preserved tissue? *In addition to PCNA, Ki67, and bcl-2, below are some additional exploratory biomarkers for early detection:*
 - *K-ras: More than 50% of patients with adenocarcinomas of the colon carry a mutant allele of K-ras genes. This mutation has a high frequency and appears early in colon cancer for early detection.*
 - *Proliferation of abberant crypt foci*
 - *APC: this is thought to be one of the earliest genetic abnormalities in the progression of colon cancer. This mutation occurs in 60% of patients with colon cancer.*

Other biomarkers could also be used. For additional information see Srivastava et al, Clinical Cancer Research, 2001, p1118-1126.

2. The sponsor developed scores for hyperplasia and mitoses upon which the sponsor is basing its claim that hyperplasia was not found in this study.

a. Do you judge the sponsor's scores to be useful? *The scoring system appears reasonable; however, without extensive validation, these could only be considered exploratory.*

b. Are you aware of any validated scores for hyperplasia? *We have not used evidence from scores of this type in recent oncology drug evaluations.*

c. Can you suggest any alternatives?

To address the concern if aliskiren is acting as potential tumor promoter, you may want to consider conducting an animal study with a specific colon carcinogen such as azoxymethane (AOM) and aliskiren. For additional information see Bissahoyo et al. Tox Sciences, 2005 p 340-345, 2005 and W. Bruce, Cancer Epi. Bio. and Prev., 2003 p401-404)

3. We did request and obtain the slides from the colonic biopsy study and we have pathologists on our staff that will examine at least a sample of them.

a. Do you have any other recommendations for analyzing the colonic biopsy study? *No. We note that no cancer or colonic hyperplasia was found in the human volunteer colonic biopsy study.*

b. Should we consider requesting one of the FDA laboratories to perform Ki 67 or PCNA assays from tissue blocks or unstained slides obtained from the sponsor? *We would not recommend this approach.*

4. The completed colonic biopsy study used the highest proposed to-be marketed dosage and its duration exceeded the earliest times at which hyperplasia was detected in rats.

a. Do you judge that this study, if negative, will adequately exclude a risk of increased rates of colon cancer in man?

It is impossible to exclude all risk. The study provides some support for safety.

b. If not, do you have any recommendations for further studies?

Volunteers were only assessed for 8 weeks. A longer period of observation (4-6 months) would have been more reassuring.

5. The sponsor is planning large cardiovascular outcome studies (about — persons exposure years apiece for both aliskiren and control) and will monitor cancer rates in those studies.

a. Do you have any recommendations for monitoring in those studies?

DDOP Clinical Answer: _____

(((

b. Would you recommend any other post-marketing studies or other commitments?

DDOP Clinical Answer: We can think of none at this time. We suggest consulting the CDER Division of Gastrointestinal Products. Also, if you plan to approve the drug, we suggest consulting the Office of Surveillance and Epidemiology (OSI) for guidance on a post marketing surveillance study.

**APPEARS THIS WAY
ON ORIGINAL**

BELOW ARE ADDITIONAL COMMENTS FROM THE DIVISION OF ONCOLOGY DRUG PRODUCTS:

- A. We suggest consulting the CDER Division of Gastrointestinal Products regarding the relationship of diarrhea and drug toxicity. The Sponsor performed a special safety study involving pre and post treatment colonic biopsies in normal subjects treated for 8 weeks with aliskiren 300 mg. The sponsor conducted this study to determine whether humans develop colonic hyperplasia as was seen in a rat study. The human colon mucosa study design, evaluation, and interpretation are best reviewed by the disciplines of gastroenterology and pathology.
- B. However, there are some areas of concern that the Cardio-Renal Division may consider:
- The rats and mice used in the carcinogenicity studies appear to have been more immature and had more immature gastrointestinal tracts than the normal humans in the colon mucosa study. The comparison of the animal and human studies may not be appropriate. Also, there are other differences with regard to the normal human study and how patients will be administered this drug. First, the duration of the drug administration in the normal humans is markedly shorter than what is expected to occur in practice (i.e., 8 weeks vs. indefinite). Second, the exclusion criteria for the normal human study, excluded those subjects who had risks for subsequent gastrointestinal pathology and who will not be excluded from receiving this drug in practice. For example, the protocol excluded patients with: a) either macroscopic or microscopic pathology at the screening colonoscopy, b) history or clinical evidence of inflammatory bowel disease (ulcerative colitis, Crohn's Disease), or microscopic, lymphocytic, collagenous, ischemic, drug-induced or other noninfective types of colitis, c) history or clinical evidence of adenomatous colon polyps or subjects with family history of familial polyposis, d) history of infective colitis within 1 year, e) history of family history of colon cancer (1st degree relatives w/ colon cancer), familial adenomatous polyposis, Gardner syndrome, GI bleed, chronic, recurrent heart burn, gastric/intestinal ulcer, and history of abdominal/GI surgery, and f) history of bloody stool or melena within the past 12 months.
 - The differential interpretation of mucosal hyperplasia adjacent to colorectal adenocarcinoma includes: a) a precancerous lesion, b) a response to a growing cancer, and c) a response to microorganisms, such as *Citrobacter freundii*. A similar pattern of mucosal hyperplasia adjacent to cancer is also found associated to adenocarcinomas of the breast and pancreas.¹
 - Increased cell proliferation and/or inhibition of apoptosis are proposed mechanisms by some authors for enhancement of carcinogenesis during the

¹ Kuniyasu et al. Am J Path. 2000;157:1523-1535.

promotion/progression phase.² Also, hyperplasia may be a precursor to malignant progression by other elements.

- The hyperplastic tissues can express high levels of pro-angiogenic molecules and thus, contribute to neoplastic angiogenesis.³ Evidence to support this comes from an animal experiment. When mouse and human colon cancer cells are implanted into the cecal wall of nude mice, the growing tumors induced hyperplasia in the adjacent mucosa. The hyperplasia adjacent to the tumor expressed high levels of pro-angiogenic molecules.⁴

In human colon cancer, mucosal hyperplasia adjacent to was a function of stage of the cancer, i.e., 94% of Dukes' C cases which had adjacent hyperplasia compared to 40% Dukes' B which had adjacent hyperplasia. The extent of hyperplasia and the production of angiogenic molecules directly correlated with the metastatic potential of the cells.⁵ This also suggested that the hyperplasia was a secondary manifestation of the malignancy and not hyperplasia progressing to malignancy.

In the mouse, colonic hyperplasia due to *Citrobacter freundii* appeared to be a defense mechanism of replacing infected cells with newly migrated, uninfected epithelium.⁶

- Proliferation markers, including Ki-67 and proliferating cell nuclear antigen (PCNA), correlate with grade, stage, and risk of recurrence. In general, the Ki-67 nuclear antigen also appears to be associated with invasive cancers, which demonstrate a worse prognosis, and appears to be the most promising single marker in predicting recurrence and progression, an increased fraction of proliferating tumor cells, and as a marker of proliferation index (i.e., an independent predictor of recurrence and tumor-specific survival). PCNA is an auxiliary protein of the DNA polymerase delta, reaching an expression peak during the S-phase of the cell cycle and playing an important role in cellular proliferation. PCNA-labeling index has been used as an intermediate biomarker in chemoprevention of colorectal cancer.⁷ For example, colonic crypt proliferation rates can be used as a marker. This can be measured with labeling techniques with PCNA and Ki67.⁸
- Normal tissues exhibit a regulated balance between cell proliferation and cell death. Programmed cell death is an important component in the processes of normal embryogenesis and organ development. A distinctive type of programmed cell death, called apoptosis, is described for mature tissues. Studies of cancer

² Zheng et al. *Carcinogenesis*. 1999;20:255-260.

