CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-985

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW
DIVISION OF PHARMACEUTICAL EVALUATION I

NDA 21-985/N000AZ	**SUBMISSION DATE**	December 4, 2006
N000BB		December 8, 2006
N000BB		December 14, 2006
N000BB		December 20, 2006

TYPE:	ADDENDUM TO ORIGINAL NEW DRUG APPLICATION
BRAND NAME:	Tekturna® Tablets
GENERIC NAME:	Aliskiren Tablets –Film Coated, Immediate Release
DOSAGE STRENGTH:	150 and 300 mg
INDICATION:	Treatment of hypertension alone and in combination with other antihypertensive agents
SPONSOR:	Novartis Pharmaceutical Corporation
PRIMARY REVIEWER:	Lydia Velazquez, Pharm.D.
TEAM LEADER:	Patrick Marroum, Ph.D.

Novartis is seeking approval of Tekturna (Aliskiren immediate-release (IR)) tablets. This will establish a new drug class of rennin inhibitors. The sponsor is seeking an indication for the treatment of hypertension alone and in combination with other antihypertensive agents. Tekturna has been developed in three tablet strengths for oral administration being 75, 150 and 300 mg tablets. The lowest 75 mg strength will not be marketed in the U.S.

This submission deals with a clinical study in which the effects of aliskiren on human colon mucosa when administered daily at doses of 300 mg for 8 weeks in healthy volunteers. This review will assess the findings from the Clinical Pharmacology perspective.

RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed the amendments to NDA 21-985 original NDA submitted on December 4, 8, 14, and 20th, 2006 for Tekturna® tablets and has the following clinical pharmacology and biopharmaceutics comments:

REVIEWER COMMENTS TO THE SPONSOR:

1. Once again as in study 2105, no direct comparison can be made between the results in the rat study and this study in humans since mucosal aliskiren concentration was not measured in rat rectum. The rectal mucosal concentration in humans is about 2 times 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: 502μg/g versus rat feces: 10900-16900 μg/g).

2. The mean colonic concentrations of Aliskiren in the rat (502 µg/g) are about 4 times lower than the mean fecal aliskiren concentrations in the rectum of man (2102.88 µg/g). Not much of a safety margin.

As a result, the follow-up ALTITUDE trial seems appropriate to conduct and report as a Phase IV commitment.

These comments are already being conveyed to the sponsor. No action is indicated.

Lydia Velazquez, Pharm.D.
Primary Reviewer
Division of Clinical Pharmacology I

FT Initialed by Patrick Marroum, Ph.D. _____

CC list: HFD-110: NDA 21-985 (DavidJ, StockbridgeN); HFD-860: (VelazquezL, MarroumP, MehtaM); CDER Central Document Room

STUDY CSP100A 2103 – A DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED, PARALLEL GROUP, MULTI-CENTER STUDY TO ASSESS THE EFFECTS ON COLON MUCOSA OF A DAILY DOSE OF ALISKIREN 300 MG ADMINISTERED ORALLY FOR 8 WEEKS IN HEALTHY VOLUNTEERS.

STUDY INVESTIGATOR AND SITE:

Site 1: [redacted]

Site 3: [redacted]

Site 4: [redacted]

(Note: Site 2 [redacted] dropped out from participation prior to IRB submission)

REPORT # 2103
EDR DATE DECEMBER 4TH, 2006
STUDY DATES: August 3 – December 3, 2006

Objectives:

Primary objective:

- To determine the occurrence of epithelial hyperplasia in mucosal biopsy sections obtained from the colon using a visual analog rating scale in subjects treated with aliskiren 300 mg daily for 8 weeks compared to subjects treated with placebo.

Secondary objectives:

- To determine the occurrence of epithelial dysplasia 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.
- To quantify the concentration of aliskiren in plasma, rectal mucosa biopsy specimens and in feces after 8 weeks of oral treatment with 300 mg aliskiren daily, and to determine any relationship between plasma, rectal mucosal and fecal concentrations of aliskiren.
- To compare the occurrence and severity of inflammation in mucosal biopsies obtained from the colon using a standard microscopic histology scoring scale in subjects treated with aliskiren 300mg daily for 8 weeks compared to subjects treated with placebo.
- To compare the occurrence of mucosal abnormalities (type and severity) during colonoscopy in subjects treated with aliskiren 300 mg daily for 8 weeks compared to subjects treated with placebo.
- To assess the safety of aliskiren 300 mg orally taken daily for 8 weeks in healthy volunteers.

Formulation:

Aliskiren 300 mg film-coated tablet taken orally once daily (Batch: X301LA/#6000937.006)

Aliskiren matching placebo tablet taken orally once daily (Batch: X314JA/#6000975.008)

Note: Expiration dates for either one was not provided.

Design: This study was a double-blind, placebo-controlled, parallel group, multiple center study to assess the effects of aliskiren 300 mg administered once daily for 8 weeks on colorectal mucosal tissue in healthy volunteers (study design illustrated in Figure 1).

Each subject participated in a 42-day screening period, seven outpatient center visits, two overnight inpatient stays, and a study completion evaluation, as described below:

Screening (Days -42 to -1), which included:

- an initial visit to assess eligibility according to the inclusion / exclusion criteria
- an inpatient visit (between Day -28 and -2) the day before the screening colonoscopy during which subjects underwent a complete bowel cleansing and remained in-house for a baseline colonoscopy procedure with mucosal biopsies

Seven study visits, which included:

- Day 1 (including pre-dose baseline assessment), Day 3 (± 1), Day 15 (± 1), Day 36 (± 1), Day 53 (±1) – outpatients visits
- One overnight stay commencing on the afternoon of Day 55, or in the afternoon of the day prior to the scheduled post-dose colonoscopy for complete bowel cleansing
- Post-dose colonoscopy (Day 56 or up to Day 60)
- Study completion visit (Day 61 ±2)

Figure 1 Study Scheme

Screening				Week 1		Week 3	Week 6	Week 8			Study Completion
Day -42 to -1				Baseline/Day 1	Day 3 ± 1	Day 15 ± 1	Day 36 ± 1	Day 53 ± 1	Day 55[2]	Day 56 or up to Day 56+4	Day 61 ± 1
Screening assessments (performed prior to colonoscopy)	Single PK fecal sampling	Bowel cleansing preparation (begin in the afternoon the day prior to scheduled colonoscopy)[1]	Screening Colonoscopy with mucosal biopsies[1]	Safety assessments and trough PK					Bowel cleansing preparation	Post dose Colonoscopy with mucosal biopsies	End of study evaluation
				First dose				24 hrs PK fecal sampling			

1: Screening colonoscopy is to be performed between Day -42 to Day -2 to allow time for pathology review.
2: Bowel cleansing preparation for post-dose colonoscopy is to occur one day prior to the schedule colonoscopy.

Subjects were randomized into 2 groups based on a ratio of two active drug-treated subjects for every-one placebo treated subject.

- **Group 1:** 300 mg aliskiren once daily for at least 8 weeks (56 days).
- **Group 2:** Matching placebo once daily for at least 8 weeks (56 days).

Study drug may have been administered up to Day 60 depending on the scheduling of the post treatment colonoscopy. All subjects received their study medication daily with water. Subjects attended the clinical unit for drug dispensing, to assess safety and tolerability of the study drug, and to obtain blood samples for measurement of plasma drug levels to ensure compliance with study medication.

A single fecal sample was collected during the screening period, and a 24-hour pooled fecal sample was also obtained after dosing beginning with the first natural bowel movement on or after Day 53 for assessment of average 24 hour fecal aliskiren concentration.

Subjects were readmitted to the clinical unit for a post-treatment colonoscopy on Days 56-60. The bowel cleansing preparation was identical to that used for the pre-treatment colonoscopy. On the day of the scheduled post treatment colonoscopy, study medication was given about 4 hours prior to the procedure.

An outpatient diary was used to record the daily administration of study medication, occurrence of adverse events, and subject reported comments. This outpatient diary also included a sample collection log to record the time of each fecal sample taken for the 24 hour pooled fecal sample.

Counting of the study medication was conducted during each outpatient clinic visit during the treatment period (i.e., Day 3 (± 1), Day 15 (± 1), Day 36 (± 1), Day 53 (±1), Day 55) to monitor subject compliance. Frequent contacts with the study subjects (at least once a week) were made by the site to ensure compliance and to follow up on any adverse events during the outpatient period.

Mucosal biopsies at Screening and after 8 weeks of treatment were obtained from the caecum, upper ascending colon, mid-descending colon, and rectum (described in detail below) to assess the presence and extent of hyperplasia, changes in mucosal structure, inflammation, and dysplasia. In addition, biopsies were obtained for analysis of secondary endpoints from the terminal ileum whenever possible, (i.e., 25 of 30 subjects) and biopsies were obtained from the transverse colon for potential future exploratory studies.

Number of subjects: Planned: 30 subjects were planned to assure that at least 22 would complete the study. Actual: 31 subjects enrolled and 30 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).

During recruitment, informed consent review, and baseline period, the subjects were informed and reminded of the following restrictions:

Smoking, physical exercise, alcohol consumption and intake of xanthine (e.g., caffeine) containing food or beverages had to follow the subjects' normal routine throughout the study.

During the course of the study, all subjects took the medication without restrictions with regard to food; however, it was advised that medication be taken following food on the first day of administration.

On the day prior to each colonoscopy procedure, subjects were asked to return to the study clinic to undergo the bowel cleansing procedure in preparation for next days' colonoscopy. Subjects had to adhere to a liquid diet and the use of laxative preparations and remained domiciled until the colonoscopy procedure completed.

ANALYTICAL METHODS:

Analytes - media and methods: Fecal, rectal mucosal and plasma aliskiren concentrations were determined by LC-MS/MS methods. The lower limit of quantitation (LLOQ) for fecal samples, rectal mucosal biopsy specimens and plasma was 1.50 µg/g, 50 ng/g, and 0.5 ng/mL, respectively.

All assays were validated and judged to be acceptable upon assessment.

PK SAMPLE COLLECTION/CALCULATIONS AND STATISTICAL ANALYSIS:

Drug concentration variables: schedule of assessments

- **Fecal aliskiren concentrations**
  Single fecal sample collection during screening
  24-hour pooled fecal sample collection beginning with the first natural bowel movement on or after Day 53.
- **Rectal mucosal biopsy aliskiren concentrations**
  Rectal mucosal biopsy samples obtained at Screening and post-treatment on Day 56-60
- **Plasma aliskiren concentrations**
  Pre-dose (Day 1, 3, 15, 36, 53, and Day 56-60
  During colonoscopy near time of biopsy (Screening and Day 56-60)

RESULTS:

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. One subject (5118) in the placebo group was observed to exhibit hyperplasia in the rectum following treatment (pre-treatment score = 0 and post-treatment score = 3).