³ Kuniyasu et al. *Am J Path*. 2000;157:1523-1535

⁴ Kuniyasu et al. *Am J Path*. 2000;157:1523-1535

⁵ Kuniyasu et al. *Am J Path*. 2000;157:1523-1535

⁶ Johnson E, Barthold. *Am J Path*. 1979;97:291-313

⁷ Jia DX, Han C. *World J Gastroentero*. 2000; 6(5):699-703

⁸ Krishnan K, Ruffin MT, Brenner DE. *Cancer Chemoprevention*. 1998;12:1079-1113.

cells show that both uncontrolled cell proliferation and failure to undergo programmed cell death can contribute to neoplasia and insensitivity to anticancer treatments.

The only proto-oncogene thus far shown to regulate programmed cell death is bcl-2. Bcl-2 was discovered by the study of chromosomal translocations in human lymphoma. Experimental studies show that bcl-2 activation inhibits programmed cell death in lymphoid cell. It is unlikely that bcl-2 is the only apoptosis gene involved in neoplasia although additional proto-oncogene await identification.

Apoptosis or programmed cell death appears to be an important mechanism in the deletion of tumor cells rather than increased cell proliferation. The bcl-2 proto-oncogene is a known inhibitor of apoptosis and may therefore allow an accumulation of genetic alterations that become propagated by cell division and potentially contribute to neoplastic development.⁹ Abnormal activation of bcl-2 gene appeared to be an early event in colorectal tumorigenesis that can inhibit apoptosis in vivo and may facilitate tumor progression.¹⁰ Thus, when bcl-2 is overexpressed, the cell cycle is deregulated and the apoptosis is prevented, eventually leading to tumor formation. This is an important cause for tumor formation.

DIVISION OF ONCOLOGY DRUG PRODUCTS (HFD-150)

January 26, 2007

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CC

NDA #21-985

HFD-150/DIV FILE

HFD-150/D PEASE

HFD-150/RWHITE

Division of Cardiovascular and Renal Products (HFD-110)

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⁹ Jia DX, Han C. World J Gastroentero. 2000; 6(5):699-703

¹⁰ Jia DX, Han C. World J Gastroentero. 2000; 6(5):699-703

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CLINICAL REVIEW

Application Type NDA 21-985
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Reviewer Name Thomas A. Marciniak, M.D.
Review Completion Date 12/05/06

Established Name aliskiren
(Proposed) Trade Name Tekturna
Therapeutic Class anti-hypertensive
Applicant Novartis

Priority Designation S

Formulation tablets
Dosing Regimen once daily
Indication treatment of hypertension
Intended Population hypertensive adults

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

From a clinical perspective I recommend that aliskiren is approvable for the treatment of hypertension pending the resolution of the one issue 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 issue that requires resolution is the following: Aliskiren causes 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 late in the review period submitted preliminary results from a colonic biopsy study in normal volunteers. While the preliminary results do not show hyperplasia in the human colonic biopsies, these results need further scrutiny before aliskiren can be judged safe for chronic human use.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

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

1.2.2 Required Phase 4 Commitments

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

1.2.3 Other Phase 4 Requests

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

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Aliskiren (Tekturna) is an inhibitor of renin, the enzyme that converts angiotensinogen to angiotensin I in the first and rate-limiting step of the renin-angiotensin-aldosterone system (RAAS). Aliskiren is the first renin inhibitor submitted for approval. Aliskiren is the first renin inhibitor submitted for approval. It is formulated as film-coated tablets for oral administration.

While the sponsor studied 75, 150, and 300 mg tablet sizes, the sponsor is proposing to market only the 150 and 300 mg sizes. The proposed indication is the treatment of hypertension.

Aliskiren has been evaluated for hypertension in a large clinical development program including five randomized, double-blind, placebo-controlled studies; six other completed active-controlled studies and a large, long-term safety study with final study reports and data; and additional on-going active-controlled studies and one placebo-controlled study in hypertension with adverse event reports available as well as smaller studies in hypertension and other indications with limited data. The initial submission included efficacy and safety data on 3,958 patients given aliskiren in the placebo-controlled studies and a total of 6,398 patients given aliskiren in all-controlled studies and the long term safety study. Of these 6,398 patients 1,714 were exposed for at least six months and 1,236 for at least one year.

1.3.2 Efficacy

Five studies used variations (e.g., some also had active-control arms, others also evaluated combinations with another antihypertensive) on the typical trial design to demonstrate antihypertensive efficacy: a randomized, double-blind, placebo-controlled trial of eight week's duration with a primary endpoint of change from baseline in seated trough cuff diastolic blood pressure (DBP). The results for the primary endpoint for these five "pivotal" aliskiren trials are shown in Table 1.

Table 1: 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
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

Results for systolic blood pressure (SBP) were similar and are shown in Table 14. These studies provide substantial evidence that aliskiren reduces blood pressure. The sponsor confirmed that the antihypertensive effect of aliskiren was sustained for at least 11 months by performing a randomized, double-blind, placebo-controlled withdrawal at the end of the long term safety Study 2302. After withdrawal 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).

Regarding control throughout the interdosing interval, Study 2201 measured cuff BP at 0, 2, 4, and 6 hours post-dosing at 4 weeks and again at 8 weeks for a subset of patients (about 60 per group). 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. Study 2308 in essential hypertensives performed ambulatory BP monitoring (ABPM). 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

we do not have concentration-response data, both of these subgroups showed slightly higher AUC and Cmax (20-30%) than the non-elderly, white population.

However, the 150 mg and 300 mg dosages do show increased efficacy in these subgroups, so limiting the marketed dosages to 150 mg and 300 mg is not unreasonable.

1.3.3 Safety

Aliskiren is a RAAS inhibitor that appears to share many of the adverse events (AEs) of other RAAS inhibitors in addition to one common predictable AE and a related potential problem plus some other rare AEs. The predictable AE is dose-related diarrhea. 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., the women, the elderly. The potential problem is whether aliskiren gastrointestinal (GI) effects can lead to hyperplasia as in rodent 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 complete results and data for the recently completed colonic biopsy study should provide useful information on this issue.

1.3.4 Dosing Regimen and Administration

I discuss dosing regimen and administration issues (interdosing interval, starting dose in special populations) in Section 1.3.2.

1.3.5 Drug-Drug Interactions

Regarding use with other antihypertensives, Study 2204 showed that BP reductions with the combination of aliskiren 75-300 mg and hydrochlorothiazide (HCTZ) 6.25-25 mg generally statistically significantly exceeded those with the corresponding monotherapies. Study 2203 failed to show similar efficacy for the combination of aliskiren with valsartan, possible due to a large placebo effect in that study. The sponsor submitted late in the review period a preliminary report and data for a second aliskiren/valsartan combination study, Study 2327—I could not complete a full review of Study 2327 for this review. The sponsor also performed Study 2305 of aliskiren 150 mg in combination with amlodipine 5 mg and Study 2307 of aliskiren 300 mg in combination with ramipril 10 mg. These latter studies are not convincing because they do not show enhanced efficacy of the maximal doses of the drugs in combination compared to the monotherapies.

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 how other RAAS inhibitors behave with amlodipine. 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.

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. These studies identified few clinically relevant interactions. 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 if co-administered with aliskiren is reasonable.

1.3.6 Special Populations

While aliskiren does not show important differences in safety in special populations, it does appear to show varying efficacy in some demographic subgroups. While BP reductions do not appear to vary significantly by gender, they do by age as shown in Table 2.

Table 2: 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	-2.5	-2.4	-7.3	-2.2
150	-5.0	-3.2	-9.6	-3.9
300	-9.3	-5.6	-10.1	-3.4
600	-10.5	-6.6	-13.8	-5.2

The elderly show a reasonable response to aliskiren 75 mg, particularly for SBP. 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 found in Study 2324, whose enrollment was limited to the elderly. Aliskiren also shows differential efficacy by race as shown in Table 3.

Table 3: Reviewer's Mean 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

The BP reductions 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 (although the results for Asians appear to be erratic likely due to lower numbers of subjects.) In multivariate regression analyses the interaction term for Asian and aliskiren use is statistically significant for DBP, the interaction term for black and aliskiren use is almost statistically significant, and the interaction term for age≥65 and aliskiren use is statistically significant for SBP.

Four pregnancies occurred during the aliskiren trials in aliskiren patients. While there have not been definite fetal abnormalities reported following these pregnancies, 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.

Abbreviations

ACE	angiotensin converting enzyme
ACEI	angiotensin converting enzyme inhibitor
ABPM	ambulatory blood pressure monitoring
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
ALT	alanine aminotransferase (SGPT)
ANCOVA	analysis of covariance
ARB	angiotensin receptor blocker
AST	aspartate aminotransferases (SGOT)
AUC	area under the curve
BID	twice a day
BMI	body mass index
BNP	brain natriuretic peptide
BP	blood pressure
BUN	blood urea nitrogen
CABG	coronary artery bypass graft
CAT	coaxial tomography
CK	creatine kinase
CI	confidence interval
CMC	chemistry, manufacturing, and controls
CRF	case report form
CVA	cerebrovascular accident
DBP	diastolic blood pressure
DSI	Division of Scientific Investigation (FDA)
ECG	electrocardiogram
EEG	electroencephalogram
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GFR	glomerular filtration rate
GI	gastrointestinal
GLP	Good Laboratory Practices
HbA1c	hemoglobin A1c
HGB	hemoglobin
HCTZ	hydrochlorothiazide
HF	heart failure
ICH	International Conference on Harmonization
IRB	institutional review board
ISE	Integrated Summary (Review) of Efficacy
ISS	Integrated Summary (Review) of Safety
ITT	intention-to-treat
IVRS	interactive voice response system
LOCF	last observation carried forward
LSM	least squares mean

LVH	left ventricular hypertrophy
MI	myocardial infarction
MRI	magnetic resonance imaging
MSDBP	mean seated diastolic blood pressure
MSSBP	mean seated systolic blood pressure
NDA	New Drug Application
NOS	not otherwise specified
NS	not significant
OD	once a day
PD	pharmacodynamics
PEY	person-exposure-year
PK	pharmacokinetic
PRA	plasma renin activity
PRC	plasma renin concentration
PTCA	percutaneous coronary angioplasty
QD	once a day
QTc	QT interval corrected (for heart rate)
RAAS	renin-angiotensin-aldosterone system
RBC	red blood cells
SAE	serious adverse event
SAS	Statistical Analysis System
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
SLE	systemic lupus erythromatosus
SPA	special protocol assessment
TIA	transient ischemic attack
ULN	upper limit of normal
US	United States

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Aliskiren (SPP100, Tekturna) is an orally active renin inhibitor, the first of its class submitted for approval. Aliskiren is (2S,4S,5S,7S)-N-(2-Carbamoyl-2-methylpropyl)-5-amino-4-hydroxy-2,7-diisopropyl-8-[4-methoxy-3-(3-methoxypropoxy)phenyl]octanamide hemi-fumarate, molecular formula $C_{30}H_{53}N_3O_6 \cdot 0.5 C_4H_4O_4$, with the chemical structure shown in Figure 1.

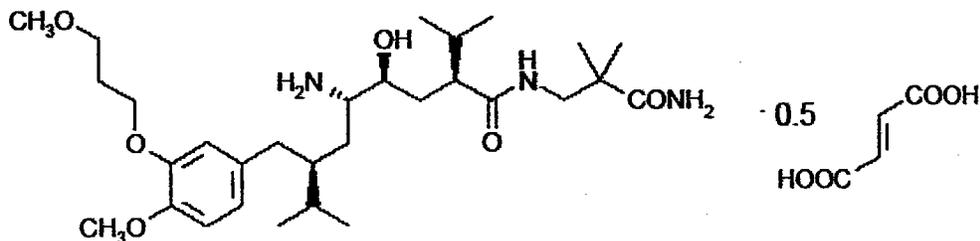


Figure 1: Chemical Structure of Aliskiren

Aliskiren is a single diastereoisomer having four chiral centers, all S-configured. The active substance is the hemi-fumarate salt of the corresponding amine, with a molecular weight of 609.8. Aliskiren is very soluble in aqueous media from pH 1-7.6.

Aliskiren is formulated as film-coated tablets for oral administration. While the sponsor studied 75, 150, and 300 mg tablet sizes, the sponsor is proposing to market only the 150 and 300 mg sizes. The initial indication is the treatment of hypertension in adults. The sponsor is proposing once daily dosing.

2.2 Currently Available Treatment for Indications

Many drugs are approved for the treatment of hypertension. The most relevant approved drugs are those that also work by inhibiting the renin-angiotensin-aldosterone system (RAAS). RAAS inhibitors approved for hypertension include angiotensin converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), and aldosterone receptor antagonists (eplerenone, spironolactone). Aliskiren works early in the system, inhibiting the conversion of angiotensinogen to angiotensin I by renin. ACEIs inhibit the conversion of angiotensin I to angiotensin II by ACE. ARBs block the action of angiotensin II at its receptor. Eplerenone and spironolactone block the effects of aldosterone, whose release is stimulated by angiotensin II.

2.3 Availability of Proposed Active Ingredient in the United States

Aliskiren is not currently marketed in this country.

2.4 Important Issues with Pharmacologically Related Products

RAAS inhibitors share certain adverse events (AEs). Because all affect aldosterone, all can cause increases in serum potassium and hyperkalemia. All, either through effects on aldosterone or angiotensin II or both, can cause decreases in renal function. In addition to these AEs shared by all RAAS inhibitors, ACEIs cause cough, presumably through effects of ACE on the bradykinin pathway. ACEIs, and to a lesser extent ARBs, cause angioedema. Whether the latter is mediated through the bradykinin pathway is not clear. Some experts have hypothesized that renin inhibitors should not cause these latter AEs, but whether they do or don't has not been confirmed in clinical trials. Finally, ARBs have recently been implicated in rare cases of rhabdomyolysis. I scrutinize all of these potential AEs of RAAS inhibitors in the ISS, Section 7.

2.5 Presubmission Regulatory Activity

The Agency met with the sponsor for an end-of-phase II meeting on February 11, 2004.

Pertinent discussion from that meeting is the following:

- The Agency advised that showing an additive effect to other RAAS inhibitors is not helpful unless maximum doses of the other RAAS inhibitors are used.
- The Agency recommended adding a 600 mg dose and/or higher dose to the aliskiren/HCTZ study to show no additional effect at higher doses in addition to the 2201 study that used a 600 mg dose showing no additional effect.
- The Agency recommended that the sponsor consider sparse sampling for determining food effects, or if they measure drug blood levels and can demonstrate that the levels are above the levels that matters, then the food effect does not matter. The sponsor should collect sparse samples in the Phase 3 clinical trials for population PK and PK/PD analyses to investigate the various covariates (i.e., concomitant medications, food, gender, age, race, etc.) that might have an effect on aliskiren's exposure.

The Division sent a letter dated June 3, 2004, to the sponsor regarding a special protocol assessment (SPA) for Study 2204. Pertinent points from that letter are the following:

- The Division advised that the dose range of aliskiren must be delineated. If bridging bioequivalence studies for the phase 2 study formulations are not done, then 600 mg and

possibly a higher dose should be included in the pivotal trials as recommended in the end-of-phase II meeting held on February 11, 2004.

- The Division noted that the bioavailability of aliskiren is highly variable. The effects of this variability would be expected to be greater at peak than at trough. There have been reports of serious adverse events (SAEs) of hypotension in the clinical studies. The BP response must be characterized throughout the interdosing interval and should be correlated with drug levels.
- The Division noted that the protocol did not include pharmacokinetic (PK) and/or pharmacodynamic (PD) assessments. The interaction between aliskiren and hydrochlorothiazide should be evaluated in this study by using a sparse sampling approach. A blood sample for aliskiren assay should be collected as close as possible to the occurrence of the adverse event.