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 the aliskiren group, there were no significant changes from baseline in the number of lymphocytes, neutrophils, or eosinophils in the surface and crypt epithelium in any of the 5 regions examined. There was a slight decrease in lymphocyte count in the surface epithelium of the ascending colon in the placebo group ($p < 0.046$; see Appendix 6, Table 5 and Appendix 6, Table 6), but no significant difference between treatment groups.

There were no significant changes from baseline in overall inflammation or in the response of any specific cell type in either treatment group in any of the 5 regions examined (Appendix 6, Table 7 and Appendix 6, Table 8).

There were no significant changes from baseline in any measure of mucosal structure in either treatment group in any of the 5 regions examined (see Appendix 6, Tables 7 and Appendix 6, Table 8).

There were 2 subjects (5106 and 5125) in the aliskiren group with indefinite dysplasia (score = 1) in the rectal mucosa at baseline. In each of these subjects, the post-treatment dysplasia score was 0. All other dysplasia scores at baseline in both groups were 0. All post-treatment dysplasia scores in both groups were 0 (see Appendix 6, Tables 7 and Appendix 6, Table 8).

There were six (6) reported cases of loose stools or diarrhea in three (3) subjects all in the aliskiren group. None of the 3 subjects with diarrhea discontinued study medication and all 3 subjects had normal post-treatment colonoscopies. Diarrhea was not associated with any consistent histopathologic change (Source: Appendix 6, Listing 2). It should be noted that 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.

Five (5) of 30 of the subjects were found to have incidental mucosal lesions at the time of colonoscopy (presented in Appendix 3, Listing 3.8 and Appendix 3, Listing 3.9). Histologic findings are summarized below:

- Subject 5110 (Placebo): Post-treatment tubular adenoma in descending colon.
- Subject 5112 (Aliskiren): Post-treatment lymphoid nodules in terminal ileum.
- Subject 5115 (Placebo): Baseline hyperplastic polyp in rectum.
- Subject 5118 (Placebo): Baseline hyperplastic polyp in descending colon.
- Subject 5122 (Aliskiren): Baseline lymphoid nodule (lymphoid hyperplasia) in terminal ileum.

Pharmacokinetics

Fecal, rectal mucosal, and plasma aliskiren concentrations are summarized below. Median plasma pre-dose aliskiren concentrations in the active treatment group varied by about 43% (12.32 to 17.60 ng/mL). All but one subject remained compliant throughout the study.

The fecal aliskiren concentration was 2265 µg/g (median) and rectal mucosal aliskiren concentration was 38.8 µg/g (median) at the end of the treatment period. Median fecal aliskiren concentration was approximately 40-fold higher than that in rectal mucosal tissue.

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 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								

Conclusions:

- Aliskiren, following daily oral administration of 300 mg for 8 weeks in healthy subjects, had no significant effect on hyperplasia or mitotic activity in mucosal biopsy sections obtained from the caecum, ascending colon, descending colon or rectum.
- Aliskiren, following daily oral administration of 300 mg for 8 weeks in healthy subjects, had no significant effects on inflammation, mucosal structure, or dysplasia in mucosal biopsy sections obtained from the terminal ileum, caecum, ascending colon, descending colon or rectum.
- Three subjects in the aliskiren group experienced diarrhea during the study, none of which required discontinuation of study drug. Diarrhea was not associated with any consistent histopathologic change.
- Exposure levels of aliskiren following oral daily administration of 300 mg for 8 weeks in healthy subjects were (median):
  - Fecal aliskiren concentration was 2265 µg/g
  - Rectal mucosal aliskiren concentration was 38.8 µg/g
  - Plasma pre-dose aliskiren concentration ranged between 12.32 and 17.60 ng/mL

REVIEWER'S COMMENT:

1. Once again as in study 2105, no direct comparison can be made between the results in the rat study and this study in humans since mucosal aliskiren concentration was not measured in rat rectum. The rectal mucosal concentration in humans is about 2 times 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: 502µg/g versus rat feces: 10900-16900 µg/g).
2. The mean colonic concentrations of Aliskiren in the rat (502 µg/g) are about 4 times lower than the mean fecal aliskiren concentrations in the rectum of man (2102.88 µg/g). Not much of a safety margin.

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/s/

Lydia Velazquez
2/28/2007 02:15:39 PM
BIOPHARMACEUTICS

CPB review of addendum

Patrick Marroum
2/28/2007 02:56:39 PM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW
DIVISION OF PHARMACEUTICAL EVALUATION I

NDA 21-985/N000	SUBMISSION DATE	February 10, 2006
N000BC		March 14, 2006
N000BZ		March 31, 2006
N000BB		April 3, 2006
N000BB		April 4, 2006
N000BC		April 5, 2006
N000SU		June 13, 2006
N000BL		June 28, 2006
N000BC		July 5, 2006
N000BM		July 6, 2006
N000C		July 11, 2006
N000BM		August 1, 2006
N000BM		September 26, 2006
N000BZ		October 6, 2006
N000BL		October 17, 2006
N000BB		October 26, 2006
N000BL		November 3, 2006
N000C		November 7, 2006
E-mail		November 20, 2006

TYPE: ORIGINAL NEW DRUG APPLICATION

BRAND NAME: Tekturna® Tablets
GENERIC NAME: Aliskiren Tablets –Film Coated, Immediate Release

DOSAGE STRENGTH: 150 and 300 mg
INDICATION: Treatment of hypertension alone and in combination with other antihypertensive agents
SPONSOR: Novartis

PRIMARY REVIEWER: Lydia Velazquez, Pharm.D.

QT REVIEWER: Christine Garnett, Pharm.D.
PHARMACOMETRICS REVIEWER: Rajnikanth Madabushi, Ph.D.

TEAM LEADER: Patrick Marroum, Ph.D.
PM TEAM LEADER: Jogarao Gobburu, Ph.D.

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Executive Summary

Novartis is seeking approval of Tekturna (Aliskiren immediate-release (IR)) tablets. This formulation will establish a new drug class of rennin inhibitors. The sponsor is seeking an indication for the treatment of hypertension alone and in combination with other antihypertensive agents. Tekturna has been developed in three tablet strengths for oral administration being 75, 150 and 300 mg tablets. The lowest 75 mg strength will not be marketed in the U.S.; but was used by the sponsor in conducting several clinical trials. In total, the sponsor has submitted 67 clinical and pharmacokinetic studies to the NDA; which includes four phase III studies (Studies 2302, 2305, 2307, and 2308) with no pharmacokinetic content. However, the five clinical studies considered to be pivotal to the approval of aliskiren in this indication include 1201, 2201, 2203, 2204, 2308 none had any pharmacokinetic content either. Thirteen in-vitro studies were also submitted to the NDA containing either metabolism or transporter/permeability data and were all worthy of review from the Clinical Pharmacology perspective.

Section 6 of NDA 21-985 includes 25 studies; which was not inclusive of all clinical pharmacology and pharmacokinetic studies. Some of the studies that should have been submitted to section 6, were submitted to Section 8. Dissolution data was incomplete and was subsequently submitted to the NDA upon request by the Agency. Two of the studies (2203 and 2204) submitted blinded an earlier formulation of aliskiren; which resulted in the need for a bioequivalence study between the clinical formulation and the FMI (final market image) formulation (study 2343).

The sponsor's proposed dissolution method and specifications for Aliskiren are acceptable and are described below:

Apparatus	USP Apparatus I (Basket
Medium	0.01N HCL
Volume	500 mL
Temperature	37° C ± 0.5° C
Q	— of label claim after 30 minutes

RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed NDA 21-985 original NDA submitted on February 10, 2006 and subsequent submissions to the NDA (see above) for Tekturna® tablets and has the following clinical pharmacology and biopharmaceutics comments:

REVIEWER COMMENTS TO THE SPONSOR:

The following Comments should be addressed by the sponsor:

A. Dosing Recommendations:

Aliskiren 75 mg dose shows effectiveness in decreasing the msDBP by week 8 and 50% of patients at this dose show a reduction of msDBP by 10 mm Hg.

Elderly - The pharmacokinetics of aliskiren were studied in the elderly (≥ 65 years). The exposure (measured by AUC) and C_{max} of aliskiren is increased in elderly by 57% and 28%, respectively.

Renal Impairment - The pharmacokinetics of aliskiren in patients with varying degrees of renal insufficiency resulted in an increase in rate and extent of exposure (AUC and C_{max}) between 0.8- to 2-fold those observed in healthy subjects following single dose administration and at steady state. Pharmacokinetic changes did not correlate with the severity of renal impairment. However, C_{min} was consistently 2-fold higher than subjects with normal renal impairment regardless of severity of renal impairment.

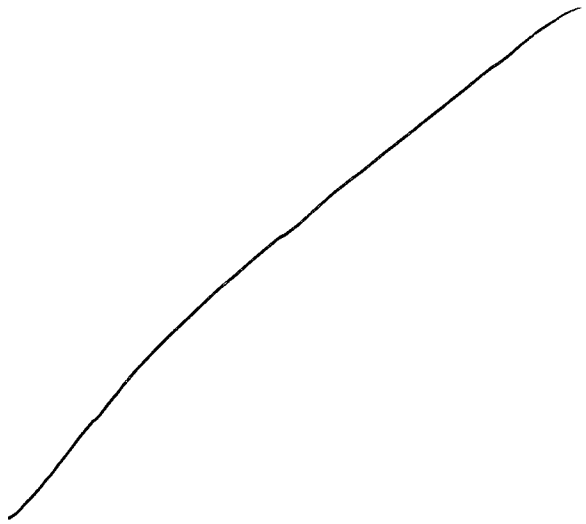
B. Assay Methodology:

The bioanalytical assay for study 2228 is missing. It remains unclear whether Aliskiren was measured by LC/MS/MS or by LC/UV since the assay methodology is reported differently in the synopsis than in the study report. The sponsor will be required to submit the assay since there's unusually high inter-subject variability in this study.

C. Labeling:

1. The following statement should be changed in the "PHARMACOKINETIC" section of the proposed label in order to align itself with all of the dose proportionality study findings that were submitted:

Proposed by Sponsor:



10 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

Summary of Important CPB Findings

Proposed Dosages and Route of Administration: The usual recommended starting dose of Aliskiren is 150 mg orally once daily. In some patients whose blood pressure is not adequately controlled, the daily dose may be increased to 300 mg. The sponsor is proposing that Aliskiren be used over a dosage range of 150 mg to 300 mg administered orally once daily.

Aliskiren at doses greater than 1800 mg have not been studied. Patients do not require doses in excess of 300 mg daily when used alone or in combination with other antihypertensive agents.