The Division met with the sponsor on July 12, 2004, to discuss the SPA letter. Pertinent discussion from that meeting is the following:

- The Division noted that it had previously recommended that the sponsor consider testing aliskiren at 600-mg or higher to adequately describe the dose response. The sponsor stated that the dose response would be further characterized in an additional study as previously recommended by the Division.
- The sponsor stated the PK of aliskiren and hydrochlorothiazide would be evaluated in other studies because of sampling handling difficulties (plasma samples have to be

They believe their additional studies would fully characterize the PK rather than including sparse sampling in the proposed study. The Division agreed but suggested that the sponsor might consider collecting the PK sparse sampling at one or two sites that had the capabilities for proper sample handling as an alternative.

The Division met with the sponsor for a pre-NDA meeting on April 20, 2005. Pertinent discussion from that meeting is the following:

- The Division requested that the case report forms be complete to include all data that were collected for serious adverse events (AEs) and include copies of the Medwatch form and other documents such as hospital discharge summaries (if they were obtained as part of the sponsor's evaluation of the AE). If a review determines that other AEs are of concern, the Division might request that you submit the case report form for review during the review period. The sponsor agreed.
- The Division expressed concern regarding the high PK variability and recommended that the sponsor look at the BP effect over the entire dosing interval using ambulatory blood pressure monitoring and the intra-individual variability preferably at the peak dose.

- A clarification dated May 25, 2005, notes that the Division agreed to review safety and efficacy of a study of aliskiren in combination with valsartan if submitted with the 120-day safety update.

2.6 Other Relevant Background Information

I do not know of any other relevant background information.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The CMC reviewer, Dr. Xavier Ysern, judges this application approvable from the CMC perspective pending satisfactory responses to some questions regarding assays and batch reprocessing specifications. Other CMC issues appear to have been addressed adequately by the sponsor and are described well in the FDA CMC review. One finding that has clinical relevance is that the drug substance is hygroscopic. Because of this

sensitivity the drug product is being packaged in aluminum blisters. Interestingly, the initial stability testing is being performed using a bracketing approach with 75 and 300 mg tablets and the 150 mg to-be-marketed tablet is not being used.

3.2 Animal Pharmacology/Toxicology

The animal pharmacology and toxicology reviewer, Dr. G. Jagadeesh, judges this application approvable from the pharmacology and toxicology perspective. Please see Dr. Jagadeesh's review for the details on pre-clinical findings. I summarize the findings most relevant to clinical issues below:

- The sponsor describes aliskiren as a highly selective renin inhibitor. Aliskiren demonstrated potent *in vitro* inhibition of human recombinant renin ($IC_{50} = 0.6$ nM) and marmoset renin ($IC_{50} 2$ nM). It was a less potent inhibitor of renin of other species, e.g., dog, rabbit, and rat (IC_{50} s of 7, 11, and 80 nM, respectively). It was inactive or only weakly active against human aspartic proteinases and HIV-1 proteinase ($IC_{50} >5000$ nM). *In vitro* receptor binding assays showed no significant affinity of aliskiren (at 10 μ M) for 16 different neurotransmitter receptors.

COMMENT: The NDA does not describe effects of aliskiren upon other RAAS components, e.g., ACE.

- Organ and tissue distribution was investigated in pigmented and albino rats following a single intravenous or single and multiple oral doses of radiolabeled aliskiren. After intravenous dosing, radioactivity was extensively distributed throughout the body, with the highest levels at 5 min post-dose being found in the liver and kidney. At 14 days post-dose, low tissue concentrations of radioactivity were detected in the choroid plexus,

eye choroid, brown fat and pituitary. Aliskiren and/or its metabolites showed apparent reversible affinity to melanin-containing structures. After single and multiple oral dosing for 10 days with radiolabeled aliskiren, overall tissue levels were low, in line with the poor to moderate oral absorption. Radioactive material was eliminated within 24 hours from all tissues, except the intestinal wall, hair follicle and brown fat. Aliskiren and/or its metabolites were not taken up into the brain.

- Exposure of the fetuses to drug-related compounds was demonstrated in rabbits after a single oral dose of 200 mg/kg ¹⁴C-aliskiren at day 17 of gestation. Fetuses were exposed to aliskiren or its metabolites. The mean ¹⁴C concentrations at 24 hours post-dose were similar as those in maternal blood.
- Aliskiren causes gastrointestinal (GI) irritation in animals. The following are examples:
 - Minimal inflammatory cell infiltration, atrophy or basophilia in the cecum or colon in rats receiving 2000 mg/kg/day in a comet assay (second day sacrifice)
 - Mucosal hyperplasia in the cecum or colon at doses of 250 (the lowest tested dose) or more mg/kg/day in rats in 4 and 13 week dietary mechanistic studies
 - Erosion and/or ulceration in the cecum and/or colon in animals receiving 750 mg/kg/day in a 13 week oral gavage study
 - Increased incidence of mucosal hyperplasia of the GI tract and erosion/ulceration of the cecum and/or colon at doses of 750 or more mg/kg/day in the rat carcinogenicity study (noted at both 52 and 104 week sacrifices)
 - Increased incidence of diffuse mucosal hypertrophy in duodenum, jejunum, cecum and colon in both sexes of transgenic mice at 1500 mg/kg/day (findings in cecum at 750 or more mg/kg/day) in a 26 week carcinogenicity study
 - Salivation, vomiting and diarrhea (but no histopathologic findings) at doses of 50 or more mg/kg/day in marmosets in a 13 week study

While hyperplasia was evident at the lowest tested dose (250 mg/kg/day) in the four week study, the 13 week mechanistic study suggested the presence of an adaptation mechanism. In the 13 week study no proliferative or inflammatory changes were noted at 250 mg/kg/day, but a maintained epithelial reaction was noted in the cecum and colon at 750 or more mg/kg/day.

- The critical issue regarding this GI irritation is whether it could lead to any long term sequelae, e.g., chronic inflammatory disease or cancer. There is some evidence that it could be neoplastic:

- Note the hyperplasia described above in the rodent studies. In addition, one colonic adenoma and one cecal adenocarcinoma were detected in the rat carcinogenicity study at the dose of 1500 mg/kg/day. Although these tumors were not detected in control animals and the incidence of large intestinal adenomas and adenocarcinomas in historical controls is low (<0.1%), the rate of GI neoplasia was judged to be not statistically significant.
- In the transgenic mouse study, focal atypical hyperplasia, a pre-neoplastic finding, was noted in the colons of animals receiving 1500 mg/kg/day (one male and three females). This is not a common spontaneous lesion in this mouse strain and the diffuse mucosal hypertrophy and focal atypical hyperplasia were not noted in concurrent control animals.

The sponsor also studied aliskiren concentrations in rat and human feces and GI mucosa. The fecal concentrations are listed in Table 4 and the GI mucosal concentrations in Table 5.

Table 4: Sponsor's Fecal Aliskiren Concentrations in Rats vs. Humans

	N	Fecal aliskiren concentration (µg/g) Mean (SD); Median	Safety Margin (Rat: Human)	Ratio of Medians (Rat: Human)
4-week rat study (TOX 0570277) - Dose = 250 mg/kg/day				
13-week rat study (TOX 057029) - Dose = 250 mg/kg/day	5	16,940 (1045); -	11.1	-
Combined 4-week and 13-week rat studies (TOX 0570277 and TOX 0570299 - combined); Dose = 250 mg/kg/day *	5	10,958 (1505); -	7.2	-
Human study (CSPP100A 2105); Dose = 300 mg/day	10	13949 (3381); 14100	9.1	11.4
	14	1527 (1316); 1234	--	--

Table 5: Sponsor's GI Mucosal Aliskiren Concentrations in Rats vs. Humans

Rat (250 mg/kg/day) [TOX R0570340]		Human (300 mg/day) (CSPP100A 2105)	
	Mean (SD) µg/g; Median		Mean (SD) µg/g; Median
Mucosa – Jejunum	70.5 (33.3); 109	Mucosa – Rectum	22.2 (15.6); 17.9
Mucosa – Ileum	99.3 (27.4); 63.7		
Mucosa – Cecum	135 (57.5); 119		
Mucosa – Colon	132 (64.7); 159		

No direct comparison can be made between the results in rats and humans, as mucosal aliskiren concentration was not measured in rat rectum. The rectal mucosal concentration in humans is about six-fold lower (mean data) than in rat colon. Rat rectal mucosal aliskiren concentration would be expected to be higher than that in colon due to local differences in luminal drug exposure (rat colonic content: 502 µg/g versus rat feces: 10900-16900 µg/g).

The sponsor notes that there was high inter-subject variability in fecal concentrations in both rats and humans. The maximum human fecal concentration, 5 mg/g, was slightly less than the minimum rat fecal concentration, 9 mg/g. The maximum human rectal mucosal concentration, 0.06 mg/g, was comparable to the minimum rat mucosal concentration in both cecum and colon.

On the other hand, aliskiren was not genotoxic in the Ames reverse mutation assay with *S. typhimurium* and *E. coli*, the *in vitro* Chinese hamster ovary cell chromosomal aberration assay, the *in vitro* Chinese hamster V79 cell gene mutation test and the *in vivo* mouse bone marrow micronucleus assay.

COMMENT: I think these data are strongly suggestive that aliskiren increases rates of GI neoplasia in rodents. That the neoplasia may be the result of a local irritant effect is not reassuring because the same local irritant effect may be active in humans, e.g., the dose-related diarrhea observed in humans. In the proposed labeling

The sponsor is performing a 3-month colonic biopsy study in humans at the 300 mg/day dosage. I suspect the sponsor is hoping that this study will mirror the results of the marmoset (primate) study, in which diarrhea was observed but histopathologic changes were not.

- Degeneration/regeneration of renal cortical tubules and arteriolar hypertrophy (attributed to hypotension and poor renal perfusion resulting from treatment) were noted in moribund and scheduled sacrificed marmosets at doses as low as 20 mg/kg/day administered for 13 weeks or more. The effects were correlated with significantly increased creatinine and blood urea values and significantly increased mean absolute and relative kidney weights. Except for creatinine and urea values, this pathology persisted in animals following a 4 or 8 week drug free recovery period. The kidney effects were not noted in rodents.
- Neurologic toxicity studies in mice and rats were negative. After single intravenous doses between 0.3 and 3 mg/kg, no significant effects were observed on global behavior, ethanol-induced sleeping time or passive avoidance in mice, nor on the motor coordination, horizontal and vertical locomotor activity, or body temperature in rats. However, convulsions were seen in one male rat given 2 gm by gavage for an *in vivo* micronucleus assay. The dose-finding for this study showed that treatment with 500, 800, 1250 or 2000 mg/kg led to severe signs of toxicity, such as ataxia, ventral recumbency, reduced locomotor activity, hunched posture, abnormal breathing, muscular hypotonia, convulsions, and deaths such that dosage was limited to 320 mg/kg in male rats and 500 mg/kg in female rats.
- Other than the expected pharmacologic effects upon BP and a small effect upon heart rate, the non-clinical cardiovascular safety studies did not identify any problems. The sponsor's summary of them is shown in Table 6.

Table 6: Sponsor's Summary of Non-clinical Cardiovascular Safety Studies

Study type	Route	Major Findings	Study number
Isolated guinea pig atria (GLP)	<i>in vitro</i>	No effects on rate and force of contraction up to 10 μ M	[604642]
Isolated rabbit heart (non-GLP)	<i>In vitro</i>	No electrophysiological effects on APD ₃₀ , QT, QTc, triangulation, reverse use-dependency, instability, proarrhythmia index, coronary flow and inter-ventricular conduction up to a maximum concentration of 100 μ M	[0350334]
hERG (non-GLP)	<i>in vitro</i>	IC ₅₀ could not be determined. IC ₃₂ = 1000 μ M	[0380193]
Anesthetized rat CV study (GLP)	<i>in vivo</i> intravenous	Dose-dependent reduction on systolic and diastolic blood pressure and a slight fall in heart rate up to the highest dose of 3 mg/kg. No effects on electrocardiogram	[604642]

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The sources of clinical data are the initial NDA submission, the 120-day safety update (which included additional study reports and data in addition to the safety update), and a large number of supplementary submissions provided in response to questions. I describe the submissions in Table 7.

Table 7: NDA Submissions

Date	Description
2006-02-10	Initial submission
2006-03-13	Adverse event listings
2006-03-14	Study numbers & titles; biopharm methods
2006-03-17	Serious adverse event reports
2006-03-31	Biopharm navigation
2006-04-03	Biopharm reports
2006-04-04	Biopharm navigation
2006-04-05	Biopharm reports
2006-04-19	Clinical diarrhea, gastrointestinal questions
2006-04-19	Biopharm info
2006-05-02	Pharmtox question
2006-06-13	120 day safety update
2006-06-22	CK rise case narrative & case report form (CRF) - 1 case
2006-06-27	Pharmtox
2006-06-28	Patient package insert
2006-07-05	Chemistry
2006-07-06	CRFs for discontinuations in Study 2203
2006-07-11	Chemistry
2006-08-01	Drop CRFs for other studies
2006-08-14	CRFs for edema, CK rise, other
2006-08-16	Valsartan combo study question
2006-08-31	Pharmtox question (historical control rate for rat colon cancer)
2006-09-15	Study 2308 CRFs
2006-09-26	Possible stroke CRFs, Study 2208 data sets
2006-09-28	Study 2327 partial results
2006-10-04	Study 2306 report & data plus other responses
2006-10-05	Safety update with Studies — report & data), and — 2304, 2323E1 (data)
2006-10-06	Stroke summary & biopharm responses
2006-10-13	Stability data
2006-10-17	Tekturna trade name change & labeling responses
2006-10-23	Brainstem strokes, CK rise, intrasubject variability
2006-10-25B	Chemistry
2006-10-25B	Additional safety update
2006-10-26	Mechanism of action explanation (no new data)

Date	Description
2006-11-02	Study report for the oral embryo-fetal development study in rabbits
2006-11-03	Elevated CK CRFs
2006-11-03A	Tekturna labeling
2006-11-07	Rat and human fecal and mucosal aliskiren levels
2006-11-09	Pediatric proposal (not reviewed)
2006-11-15	Dose-response modeling
2006-11-16	CMC quality responses
2006-11-17	Treatment durations by treatment group

4.2 Tables of Clinical Studies

The sponsor submitted with the initial NDA submission a set of ten studies with both efficacy and safety data in hypertensive patients. The sponsor also included a thorough QTc study in the initial NDA submission. In addition, the sponsor submitted with the 120-day safety update study reports and data for four additional studies. These studies are included along with the initial eleven studies in Table 8. The prior sponsor Speedel performed several small (<30 patients), short-term, open-label studies in hypertension and in other indications. The Speedel hypertension studies are listed in Table 9 and the studies in other indications in Table 10. (I checked the study reports regarding the basic results and adverse events—I did not find any noteworthy results or adverse events, and hence I have not included detailed reviews of them in this review.) The sponsor also has several on-going studies from which pertinent adverse events, e.g., strokes, have been reported. These on-going studies are listed in Table 11. Finally, the sponsor has conducted other clinical studies in normal volunteers with pharmacokinetic (PK) endpoints. Please see the FDA clinical pharmacologist’s review for tabulations and reviews of those studies. I did examine these studies for adverse events. In particular, I have incorporated the dose-related, GI adverse events from the PK studies (including the thorough QTc study) at higher dosages into the Integrated Summary of Safety.