Formulations used in Pivotal Clinical Trials: Several formulations were used in clinical trials submitted. In an effort to blind medications used for some of the clinical studies, the sponsor inadvertently created a new formulation according to SUPAC Guidance since backfill material was used as filler when aliskiren was over-encapsulated.

Novartis SPP100 formulations used in Clinical Studies: 75mg dosage strength

Component	75mg tablet in capsule (uncoated MF) 6001149.001 (mg/capsule)	75mg film-coated tablet in capsule (MF) 6001149.002 (mg/capsule)	75mg film-coated tablet (FMI) 3764313.004 and 3764313.007 (mg/tablet)	Function
Tablet / Film-coated tablet				
SPP100 hemifumarate				Active substance
Cellulose microcrystalline (Ph. Eur./NF)				
Crospovidone (Ph. Eur. / NF)				
Povidone (Ph. Eur./ USP)				
Magnesium stearate (Ph. Eur./NF)				
Colloidal silicon				
Tablet target weight				
Film coating				
Total weight of the film coated tablet				
Capsule backfill				
Total capsule backfill				
Weight of shell				
Total weight of capsule			—	

MF: market formulation, FMI: final market image

For the 75 mg strengths, formulation number 6001149.001 (first column) was used in phase II study 2203 and formulation number 6001149.002 (second column) was used for phase II study 2204 both considered to be pivotal by the Clinical Division for assessment of approvability.

Novartis Aliskiren Formulations used in Clinical Studies: 150mg dosage strength

Component	150mg tablet in capsule (uncoated MF) 3768785.002 (mg/capsule)	150mg film-coated tablet in capsule (MF) 3768785.004 (mg/capsule)	150mg film-coated tablet (FMI) 3765070.005 3765070.008 and 3765070.010 (mg/tablet)	Function
Tablet / film-coated tablet				
SPP100 hemifumarate				Active substance
Cellulose microcrystalline (Ph. Eur./NF)				
Crospovidone (Ph. Eur. / NF)				
Povidone (Ph. Eur./ USP)				
Magnesium stearate (Ph. Eur./NF)				
Colloidal silicon				
Tablet target weight				
Film coating				
Total weight of the film coated tablet			**357.00**	
Capsule backfill				
			—	
			—	
			—	
Total capsule backfill				
Weight of shell			—	
Total weight of capsule			—	

MF: market formulation, FMI: final market image

For the 150 mg strengths, formulation number 3768785.002 (first column) was used in phase II study 2201 and formulation number 3768785.004 (second column) was used for phase II studies 2203 and 2204 both considered to be pivotal by the Clinical Division for assessment of approvability. The later formulation was also used for bioequivalence study 2343 in order to establish bioequivalence between the MF and FMI formulation. Formulation number 3765070.008 (third column) was used in phase III study 2308.

Novartis Aliskiren Formulations used in Clinical Studies: 300mg dosage strength

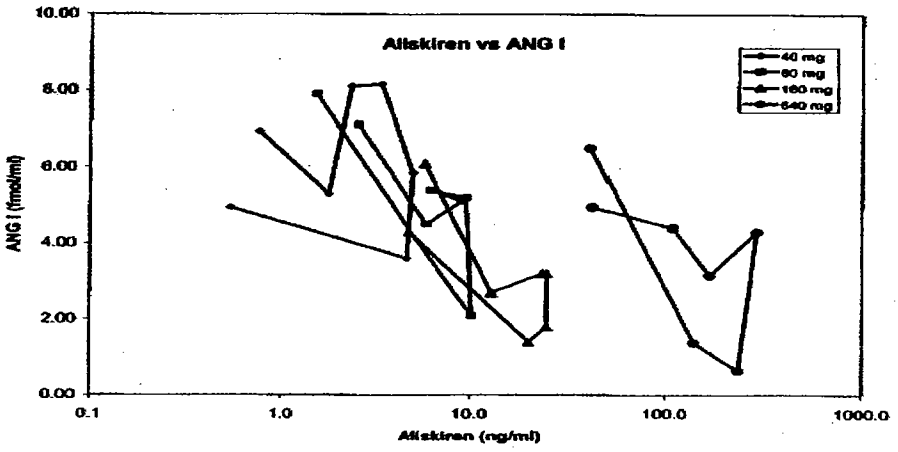
Component	300mg tablet in capsule (uncoated MF) 3768801.002 (mg/capsule)	300mg film-coated tablet (MF) 6000937.001 and 6000937.005 (mg/tablet)	300mg film-coated tablet (FMI) 6000937.004, 6000937.006 and 6000937.007 (mg/tablet)	Function
Tablet / film-coated tablet				
SPP100 hemifumarate				Active substance
Cellulose microcrystalline (Ph. Eur./NF)				
Crospovidone (Ph. Eur. / NF)				
Povidone (Ph. Eur./ USP)				
Magnesium stearate (Ph. Eur./NF)				
Colloidal silicon				
Tablet target weight				
Film coating				
Total weight of the film coated tablet			**706.00**	
Capsule backfill				
		—	—	
		—	—	
		—	—	
Total capsule backfill		—		
Weight of shell		—	—	
Total weight of capsule		—	—	

MF: market formulation, FMI: final market image

Formulation number 3768801.002 (first column) was used for phase II study 2201 while formulation number 6000937.001 and 6000937.005 (second column) were used for phase II studies 2203 and 2204, respectively. Formulation number 6000937.006 (third column) was used in phase III study 2308.

Exposure-Response Relationship in terms of Efficacy and Safety: When concentration versus decrease in Angiotensin I were measured in healthy male volunteers, Angiotensin I decrease was concentration dependent and were lower after 8 days of dosing. Formulation administered in this study (02MD) was a liquid suspension.

Aliskiren vs ANG I – All Doses



- Aliskiren shows dose response for reduction of blood pressure (both mSDBP and mSSBP at trough by 8 weeks) as well as for increasing the risk for diarrhea over the dose range of 75 - 600 mg studied in the placebo controlled trials as shown in Figure 1. Approximately 50% of patients dosed with 75 mg of aliskiren show a drop in msDBP by at least 10 mm Hg by week 8 compared to 65% with 600 mg daily dose as demonstrated in Figure 2.

Figure 1: [redacted] patients should be titrated to a maximum of 300 mg daily dose of Aliskiren.

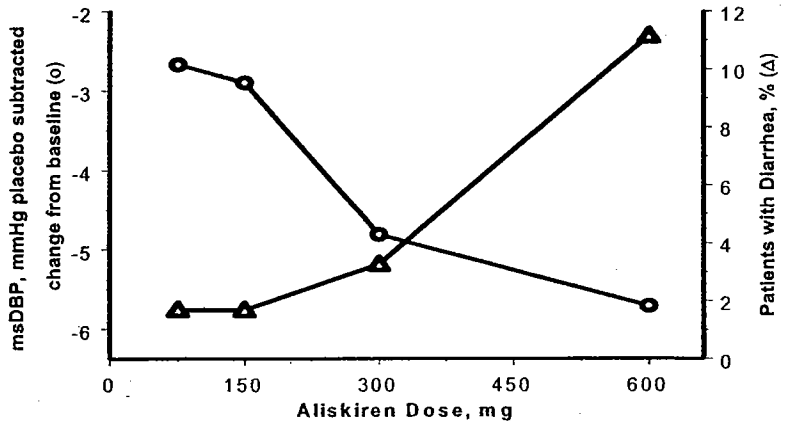
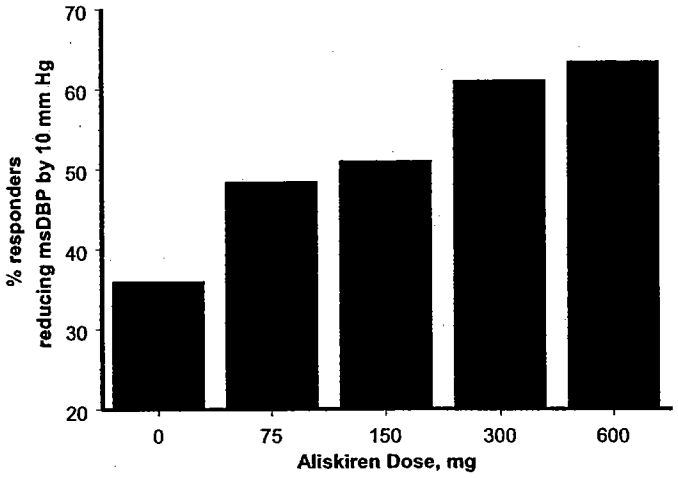
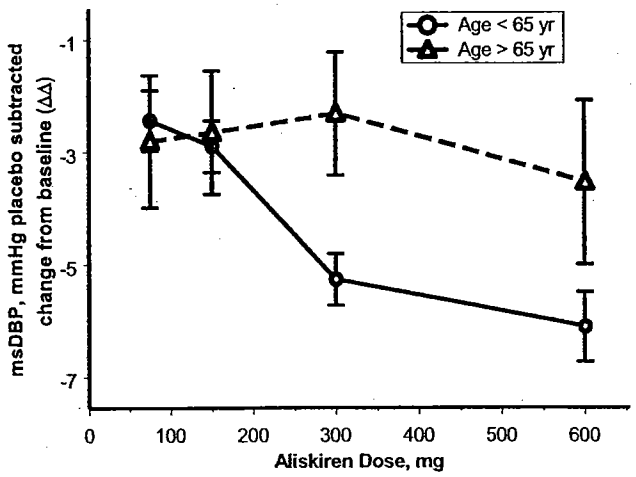


Figure 2: 50% of the patients respond to 75 mg Aliskiren.



- Mean effects on lowering of msDBP for the doses studied generally plateau by week 4. Hence, 4 weeks is a reasonable period before the next dose titration.
- In elderly patients i.e., above 65 years age, no additional benefit in blood pressure reduction is gained by increasing the dose from 75 mg to 300 mg aliskiren as demonstrated in Figure 3. Approximately 55% of the patients responded to aliskiren treatment irrespective of doses in the range of 75 – 300 mg.

Figure 3: Aliskiren dose higher than 75 mg does not provide substantial benefit in elderly. (*LS Mean msDBP obtained from MMRM analysis).*



- The risk for diarrhea was similar across the subgroups of gender and age.

Exposure-response support of dosing regimen: 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 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. Study 2324 is a study in elderly (age ≥ 65) hypertensives that included ABPM. The ABPM data do not show a pronounced peak effect for aliskiren but, after a plateau, gradual diminishing of BP reductions during the second half of the interdosing interval. Aliskiren 75 mg was comparable to or slightly better than 150 mg and little different than 300 mg. The ratios of mean daytime to mean nighttime ambulatory BP for aliskiren range from 0.59 to 0.90. The withdrawal studies show a gradual rise in BP over several weeks after withdrawal of aliskiren, suggesting a sustained effect not directly proportional to drug levels. Overall these data are weakly supportive of the proposed once daily dosing. More data. will help to confirm that once daily dosing is adequate.