Table 8: Studies Supporting Efficacy and Safety in Hypertension

#	N	Wks	Aliskiren/Coadmin	Control	Comment
03HTN	8	8	75, 150	None	Speedel ABPM pilot; forced titration 4 wks each dose; different formulation
04HTNDR	226	4	37.5, 75, 150, 300	Losartan 100	Speedel ABPM dose-ranging; different formulation
1201	455	8	75, 150, 300	Placebo	Japanese
2201	652	8	150, 300, 600	Placebo, irbesartan 150	Peak-to-trough; randomized withdrawal; different formulation
2203	1123	8	75, 150, 300, combos 75/80, 150/160, 300/320	Placebo, valsartan 80, 160, 320, 160/HCTZ 12.5	Combo with valsartan; 75, 150 overencapsulated (75 tablet rather than FCT)
2204	2776	8	75, 150, 300, most combos	Placebo, HCTZ 6.25, 12.5, 25	Combo with HCTZ; 75, 150 overencapsulated
2208	283	1	300, 1200	Placebo, moxifloxacin	Thorough QTc study
2302	1955	52	150-300 ± HCTZ 12.5-25	Placebo during last 4 wk withdrawal in	Long term safety

#	N	Wks	Aliskiren/Coadmin	Control	Comment
				subset	
2302E1	198	16	300/HCTZ 25	None	Safety update; extension to 2302
2303	183	8	150-300 ± HCTZ 25	Lisinopril 20-40 ± HCTZ 25	Safety update
2305	545	6	150/amlodipine 5	Amlodipine 5, 10	
2307	737	8	300 & combo	Ramipril 10	Diabetics; ABPM
2308	672	8	150, 300, 600	Placebo	Randomized withdrawal; ABPM
2323	1107	26	150-300 ± amlodipine 5-10	HCTZ 12.5-25 ± amlodipine 5-10	Safety update; second 26 week period not reported in safety update
2324	355	8	75, 150, 300	Lisinopril 10	Safety update; age ≥ 65; ABPM

Table 9: Other Small Studies in Hypertension

#	N	Wks	Aliskiren/Coadmin	Control	Comment
CRD07	23	6	150; 150/HCTZ 25	None	Two 3 week periods: group 1 (6) responders continue; group 2 (17) HCTZ 25 added; ABPM: aliskiren decreased BP & HCTZ added
CRD08	21	9	75, 150/ramipril 5	Ramipril	Three 3 week periods: ramipril, then + 75, then +150; ABPM: decreases with aliskiren NS
CRD09	23	9	75, 150/irbesartan 150	Irbesartan	Three 3 week periods: irbesartan, then + 75, then +150; ABPM: aliskiren added to nighttime but not daytime reductions

Table 10: Small Studies in Other Indications

#	Indication	N	Wks	Aliskiren	Control	Comment
CR	/	/	/	/	/	/
/	/	/	/	/	/	/

Table 11: Ongoing Studies with Adverse Event Reports Only

#	N*	Wks	Aliskiren/Coadmin	Control	Comment
/	/	/	/	/	/
2304	672 (28)	12	150-300; 150-300/atenolol 100	Atenolol 100	Forced titration at 6 wks; 3 groups
2306	846 (847)	26	150-300 ± HCTZ 12.5-25	Ramipril 5-10 ± HCTZ 12.5-25	Titration-to-effect; randomized withdrawal

#	N*	Wks	Aliskiren/Coadmin	Control	Comment
2316	480 (7)	36	150-300; 150-300/losartan 100	Losartan 50-100	Hypertension with LVH; 3 groups
2327†	1784 (526)	8	150-300; 150-300/valsartan 160-320	Placebo; valsartan 160-320	Forced titration at 4 wks; 4 groups

* planned (enrolled per NDA submission); † a preliminary report and data for this study were submitted late in the review period

4.3 Review Strategy

I initially reviewed all of the controlled trials included in the initial submission and 120-day safety update (Table 8) in standalone reviews. I performed detailed reviews of the placebo-controlled trials, the pivotal ones for approval, and more cursory reviews of the trials lacking a placebo arm. I then performed an integrated review of safety summarizing all of the data from the Table 8 trials as well as noteworthy adverse events from the other trials, including the ongoing trials in Table 11. For my integrated review of efficacy I relied primarily upon analyses of the placebo-controlled trials, supplementing the analyses of these trials with ones from the other trials when issues could be elucidated by the non-placebo-controlled trials, e.g., Study 2324 was restricted to the elderly but used ABPM, so its results are relevant to effects in the elderly and to effects throughout the interdosing interval.

4.4 Data Quality and Integrity

I identified sites for DSI audits by selecting the larger US sites from the placebo-controlled studies that showed a large placebo effect. My rationale for the latter criterion is that we have seen several large antihypertensive factorial studies (including one in this submission) fail recently because of a large placebo effect. My speculation is that these may be the sloppier sites or ones that try to show a large effect to please the sponsor. DSI audited three such sites:

1. One site had randomized 22 patients in Study 2201, 16 patients in Study 2203, and 2 subjects in Study 2305. DSI found that this site had conducted the studies adequately and concluded that data from this site were acceptable.
2. Another site had randomized 30 patients in Study 2201. DSI noted that eight patients were inadvertently given study drug during the single-blind placebo run-in period and that this mistake was not reported to the IRB. DSI also noted that the investigator did not follow the investigational plan in that one patient was terminated and then re-enrolled without the sponsor's permission and six BP measurements were misrecorded in the CRFs. Despite these problems DSI recommends that most of the data from this site can be used to support approval if the effects of the misrecorded BPs are considered.

3. A third site had randomized 21 patients in Study 2201, seven patients in Study 2302, and 10 patients in Study 2308. DSI noted that the investigator failed to follow the protocol for Study 2308 in that eight patients were given the last dose of study drug at visit 7 while the protocol specified that study drug was not to be given at visit 7. DSI concluded that the data for this site may still be used for approval.

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 as detailed above, DSI did not find any disqualifying problems at the sites.

I did not identify any atypical problems with the efficacy data. As mentioned in the first paragraph, some of the studies did appear to be confounded by high placebo effects. Several of the studies in which ABPM was used also appeared to have substantial rates of invalid readings. However, neither of these problems seemed greater than those seen in other recent antihypertensive submissions.

Regarding adverse event reporting, 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.

4.5 Compliance with Good Clinical Practices

The sponsor claims that all studies were conducted in full compliance with Good Clinical Practice. All of the current sponsor's studies were closely monitored by its personnel or a contract organization for compliance to the protocol and the procedures described in it. They were also monitored to insure the safety of the patients and the ethical procedures required by the following directives:

1. Declaration of Helsinki and amendments, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Patients).
2. Directive 91/507/EEC: The Rules Governing Medicinal Products in the European Community.
3. US 21 Code of Federal Regulations dealing with clinical studies, parts 50 and 56, concerning informed patient consent and Institutional Review Board approval.

I have not identified any problems that suggest that these claims are untrue.

4.6 Financial Disclosures

The sponsor obtained investigator financial disclosure forms for Studies 2201, 2203, 2204, 2302, 2305, 2307, and 2308. The sponsor also solicited financial disclosures from the Japanese Study 1201 but did not obtain any. Response rates from U.S. investigators were 100% but response rates from foreign investigators were "<100%".

Of the returned forms only two identified possible conflicts of interest: One investigator from Study — reported "Grants, Honoraria, Travel Expenses" exceeding \$25,000 and one investigator from Study — reported "Consultant, speaker" exceeding \$25,000.

COMMENT: The two potential conflicts of interest could not prejudice the results greatly even if there were overt manipulation. As the sponsor notes, the multiple sites with small percentages of total study patients and the double-blind design of the pivotal studies makes manipulation of overall study results unlikely.

5 CLINICAL PHARMACOLOGY

The following is a summary of the clinical pharmacology findings most relevant for understanding the clinical studies and projecting clinical use of aliskiren. For more details see the FDA clinical pharmacology review.

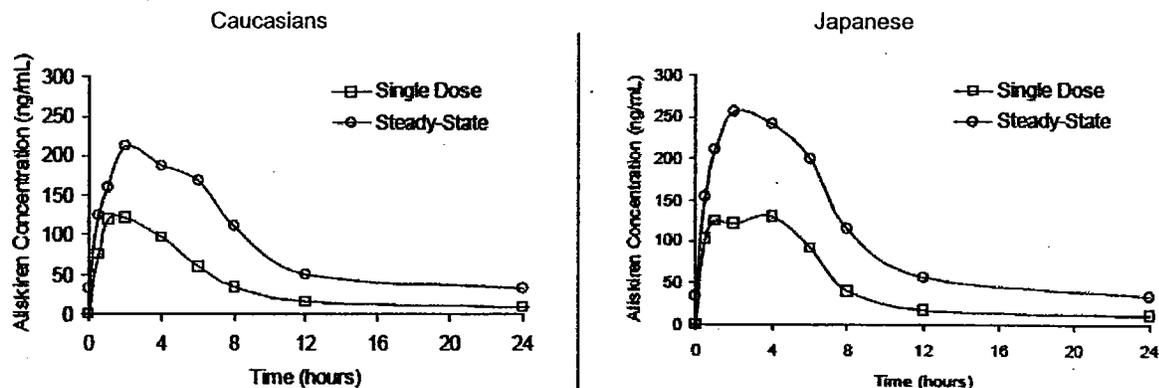
5.1 Pharmacokinetics

Aliskiren is highly soluble in water and binds moderately to plasma proteins (about 50%). In *in-vitro* studies using Caco-2 cells it showed low to moderate intrinsic permeability and was a substrate for P-glycoprotein. The mean absolute bioavailability in humans is low (2.6%). A high fat meal reduces bioavailability further, producing reductions in AUC of 62-71% and in C_{max} of 81-85%, with a delay in T_{max} of about an hour. However, the sponsor alleges that these food effects are not important because inhibition of plasma renin activity was similar under both fed and fasted conditions.

The time course of aliskiren serum concentrations following single doses and after repeat dosing in both Caucasians and Japanese is shown in Figure 2.

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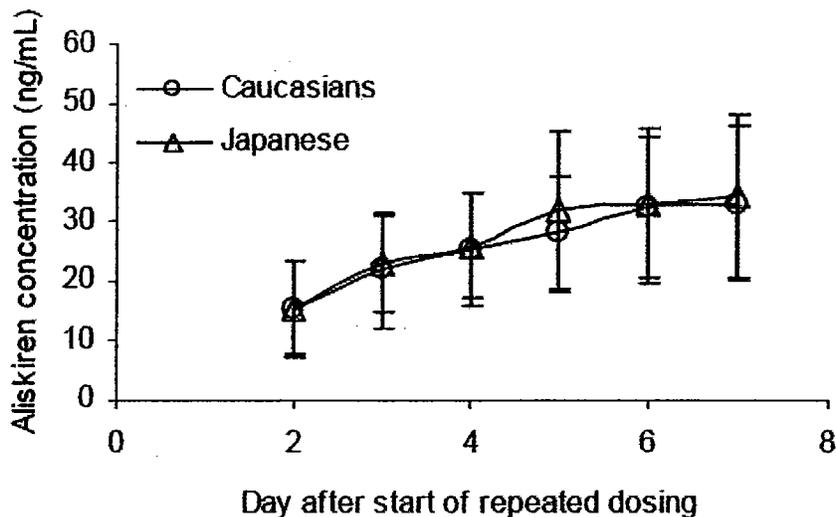
Figure 2: Sponsor's Time Courses of Aliskiren Concentrations after Single and Repeat Daily Dosing of Aliskiren 300 mg in Study 2202



While the sponsor usually quotes a long terminal half-life (>24 hours) to justify once daily dosing of aliskiren, the above curves suggest a biphasic elimination with the initial phase having a much shorter half-life, in the vicinity of six hours. For 300 mg dosing the C_{max}/C_{min} ratio is about $210/30 = 7$.

The sponsor alleges that plasma concentrations reach steady-state after 5-7 days. The trough plasma concentrations following daily dosing with aliskiren 300 mg are shown in Figure 3.

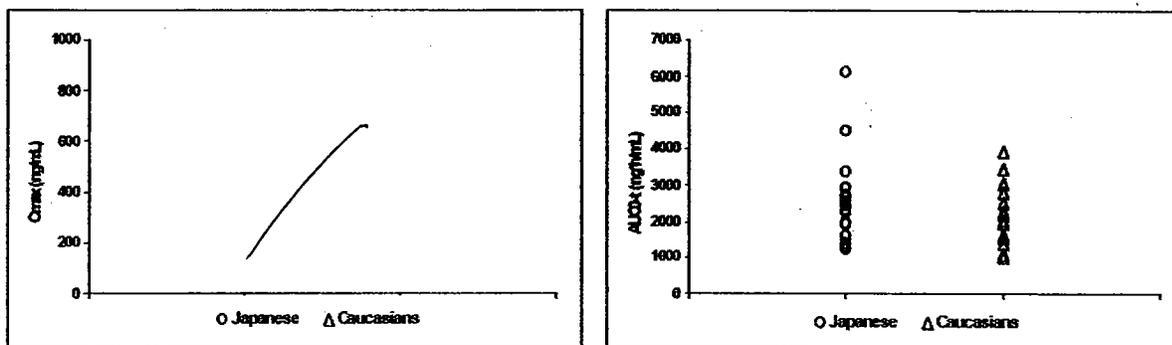
Figure 3: Sponsor's Mean Trough Plasma Concentrations after Repeat Daily Dosing of Aliskiren 300 mg in Study 2202



While the trough plasma concentrations appear to be approaching steady-state at seven days, the curves above do not confirm that a plateau has been reached.

Aliskiren shows fairly wide intra- and intersubject variability in PK. In Studies 2211 and 2214 the 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%. The variability is shown graphically by the scatterplots in Figure 4 of the individual values for C_{max} and AUC at steady-state in Study 2202.

Figure 4: Sponsor's Individual C_{max} and AUC Values after Repeat Daily Dosing of Aliskiren 300 mg in Study 2202



C_{max} and AUC were dose proportional in the range 75 to 600 mg. The values for C_{max} and AUC, as well as T_{max} , are shown in Table 12.

Table 12: Sponsor's Mean (SD) of PK Parameters after Single Dose Administration to Healthy Subjects in Study 2205

Dose	T_{max}^* (hr)	C_{max} (ng/mL)	AUC_{0-t} (ng-h/mL)	$AUC_{0-\infty}$ (ng-h/mL)
75	1	26 (31)	266 (235)	356 (217) [†]
150	2.5	72 (62)	530 (360)	627 (401) [‡]
300	3	202 (119)	1480 (806)	1620 (895)
600	2	420 (325)	3240 (1950)	3520 (2130)

*Median

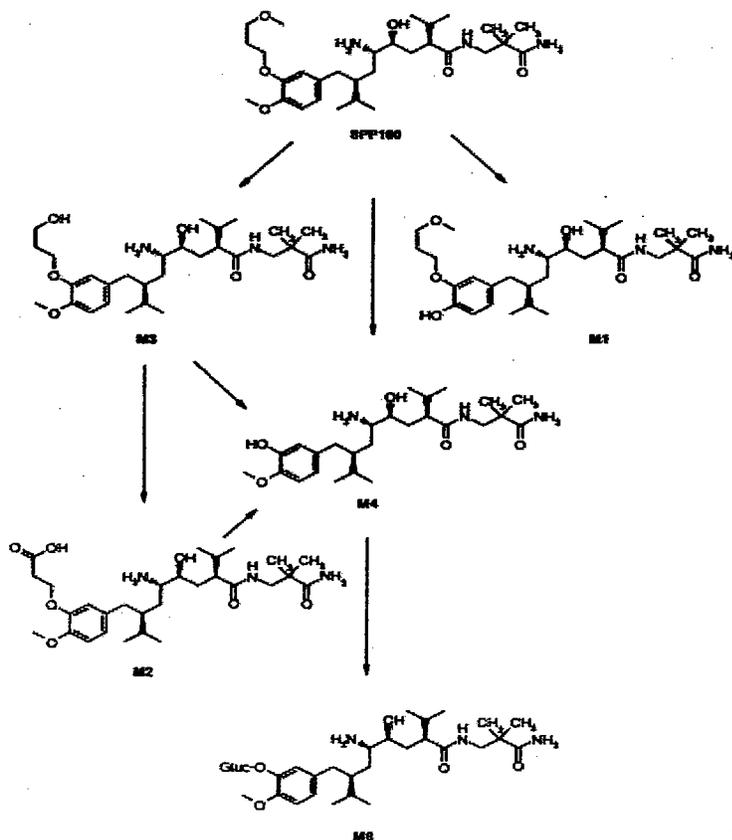
Following oral administration of 300 mg ^{14}C radiolabeled aliskiren, 91.5% of the radioactivity was recovered within 7 days. The majority of the radioactive dose (91%) was eliminated in the feces as unchanged drug (mostly unabsorbed) with 0.6% of the radio-labeled dose eliminated in the urine. The sum of oxidized metabolites in excreta amounted to approximately 1.4% of the dose.