Response Endpoints: The major endpoint is decrease in blood pressure since the indication is for treatment of hypertension with Aliskiren. The endpoints being measured is Systolic and Diastolic sitting blood pressure as well as decrease in Angiotensin I.

Single and Multiple Dose Pharmacokinetic Parameters for Aliskiren: Below are the single and multiple dose pharmacokinetic parameters for Aliskiren at the proposed doses for marketing in the fasted state:

	Route	Dose	Formul	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	t½ (h)	CL/F (L/h)
Single Dose	PO	150mg	capsule	72-148	0.5-2.5	530-663	570-720	27	230
Single Dose	PO	300mg	capsule	186-215	2-3	1124-1480	1274-2437	30-54	150-263
Multiple Dose	PO	300mg	capsule	321-403	2-4	2135-2519			

No multiple dose pharmacokinetic data was available with the 150 mg capsule in the fasted state. Aliskiren's metabolite pharmacokinetic characteristics have not been evaluated since Aliskiren undergoes minimal metabolism.

Pharmacokinetics in the Targeted Population: No pharmacokinetic studies have been performed in hypertensive patients.

Bioavailability of Aliskiren: A mass balance study was conducted where the bioavailability of 300 mg of [^{14}C]SPP100 and its metabolites in healthy male subjects was determined. Aliskiren was administered as an oral solution with the urinary and fecal excretion of Aliskiren and its metabolites determined. About 3% of the administered dose is actually absorbed. No other bioavailability data is available.

An open-label exploratory study was conducted where correlations between fecal, rectal mucosal biopsy specimens, and plasma concentrations in humans as well as in the rat (250 mg/kg/d) were attempted. Unfortunately, no direct comparisons can be made between the results in rats and humans since mucosal aliskiren concentrations were not measured in rat rectum and that was the only sight biopsied and measured in humans. However, the colonic concentrations of Aliskiren in the rat (502 µg/g) are up to three times lower than the fecal Aliskiren concentrations in the rectum of humans (1527 µg/g).

Distribution Characteristics of Aliskiren: Protein binding of Aliskiren is about 40% and the blood to plasma ratio is about 0.61.

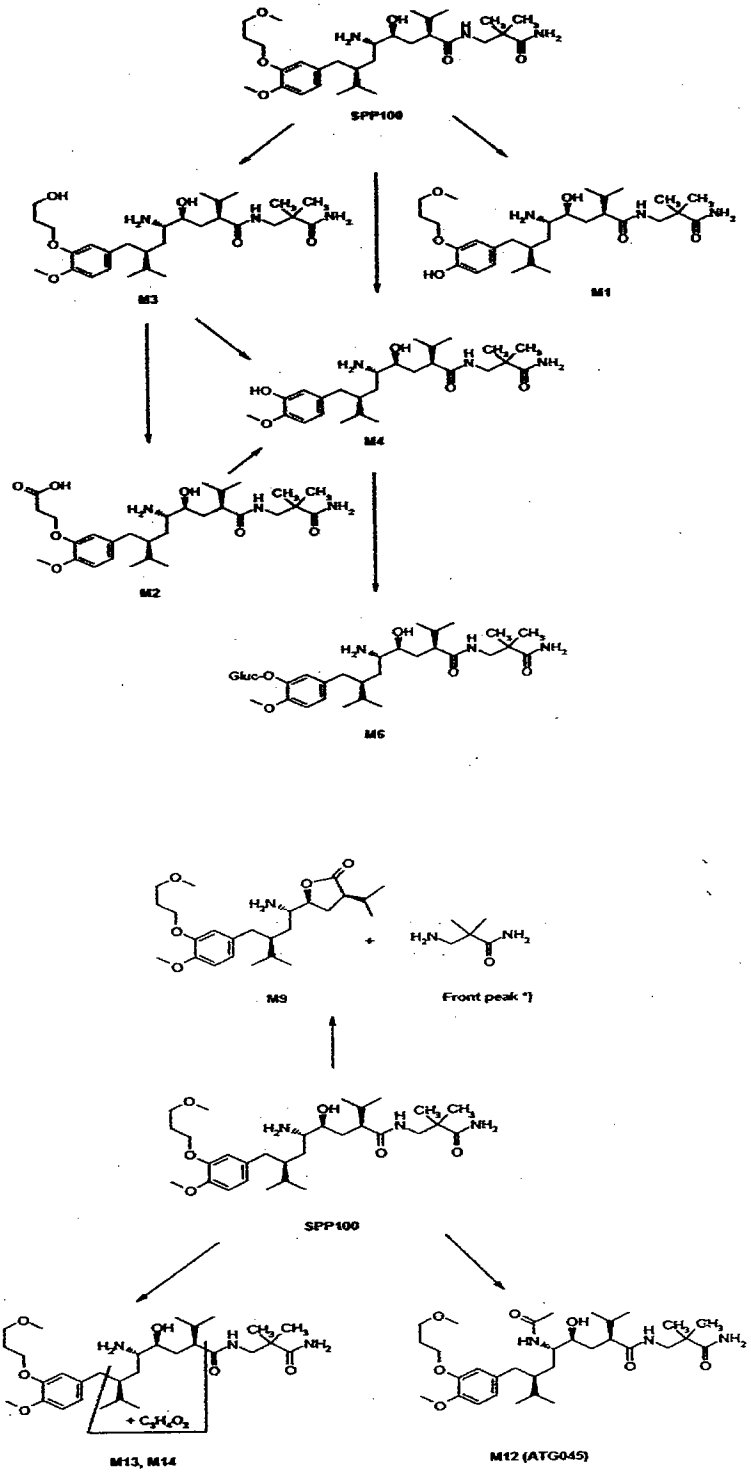
Characterization of the Metabolic Pathway: Two metabolites (M1 to M4) are formed by oxidation and account for about 1.4% of the dose administered. A trace of M4 was excreted in the form of a glucuronic acid conjugate M6. A further trace metabolite (front peak) was formed through hydrolysis of the amino-isobutyramide group. Trace metabolites (M12, M13, and M14) were detected in feces. M13 and 14 are isomers and were characterized only partially. The fecal metabolites appear to be artifacts formed from unabsorbed SPP100, possibly by microbial metabolism.

Table 4 Metabolites in excreta [% dose] (means of N=4, SD)

Metabolite		Urine	Feces	Total	SD
Front peak	not identified *	<0.1	0.1	0.1	0.1
M6	O-glucuronide of M4	<0.1		<0.1	
M2	carboxylic acid (oxidized side chain)	<0.1	0.5	0.6	0.5
M4	phenol, O-dealkylated	<0.1		<0.1	
M3	alcohol, O-demethylated	<0.1	0.6	<0.6	0.4
M1	phenol, O-demethylated		0.1	0.1	0.1
SPP100		0.4	77.5	79.8	3.0
P 62	M12: N-acetyl derivative; M13, M14: partly characterized (+$C_3H_4O_2$)		1.0	1.0	0.1
traces	unidentified	<0.1	1.5	1.6	0.7
not analysed			9.7	9.7	3.1
Total ^{14}C		0.6	90.9	91.5	4.5

* not unambiguously identified, possibly 3-amino-2,2-dimethylpropionamide, or a product of hydrolysis

Proposed main biotransformation pathways in man



Routes of Elimination: Aliskiren is mainly eliminated via the fecal route since most of the drug is not absorbed (bioavailability of about 3%). About 0.6% of the dose is eliminated renally (23% of the amount absorbed) with the remainder via the biliary/fecal route.

Dose Proportionality: Aliskiren slightly deviates from being truly dose proportional. At doses ranging 40 to 1800mg, the pharmacokinetics can increase as much as 2.6—fold with doubling of the dose. Three separate studies addressed the dose-proportionality of Aliskiren. The first study was a single dose, open-label, four-period, four-treatment, cross-over, randomized study in healthy subjects that utilized a different assay (HPLC) than the other two studies that follow (2205):

Dose	T_{max} (hr)	C_{max} (ng/ml)	AUC_{0-t} (ng·h/mL)	$AUC_{0-\infty}$ (ng·h/mL)	$T_{1/2}$ (hr)	CL/F (L/h)
75	1	26 (31)	266 (235)	356 (217)†	54 (16)†	294 (178)†
150	2.5	72 (62)	530 (360)	627 (401)‡	41 (11)‡	321 (165)‡
300	3	202 (119)	1480 (806)	1620 (895)	37 (8)	254 (166)
600	2	420 (325)	3240 (1950)	3520 (2130)	34 (7)	222 (115)

Median, †n=23, ‡n=29

The second study (CRD16) investigated higher doses of Aliskiren in sequential groups where doses of 850, 1200, and 1800 mg of Aliskiren were investigated administered as single as well as multiple doses in male subjects using the RIA assay:

	Dose of Aliskiren					
	850 mg		1200 mg		1800 mg	
Parameter	Day 1 (N=6)	Day 11 (N=6)	Day 1 (N=6)	Day 11 (N=6)	Day 1 (N=6)	Day 11 (N=5#)
$AUC(0-t_z)$ (ng.h/mL)	2141 (25.2)	NC	4397 (43.3)	NC	5561 (78.9)	NC
$AUC(0-\tau)$ (ng.h/mL)	1580 (26.2)	5609 (50.9)	3368 (47.0)	9576 (66.7)	4245 (77.4)	10625 (28.5)
$AUC(0-\infty)$ (ng.h/mL)	2523 (30.6)	NC	4765 (42.7)	NC	6037 (79.8)	NC
C_{max} (ng/mL)	207 (57.3)	652 (35.9)	357 (68.2)	931 (67.6)	543 (41.7)	1053 (41.0)
t_{max} † (h)	3.00 (1.00-6.00)	3.50 (0.500-6.00)	3.00 (0.500-6.00)	3.00 (1.00-6.00)	0.750 (0.500-10.0)	3.07 (1.00-6.00)
C_{min} (ng/mL)	19.2 (32.6)	106 (60.1)	42.2 (39.9)	188 (78.7)	53.0 (86.9)	170 (25.9)
$AUC(0-t_z)$ (norm)	211 (16.9)	NC	300 (35.9)	NC	238 (94.3)	NC
$AUC(0-\tau)$ (norm)	156 (18.8)	553 (42.4)	230 (39.2)	653 (57.2)	181 (94.0)	441. (36.9)
$AUC(0-\infty)$ (norm)	249 (24.2)	NC	325 (35.1)	NC	258 (94.6)	NC
C_{max} (norm)	20.4 (55.1)	64.3 (34.0)	24.3 (58.4)	63.4 (58.9)	23.2 (57.7)	43.7 (43.1)
C_{min} (norm)	1.89 (27.7)	10.4 (53.9)	2.88 (34.6)	12.6 (71.0)	2.27 (107)	7.07 (35.2)
$t_{\frac{1}{2}}$ (h)	32.3 (64.2)	30.0 (68.4)	24.1 (15.1)	31.2 (27.2)	23.9 (31.8)	27.1 (28.6)
MRT (h)	31.6 (54.6)	26.1 (34.2)	23.0 (12.3)	28.6 (13.6)	22.7 (28.9)	25.6 (9.19)
RA_1	1.60 (14.8)*	3.55 (50.2)	1.41 (5.62)*	2.84 (39.2)	1.44 (10.2)*	2.84 (45.2)
RA_2		3.16 (93.4)		2.61 (14.7)		2.02 (55.0)
RL		2.22 (49.1)		2.01 (39.0)		1.97 (48.3)

Source: Section 10.3 (Table 3)
Geometric mean (CV%) data are presented
† Median (min-max)
N= Number of subjects studied
# Subject 19 withdrawn from study (received his last dose on Day 7)
(norm) = Normalised for dose and body weight (mg/kg)
NC = Not calculated
τ = 24 h
* = predicted value

The third study (02 MD) investigated dose proportionality at doses ranging from 40 mg to 600 mg administered as both single and multiple doses in male subjects utilizing an RIA assay methodology:

Pharmacokinetic Parameters			
Dose (mg)	C_{max} (ng/ml)	t_{max} (h)	AUC (ng/ml*h)
	Single Dose (Day 1)		
40	5.1 ± 2.1	1.6 ± 1.8	28.5 ± 13.5
80	11.0 ± 3.6	2.8 ± 2.5	96.4 ± 31.6
160	21.5 ± 9.6	2.7 ± 2.1	214.8 ± 73.5
640	146.2 ± 61.6	2.1 ± 1.1	1193.4 ± 588.6
	Multiple Dose (Day 8)		
40	6.2 ± 2.9	2.1 ± 3.1	46.7 ± 29.2
80	12.7 ± 4.0	1.8 ± 2.4	136.9 ± 54.0
160	39.1 ± 24.6	4.1 ± 2.4	362.7 ± 146.5
640	335.1 ± 196.2	3.2 ± 1.8	2972.5 ± 1263.2

Intra- and Inter-subject Variability Comparisons: Two drug interactions studies explored both types of variability. Aliskiren inter-subject variability is higher than intra-subject variability.

Inter-subject variability (%) of C_{max} and AUC for aliskiren

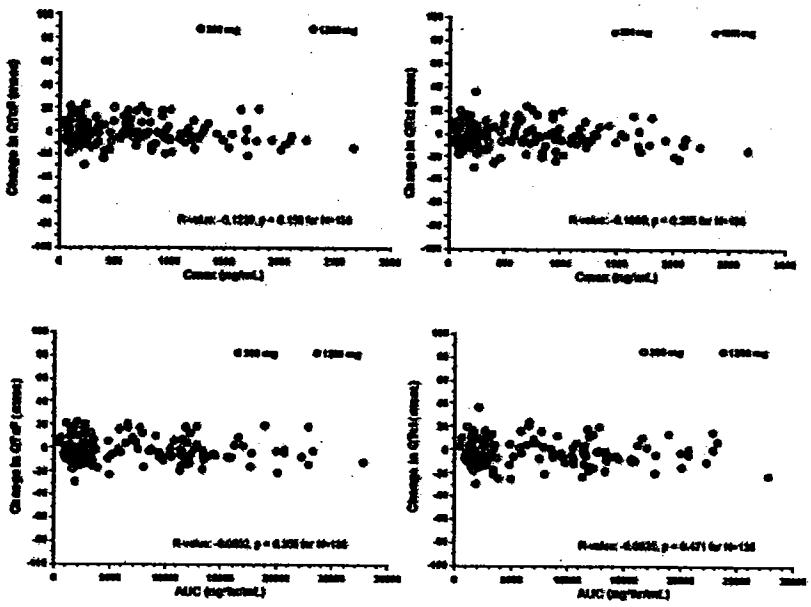
Study No.	C_{max}^{ss}	$AUC_{0-\tau}$
2211	50, 75	46, 50
2214	36, 48	29, 31

Intra-subject variability (%) of C_{max} and AUC for aliskiren

Study No.	C_{max}	$AUC_{0-\tau}$
2211	39	21
2214	37	18

Aliskiren Impact on the QT/QTc Interval:
A study measuring the impact of Aliskiren on the QTc interval in humans was conducted. The findings are preliminary in nature since reviewing the ECGs was not possible due to not being submitted. As a result, we are unable to verify the appropriateness of QT measurements made by the sponsor. However, based on the preliminary assessment, the QTc results did not cross the threshold of regulatory concern as demonstrated below:

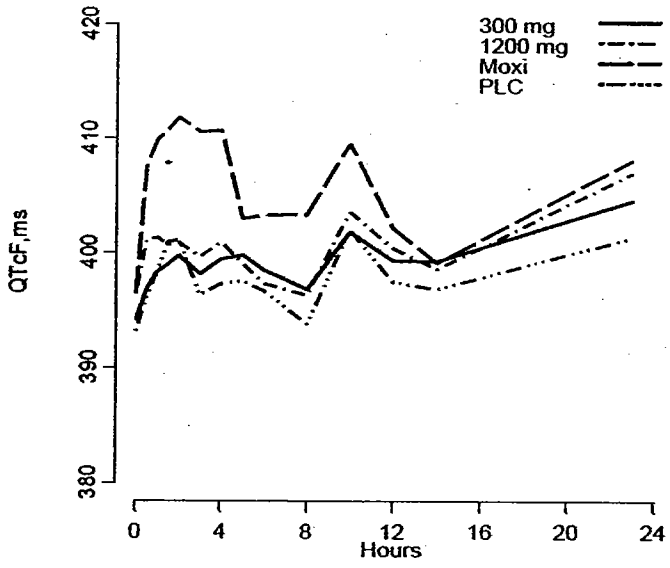
. Change in QTc (at Tmax) as a Function of Aliskiren Cmax and AUC



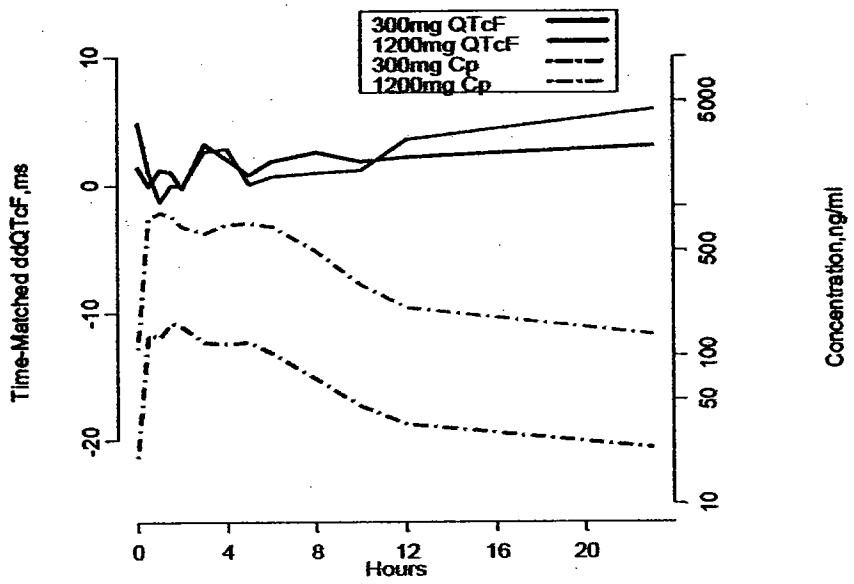
No correlation was observed between QTc interval, Cmax and AUC.

Time-Course of Mean QTcF Interval

(QTcF = QT corrected for RR interval on ECG by Friderica's method)



Time Course of Mean ddQTcF Intervals Overlaid with Mean Aliskiren Concentrations



Age Differences in Aliskiren Pharmacokinetics: Aliskiren exposure is increased by 55% in the 65 to 74 year age group and by 67% in the ≥ 75 year age group. These findings are of clinical significance

Pharmacokinetics: The primary pharmacokinetic variables for aliskiren for the different age groups are summarized in the table below.

Primary Pharmacokinetic Variables for the Evaluation of Age on Aliskiren Pharmacokinetics

Age Group 18-45 years	C_{max} (ng/mL)	t_{max} (h)	$AUC_{(0-t)}$ (ng•h/mL)	$AUC_{(0-\infty)}$ (ng•h/mL)	$t_{½}$ (h)
N	28	28	28	28	28
Arithmetic Mean	374.5	1.8	1560	1649	60.6
Geometric Mean	290.2	1.5	1312	1399	58.4
Median	273.5	2.0	1300	1415	60.9
CV%	77.6	47.7	62.6	60.9	26.3

Age Group 65-74 years	C_{max} (ng/mL)	t_{max} (h)	$AUC_{(0-t)}$ (ng•h/mL)	$AUC_{(0-\infty)}$ (ng•h/mL)	$t_{½}$ (h)
N	16	16	16	16	16
Arithmetic Mean	451.8	1.9	2410	2583	69.6
Geometric Mean	351.0	1.4	2056	2204	68.7
Median	356.0	2.0	1984	2120	66.7
CV%	90.2	67.1	69.5	68.9	17.9

Age Group ≥75 years	C_{max} (ng/mL)	t_{max} (h)	$AUC_{(0-t)}$ (ng•h/mL)	$AUC_{(0-\infty)}$ (ng•h/mL)	$t_{½}$ (h)
N	13	13	13	13	13
Arithmetic Mean	604.1	2.0	2611	2814	69.7
Geometric Mean	395.2	1.5	2020	2184	68.9
Median	277.0	1.5	1995	2117	71.1

Gender Differences in Aliskiren Pharmacokinetics: The sponsor pooled data from seven studies in order to explore pharmacokinetic differences between genders (78 females, 107 males). After applying weight adjustments, there seems to be no pharmacokinetic differences between groups.

Racial Differences in Aliskiren Pharmacokinetics: A cross-study analysis on the same studies used for a gender analysis above was performed in order to assess any pharmacokinetic differences between Caucasians, Blacks, Hispanics, and Orientals. Definition of Oriental was not provided and it is not clear if all subjects in the "Other" category are of Hispanic origin. A definition for Hispanics was not provided. Below are the results:

	Caucasians	Blacks	Oriental	Other
C_{max} (ng/mL) [CV%]	268 [68%]	289 [62%]	250 [42%]	351 [56%]
AUC_{0-t} (ng.h/mL) [CV%]	1889 [49%]	2253 [53%]	1566 [29%]	1986 [44%]

The labeling

Evidence of Pharmacokinetic Changes in Renal Impairment: Patients with renal impairment were compared pharmacokinetically to matched-healthy control subjects (Study 2209). Aliskiren AUC was 290% greater in the moderate renal impairment group (713.6 versus 2068.7 ng·h/mL) and 80% in the severe renally impaired group (543.7 versus 982.4 ng·h/mL) when compared to age and weight-matched healthy subjects on day 1 of treatment.