The sponsor alleges that metabolism plays a minimal role in the elimination of aliskiren. *In vitro* studies using ³H-aliskiren and liver microsomes from rats, marmosets and humans yielded qualitatively similar metabolite patterns across species. Quantitatively, the metabolism rate was in the following rank order marmoset > man > rat. Two main metabolites were found in all species (peak P2 and P3 = M4 and M1/M3). Partial chemical structures were proposed for three metabolites. Following oral administration of 300 mg of ¹⁴C-aliskiren, the aliskiren plasma concentration-time curve and total radioactivity-time curve were parallel with only small differences (10-20%) between the two curves indicating low exposure to metabolites. The majority of ¹⁴C-labeled drug absorbed following oral administration was excreted unchanged in the feces via the hepatobiliary route. The main biotransformation pathways of aliskiren in humans are shown in Figure 5. Minor metabolic pathways observed included oxidative O-dealkylations at the phenolic moiety and at its side chain. The oxidized metabolites M1, M2, M3 and M4 were excreted. Traces of a glucuronic acid conjugate (M6) and of a hydrolysis product (M9) were observed. The same metabolites were found in human as observed previously in rat and rabbit. Three additional metabolites were detected in human feces (M12-M14), amounting to 1% of the dose in total. The sponsor hypothesizes that they are artifacts formed by microbial degradation of unabsorbed aliskiren in the gut. The NDA does not document the activities of the metabolites.

In vitro experiments with human liver microsomes and recombinant human CYP450 isoenzymes demonstrated a low apparent intrinsic hepatic clearance of 41 µl/mg/min and identified CYP3A4 as the major enzyme responsible for metabolism of aliskiren. *In vitro* studies showed that aliskiren does not inhibit any of the CYP450 enzymes at therapeutic concentrations (IC₅₀ > 200 µM). The sponsor did not perform specific studies to assess metabolic induction.

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Figure 5: Sponsor's Main Biotransformation Pathways of Aliskiren in Humans



In elderly subjects (>65 years) compared to young adults (18-40 years), aliskiren mean AUC and C_{max} were increased by 57% and 28%, respectively. Exposure in males compared to females was slightly lower (AUC by 24%, and C_{max} by 30%). Mean C_{max} and AUC following a single dose and at steady state were approximately 20% higher in Japanese. 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.

COMMENT: I note the following issues based on the PK data that should be addressed in the clinical studies in hypertension:

1. *There is a substantial food effect. Ideally the sponsor should have studied whether BP reductions vary with varying fixed timings relative to meals, whether BP reductions vary for an individual with different administrations relative to meals, and whether a bedtime administration may be preferable.*

2. *The PK data alone don't justify once daily dosing.*
3. *Aliskiren shows fairly wide intra- and inter-individual variation in PK. Whether this PK variability leads to similar BP variability needs to be scrutinized.*
4. *The sponsor dismisses renal excretion (0.6% of administered dose) and metabolism (1.4% of administered dose as oxidized metabolites in feces) as minimal and unimportant. However, because the absorbed portion of the administered dose is only about 2.6%, renal excretion represents about 23% of absorbed dose and metabolites represent 54% of the absorbed dose. That these latter numbers are the meaningful ones is shown by the renal impairment study, which revealed an increased exposure to aliskiren in patients with mild-to-moderate renal impairment.*
5. *The elderly should have lower dosing considered and studied.*

5.2 Pharmacodynamics

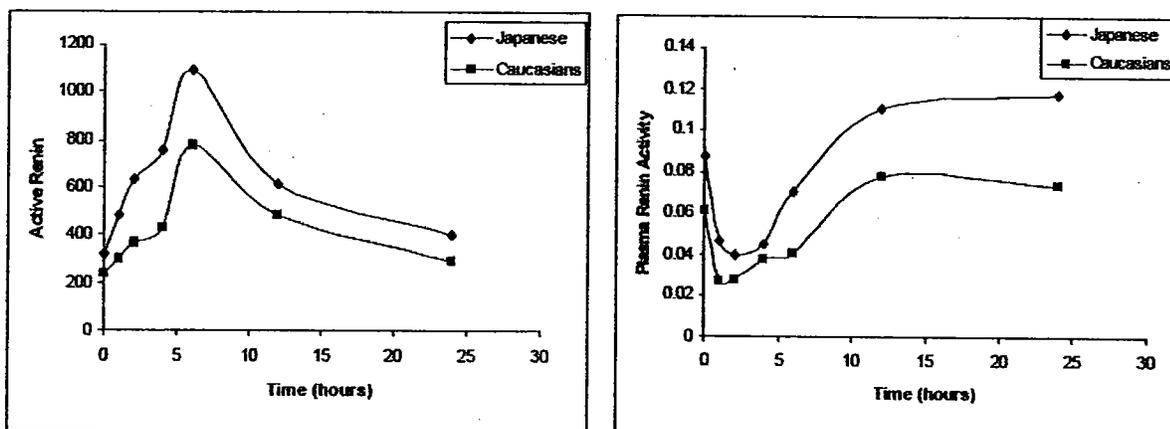
The sponsor describes aliskiren as a selective renin inhibitor. The sponsor's summary of the study establishing that aliskiren is a renin inhibitor, from the NDA's Nonclinical Summary, is the following:

"The inhibitory potency of aliskiren against human renin was measured using human recombinant renin tetradecapeptide substrate. Angiotensin I generated during the incubation was measured by radioimmunoassay. To test for selectivity of aliskiren against renin, the compound was also tested against various other human aspartic proteinases. Assays were performed using human cathepsin D, E, and pepsin with the synthetic peptide Lys-Pro-Ile-Glu-Phe-Nph-Arg-Leu as substrate, and using HIV-1 proteinase with the synthetic peptide Lys-Ala-Arg-Ile-Nle-Nph-Glu-Ala-Nle-NH₂.

"Aliskiren inhibited human renin with an IC₅₀ value in the sub-nanomolar range (0.6 nM). In contrast, aliskiren was inactive or only weakly active against human aspartic proteinases and HIV-1 proteinase (IC₅₀ > 5000 nM)."

The sponsor demonstrated in clinical studies that renin activity is reduced in humans. The time course of renin activity following repeat daily dosing of aliskiren 300 mg is shown in Figure 6.

Figure 6: Sponsor's Time Courses of Renin Activity after Repeat Daily Dosing of Aliskiren 300 mg in Study 2202



The sponsor also measured RAAS hormones in other studies with similar results. In Study MD02 the sponsor measured plasma renin activity, angiotensin I, and angiotensin II following single and repeat dosing of aliskiren in healthy volunteers. These parameters are shown in Figure 7, Figure 8, and Figure 9 respectively and the corresponding plasma aliskiren levels in Figure 10.

Figure 7: Sponsor's Plasma Renin Activity in Study MD02