After multiple dosing, exposures were 2.5-fold in the mild group (1109.4 versus 2799.0 ng·h/mL), 2.1-fold in the moderate group (1165.8 versus 2449.3 ng·h/mL) and virtually no difference between groups in the severe group. However, a 4.4-fold increase in C_{min} in the severe group (7.8 versus 34.1 ng/mL) and a 27% decrease in oral clearance (357204 versus 262254 mL/h) were observed in the severe group. Increases in exposures did not seem to correlate with severity of renal impairment when AUC and Cmax were compared. When Cmin was compared across all renal impairment groups, a 2-fold increase was observed regardless of severity of renal impairment when compared to healthy volunteers.

Pharmacokinetic differences in Type II Diabetic patients: No differences in pharmacokinetics were observed in this patient population when compared to normal healthy volunteers.

Evidence of a Drug Interaction between Aliskiren and Other Drugs: Seventeen drug interaction studies were performed and reviewed. Twelve studies either had no pharmacokinetic changes observed or the changes were of no clinical significance. The remaining five studies with pharmacokinetic changes worthy of mention are listed below:

Study Number	Drug and Dose Study Design	Results
2209	**Irbesartan** 300 mg **Aliskiren** 300 mg **Multiple Dose**	**Aliskiren data only** **Mild (healthy)** 30% reduction Cmax, 15% reduction in AUC, Tmax reduced by 66%, 20% increase in CL/F **Moderate (healthy)** 15% increase Cmax, 10% reduction AUC, Tmax reduced by 55%, 38% increase in CL/F **Mild (renal)** 55% reduction Cmax, 28% reduction in AUC, 156% increase in Tmax, no change in CL/F **Moderate (renal)** 9% reduction Cmax, No change in AUC, no change in Tmax or AUC **Note:** When comparing the healthy group to the renal impairment group after Irbesartan administration, Aliskiren exposures in the renal impairment group (mild and moderate) increase by 130%. Labeling recommendations regarding dosage adjustments not necessary.
2211	**Furosemide 20 mg (max initial dose 80 mg)** **Aliskiren 300 mg** **Multiple Dose**	**Furosemide 46% reduction in Cmax, 26% reduction in AUC, 55% increase in Tmax** **Aliskiren 12% reduction in Cmax, 5% reduction in AUC, Tmax unchanged**
2221	**Ramipril 10 mg** **Aliskiren 300 mg** **Multiple Dose**	**Ramipril No change of clinical significance** **Ramiprilat No change of clinical significance** **Aliskiren 31% increase in Cmax, 12% increase in AUC, 29% increase in Tmax**
2334	**Ketoconazole 200mg Q12h** **Aliskiren 300 mg** **Multiple Dose**	**Ketoconazole not assessed** **Aliskiren 81% increase in Cmax, 76% increase in AUC, 57% decrease in CL/F** No labeling recommendation on dose reduction is necessary;
CSPP100A 2234	**Atorvastatin 80 mg** **Aliskiren 300 mg** **Multiple Dose**	**Atorvastatin changes not clinically significant** **o-hydroxy Changes not clinically significant** **p-hydroxy Changes not clinically significant** **Aliskiren 50% increase in Cmax, 47% increase in AUC** Labeling recommendation on dose reduction not necessary.

In-Vitro Metabolic Studies:

Based on in-vitro data, Aliskiren is about 30% metabolized with the rest of the drug remaining intact. Human cytochrome P450 is involved with CYP3A4 and minimally 2D6 being the contributors of the oxidative metabolism. Studies are summarized below:

STUDY	DESCRIPTION/OBJECTIVE	RESULTS
DM(EU) 18/1994	To investigate metabolic stability of Aliskiren in postmitochondrial liver fraction (S12) from man. Aliskiren was incubated	Aliskiren was metabolized in postmitochondrial fraction of human liver with 2/3 remaining intact after 120 min of incubation. Three metabolites (P3,

	with human liver post mitochondrial fraction and analyzed.	P4 and P5) were found. Molecular structure of metabolites was not determined. Aliskiren is considered to be metabolically stable in human liver postmitochondrial fractions.
DMPK R0101129	Identification of human cytochrome P450 enzymes involved in the oxidative metabolism of SPP100 was investigated.	CYP3A4 (99.6 %) and CYP2D6 (0.4 %) were the major contributors toward the metabolism of aliskiren when incubated with human liver microsomes. Chemical (ketoconazole) and biological (monoclonal antibody) inhibitors effectively inhibit aliskiren metabolism by CYP3A4.
DMPK 1997/452	In vitro biotransformation of Aliskiren by human liver microsomes was investigated. Aliskiren was incubated with human liver microsomes containing an NADPH generating system. Formed metabolites were analyzed.	Aliskiren was metabolized to its derivative without the metoxyproply side chain and demethylated further to other compounds. The precise molecular structures were not completely determined. More than 95 % of aliskiren in supernatant fraction was converted to metabolites after 120 min of incubation in conc < 10 µM. Since the sponsor used purified human liver microsomes, the metabolite proportions were higher in comparison to study #18-1994.
PCS(EU) R0101128	The inhibition capacity of SPP100 on specific CYP450 enzymes in human liver microsomes was determined. Inhibition capacity of aliskiren on CYP subtypes was investigated using a specific substrate for each subtype.	**Aliskiren does not inhibit CYP2C9, 2C19, and 2D6 at clinical concentrations.**
DMPK R0 101128-01	The inhibition capacity of SPP100 on CYP3A4/5 using two different substrates specific for CYP3A4/5 was determined.	**Aliskiren does not inhibit CYP3A4/5 at clinical concentrations.**
DMPK R0500381	Determination of the hepatic uptake clearance of SPP100 using primary human hepatocytes was conducted and the identification of the involved transporters using cRNA injected Xenopus laevis oocytes was also determined.	**PSC833 did not influence the uptake of Aliskiren into human hepatocytes.** This study was conducted for the clarification of the possible hepatic uptake mechanism in humans. Human OATP1 is a candidate for hepatic uptake of aliskiren. However, it's expressed mainly in brain and hepatic expression was relatively low. Thus, the precise mechanism of hepatic uptake of aliskiren is still controversial.

In-Vitro Permeability and Transporter Studies:

Aliskiren is a substrate for MDR1 and it has a <20% inhibitory effect on MXR. PSC833 has a concentration-dependent influence on Aliskiren's permeability via an inhibition interaction at the efflux transporter level. Transport capability of aliskiren is concentration and direction dependent. Basolateral to apical transport is greater than that of apical to basolateral transport possibly due to the existence of a potential efflux pump on the apical membrane. Results seem to support the conclusion that aliskiren is actively transported by MDR1. Studies are summarized below:

STUDY	DESCRIPTION/OBJECTIVE	RESULTS
DMPK R100670	To determine the predictive absorption on the involvement of active transporters of aliskiren across the intestinal barrier using Caco-2 mono layer cells. To determine the direction of aliskiren transport.	Aliskiren was moderately permeable and transported both from the apical-basolateral and basolateral-apical direction evenly. **NOTE:** Results differ from study R0200734. May be due to using free base form of Aliskiren and the to-be-marketed formulation will be the hemifumarate form. According to results from study R0200734 using hemifumarate had extremely low

		absorption (less than mannitol).
DMPK R0400107	Determination of the interaction with the human MDR1, MRP2 and BCRP (MXR) transporters to determine the types of ABC transporters involved in Aliskiren transportation.	Aliskiren was a substrate for MDR1 (Conc. Range 1 - 10μM); but not for MRP2 and MXR.
PCS(EU) R0400151	To determine the effect of the potential efflux pump modulator PSC833 on the permeation potential of SPP100 using Caco-2 cells. Apical to basolateral transportation (upper chamber to lower chamber), basolateral to apical transportation and effect of transport inhibitor on SPP100 (1μM) were determined in the presence of PSC833.	SPP100 is a moderate affinity, moderate capacity substrate for the efflux pump involved in its transport. The inhibition kinetics of PSC833, revealed an IC_{50} value of about 0.1μM, indicative of a high inhibitor potential for PSC833. PSC833 is likely to have a conc.-dependent influence on SPP100 permeability by an inhibition interaction at the efflux transporter level.
DMPK R0400734	To determine the possible involvement of Organic Cation Transporter (OCT) on aliskiren transportation.	The affinity of aliskiren to hOCT1 was low and almost no affinity to hOTC3. Thus, transport of aliskiren is not likely to occur through this transporter. However, the incubation time for the uptake was only 1 sec; which is sufficient for binding but not enough time for uptake. As a result, it's not possible to evaluate this study thoroughly.
DMPK R0200734	The predictive absorption, particularly the involvement of a non-passive diffusion system in the transport of SPP100 across the intestinal barrier was determined. Transporter identification for SPP100 in the presence of potent efflux system inhibitors CsA (10μM) and Verapamil (100μM) was investigated. Caco-2 cells were cultured on permeable polyethylene terephthalate membranes. Apical to basolateral transportation (upper chamber to lower chamber) or basolateral to apical transportation and effect of transport inhibitor were determined.	Transport capability of aliskiren was dependent on direction. Basolateral to apical transport was significantly greater than that of apical to basolateral transport. **This could be explained by the existence of a potential efflux pump on the apical membrane, such as MDR 1. The results support the conclusions that the efflux system involved in Aliskiren transport is MDR1.** Potential transporter inhibitor cyclosporine A (CsA) increased apical to basolateral aliskiren transportation. However, Verapamil, another transporter inhibitor had no effect on aliskiren transportation from the apical to basolateral direction.

Demonstration of Bioequivalence: The sponsor conducted two of their Phase III clinical trials (Studies 2203 and 2204) with an overencapsulated formulation of the 150 mg strength for blinding purposes; but created another formulation since the backfill material constituted a SUPAC IR level-3 change in the formulation's components and composition. Demonstration of bioequivalence (study 2343) between the clinical trial formulation and the to-be-marketed formulation (Final Market Image-FMI) was required for the 150 mg strength.

Study 2343 was a single-dose, randomized, open-label, 4-period, replicate, cross-over, fasted study. Results below seem to indicate a lack of bioequivalence between the blinded/over-encapsulated clinical trial formulation and the FMI in regards to extent of exposure:

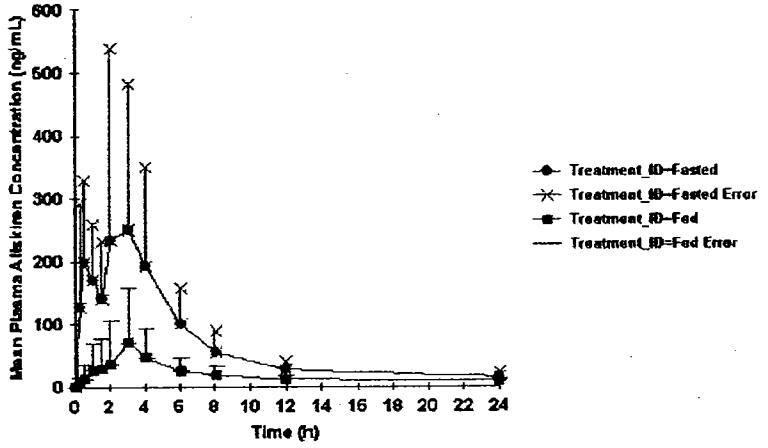
Treatment	t_{max} (h) Median (min; max)	C_{max} (ng/mL) Mean ± SD (CV %)	$AUC_{(0-t)}$ (ng•h/mL) Mean ± SD (CV%)	$AUC_{(0-\infty)}$ (ng•h/mL) Mean ± SD (CV %)	$AUC_{(0-tmax)}$ (ng•h/mL) Mean ± SD (CV %)
Overencapsulated Tablet	1.5 (0.28; 6.0)	98.2 ± 85.5 (87.0%)	598.3 ± 425.1 (71.0%)	663.8 ± 467.8 (70.5%)	75.1± 82.3 (109.6%)
FMI Tablet	1.0 (0.25; 6.2)	119.6 ± 91.1 (76.1%)	654.6 ± 351.4 (53.7%)	719.8 ± 389.4 (54.1%)	71.7 ± 80.2 (112%)
Geometric Mean Ratio – Overencapsulated Tablet : FMI Tablet (90% CI)	–	0.80 (0.70, 0.90)	0.88 (0.82, 0.96)	0.89 (0.83, 0.97)	1.07 (0.85, 1.36)

Aliskiren C_{max} of the over-encapsulated tablet was 82% of the FMI tablet (18% less than the reference). The 90% CI was 70 to 90% with a Geometric mean ratio of 0.80, which is within the 90% CI. The difference in Aliskiren C_{max} is of no clinical significance. The $AUC_{0\text{-}tmax}$ was 5% greater for the over-encapsulated in comparison to the FMI formulation. Again, not of any clinical significance even though the 90% CI was 85 to 136% and the Geometric mean ratio was 1.07.

Aliskiren 300 mg was not over-encapsulated and did not require a bioequivalence study.

Food Effect: Food had a significant impact on the rate and extent of absorption of Aliskiren with an observed C_{max} that was 80% lower (453.2 and 92.4 ng/mL, respectively) under fed conditions and a CV% of 68 and 103% (fasted to fed). T_{max} was delayed by one hour (2.1 versus 3.2 hours, fasted to fed with a CV% of 60.8 and 51.6%, respectively) and Aliskiren $AUC_{0\text{-}t}$ dropped by 70% (2315 versus 707 ng·h/mL with a CV% 50.3 and 61.4%). The $AUC_{0\text{-}\infty}$ also dropped by 69% (from 2437 to 767 ng·h/mL) when food was given. The CV% was 49 and 60.5%, respectively. Aliskiren's half-life decreased from 54 to 46 (15%) hours when food was given and the clearance increased from 150550 mL/h under fasted to 577002 mL/h under fed conditions (280%) indicating that the small amount absorbed upon drug administration with food underwent increased oral clearance.

Mean Aliskiren concentrations under fed and fasted conditions in healthy volunteers



Assay Validation: Aliskiren concentrations were analyzed by a validated HPLC-MS/MS or a LC-MS/MS method with a LOQ of 0.5 ng/mL in plasma and 5 ng/mL for urine.

For dose proportionality study 0024, Aliskiren was analyzed by a solid phase RIA method and validated in the range of 0.1358 to 905 ng/mL in plasma and 113.125 to 13575 ng/mL in urine.

The bioanalytical assay for study 2228 is missing. It remains unclear whether Aliskiren was measured by LC/MS/MS or by LC/UV since the assay methodology is reported differently in the synopsis than in the study report. The sponsor will be required to submit the assay since there's unusually high inter-subject variability in this study. Reliability of study results is dependent on the validated assay results. Demonstration of consistency, linearity and accuracy of the assay is pivotal in assessing the study results.

Dissolution: The sponsor's proposed dissolution method and specifications for Aliskiren are acceptable and are described below:

Apparatus	USP Apparatus I (Basket
Medium	0.01N HCL
Volume	500 mL
Temperature	37° C ± 0.5° C
Q	✓ of label claim after 30 minutes

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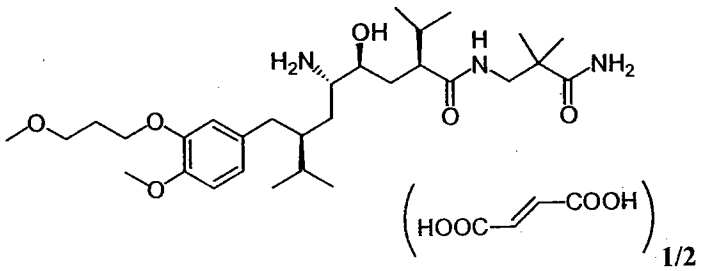
QUESTION BASED REVIEW

I. GENERAL ATTRIBUTES OF THE DRUG

A. WHAT ARE THE HIGHLIGHTS OF THE CHEMISTRY AND PHYSICAL-CHEMICAL PROPERTIES OF THE DRUG SUBSTANCE?

Aliskiren is an orally active, nonpeptide selective rennin inhibitor. It targets the rennin angiotensin system (RAS) at its point of activation by binding to the rennin enzyme, thereby blocking the conversion of angiotensinogen to angiotensin I (Ang I). Aliskiren is chemically described as (2S,4S,5S,7S)-N-(2-Carbamoyl-2-methylpropyl)-5-amino-4-hydroxy-2,7-diisopropyl-8-[4-methoxy-3-(3-methoxypropoxy)phenyl]-octanamide hemifumarate and its structural formula is



Molecular formula: $C_{30}H_{53}N_3O_6 \cdot 0.5\ C_4H_4O_4$

Aliskiren is a white to slightly yellowish crystalline powder with a molecular weight of 609. 8 (free base- 551.8). It is soluble in phosphate buffer, n-Octanol, and highly soluble in water.

B. WHAT ARE THE HIGHLIGHTS OF THE FORMULATION OF THE DRUG PRODUCT?

The sponsor has developed an immediate-release product that is a film-coated tablet. Aliskiren is being developed in two tablet strengths (150 and 300 mg tablets) for oral administration.

The two strengths are compositionally proportional as demonstrated below.

Component	**150 mg (mg/tablet)**	**300 mg (mg/tablet)**	**Function**
Aliskiren Hemifurate			Active substance
Cellulose Microocrystalline (Ph.Eur/NF)			
Crospovidone (Ph.Eur/NF)			
Povidone (Ph.Eur/NF)			
Magnesium stearate (Ph.Eur/NF)			
Colloidal Silicon			
Tablet Target Weight			
Film Coating			
Total weight	357.00	706.00	

Inactive ingredients such as hypromellose, iron oxide colorants, polyethylene glycol, talc, and titanium dioxide were used in the

C. WHAT IS THE PROPOSED MECHANISM OF ACTION AND THERAPEUTIC INDICATIONS?

Rennin is secreted by the kidney in response to decreases in blood volume and renal perfusion. This response initiates a cycle that includes the rennin angiotensin system (RAS) and a homeostatic feedback loop. Rennin cleaves angiotensinogen to form the inactive decapeptide angiotensin I (Ang I); which is converted to the active octapeptide angiotensin II (Ang II) by angiotensin converting enzyme (ACE) and non-ACE pathways. Ang II is a powerful vasoconstrictor and leads to the release of catecholamines from the adrenal medulla and prejunctional nerve endings. It also promotes aldosterone secretion and sodium reabsorption. Together, these effects increase blood pressure. Chronic increases in Ang II result in the expression of markers and mediators of inflammation and fibrosis that are associated with end organ damage. Ang II also inhibits rennin release, thus providing a negative feedback to the system. Elevated plasma rennin activity (PRA) has been independently associated with increased cardiovascular risk in hypertensive and normotensive patients.

Aliskiren is a rennin inhibitor that targets the cycle at its point of activation, inhibiting the conversion of angiotensinogen to Ang I. This action suppresses the entire system, resulting in a reduction in PRA, Ang I, and Ang II. All agents that inhibit this system, including rennin inhibitors, suppress the negative feedback loop, leading to a compensatory rise in plasma rennin concentration. When this rise occurs during treatment with ACE inhibitors and ARBs, it is accompanied by increased levels of PRA. During treatment with aliskiren, the feedback loop effects are neutralized. As a result, PRA, Ang I and Ang II are all reduced, whether aliskiren is used as monotherapy or in combination with other antihypertensive agents.

Aliskiren is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

D. WHAT ARE THE PROPOSED DOSAGES AND ROUTE OF ADMINISTRATION?

The usual recommended starting dose of Aliskiren is 150 mg orally once daily. In some patients whose blood pressure is not adequately controlled, the daily dose may be increased to 300 mg. It may be used over a dosage range of 150 mg to 300 mg administered orally once daily.

Aliskiren at doses greater than 1800 mg have not been studied. Patients do not require doses in excess of 300 mg daily when used alone or in combination with other antihypertensive agents.

II. GENERAL CLINICAL PHARMACOLOGY

A. WHAT CLINICAL PHARMACOLOGY AND CLINICAL STUDIES WERE SUBMITTED TO SUPPORT DOSING OR CLAIMS?

A total of 67 clinical/clinical pharmacology studies were to be submitted to the NDA of which 37 were reviewed for Clinical Pharmacology/Pharmacokinetic content. Twenty-nine studies were not reviewed because there was no pharmacokinetic data, the pharmacokinetic data was redundant in nature and offered no new information to the review from the CPB perspective, or had not been submitted (9 studies) by the date

originally promised by the sponsor. An additional thirteen studies were submitted with in-vitro metabolism and/or permeability/transporter data of which all were reviewed.

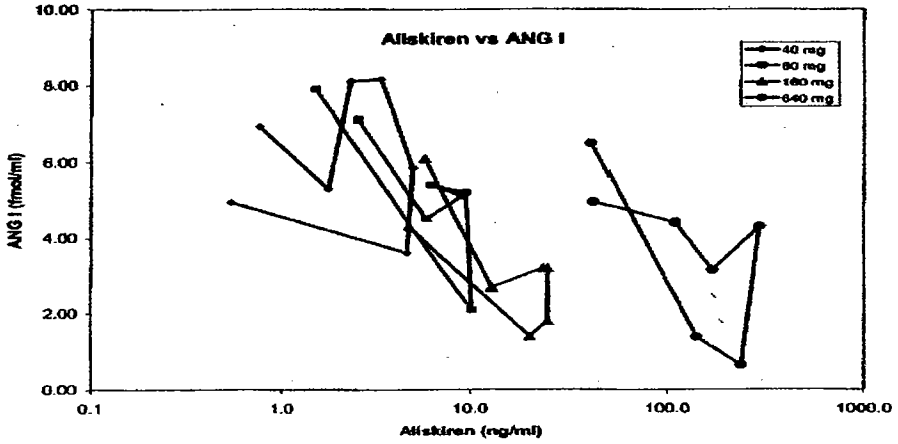
B. WHAT IS THE BASIS FOR SELECTING THE RESPONSE ENDPOINTS AND HOW ARE THEY MEASURED IN CLINICAL PHARMACOLOGY STUDIES?

The major endpoint is decrease in blood pressure since the indication is for treatment of hypertension with Aliskiren. The endpoints of interest being measured is Systolic and Diastolic sitting blood pressure.

C. WHAT ARE THE CHARACTERISTICS OF THE EXPOSURE-RESPONSE RELATIONSHIPS FOR EFFICACY?

When concentration versus decrease in Angiotensin I were measured in healthy male volunteers, Angiotensin I decrease was concentration dependent and were lower after 8 days of dosing. Formulation administered in this study (02MD) was a liquid suspension.

Aliskiren vs ANG I – All Doses



Aliskiren displays a dose dependent lowering of both mean sitting diastolic blood pressure (msDBP) and mean sitting systolic blood pressure (msSBP) across all the studies, though not all the reductions were statistically significant (Figure 1A, B).

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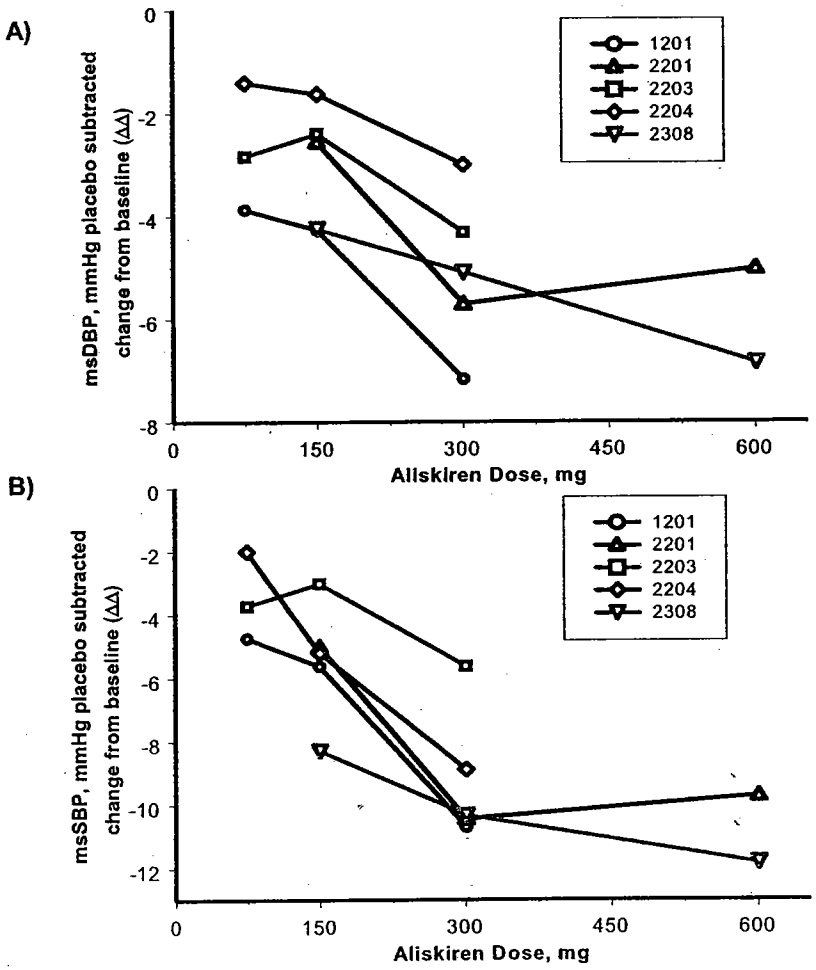
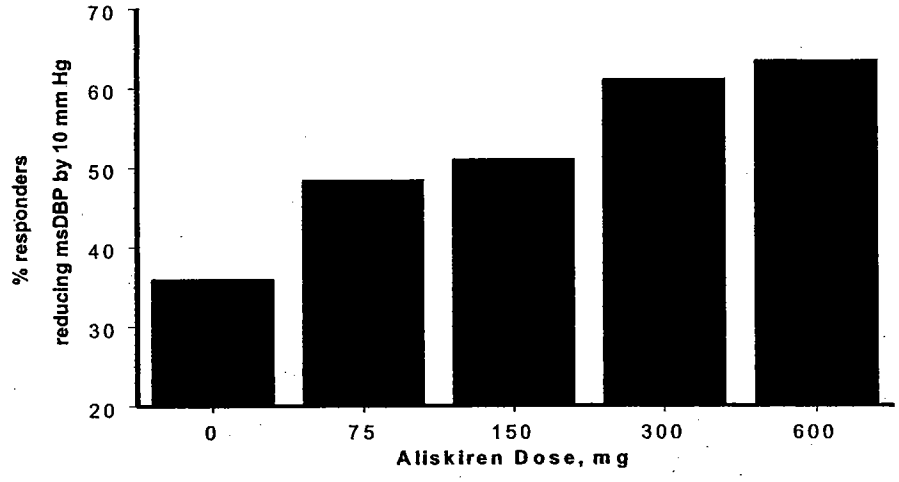
Figure 1: Aliskiren shows dose dependent lowering of blood pressure.



Further, the proportion of responders (drop in msDBP by at least 10 mm Hg by week 8 and the msDBP at trough less than 90 mm Hg) also showed a dose dependency for the pooled data as shown in Figure 2.

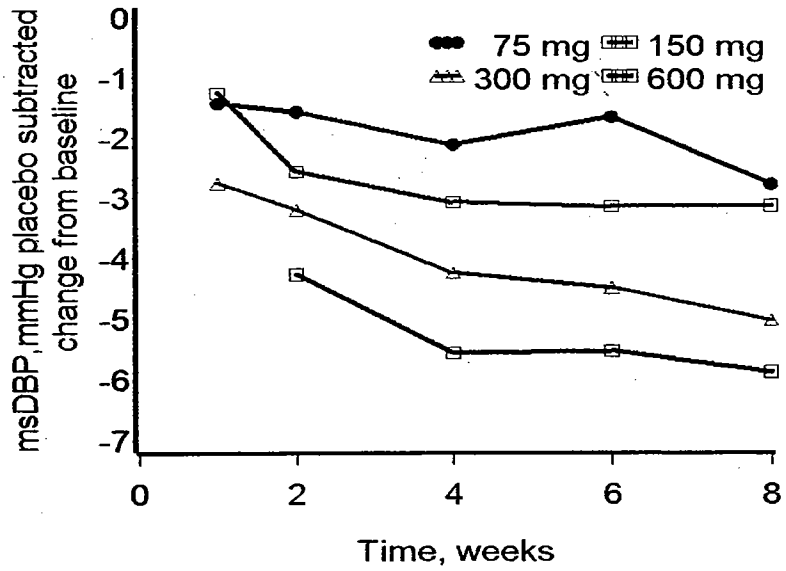
Figure 2: 50% of the patients respond to 75 mg Aliskiren.



Mean effects on lowering of msDBP for the doses studied generally plateau by week 4 as shown in figure 3.

Figure 3: Blood pressure lowering effects of aliskiren treatment tend to plateau by week four.

(LS Mean msDBP obtained from MMRM analysis)



The dose-response relationship seen across the trials was consistent between gender (Figure 4); but not in the elderly population (age >65 years) as demonstrated in Figures 5 and 6B. However, 75 mg Aliskiren showed reduction in placebo subtracted msDBP. The proportion of responders for the 75, 150 and 300 mg doses in the elderly was similar (~55%), while in patients < 65 years of age, a dose-dependent increase in percent responders was observed (Figure 3 and 4A). Aliskiren 600 mg shows higher

response (66%) in elderly. However, the higher dose is associated with higher incidence of diarrhea; which will be discussed later. This lack of dose dependent response in elderly patients is supported by the results of Study 2324, which was aimed at evaluating the blood pressure lowering effects for the change from baseline to endpoint in mean 24-hour ABPM in patients ≥ 65 years age with essential hypertension. Study 2324 did not demonstrate a dose-response relationship between treatment with aliskiren 75 mg and 300 mg. An important point to note was that no additional benefit was achieved with doses higher than 75 mg in elderly.

Figure 4: Aliskiren dose-response across gender is similar. (*LS Mean msDBP obtained from MMRM analysis).*

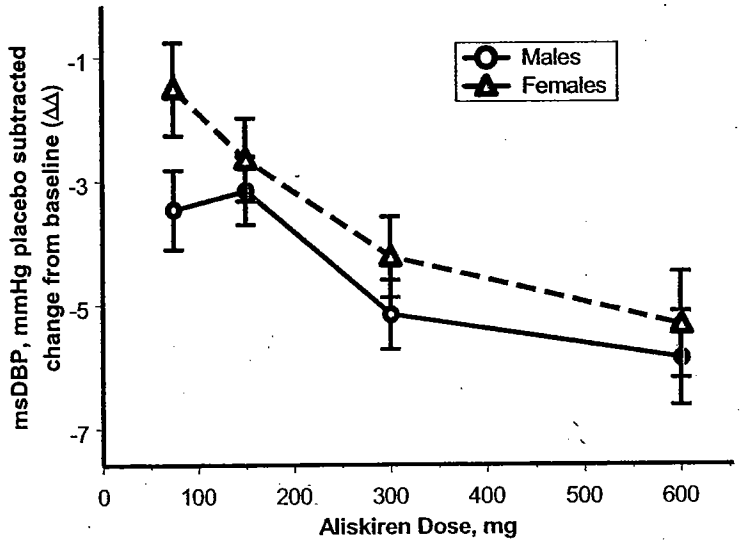


Figure 5: Aliskiren dose higher than 75 mg does not provide substantial benefit in the elderly. (*LS Mean msDBP obtained from MMRM analysis).*

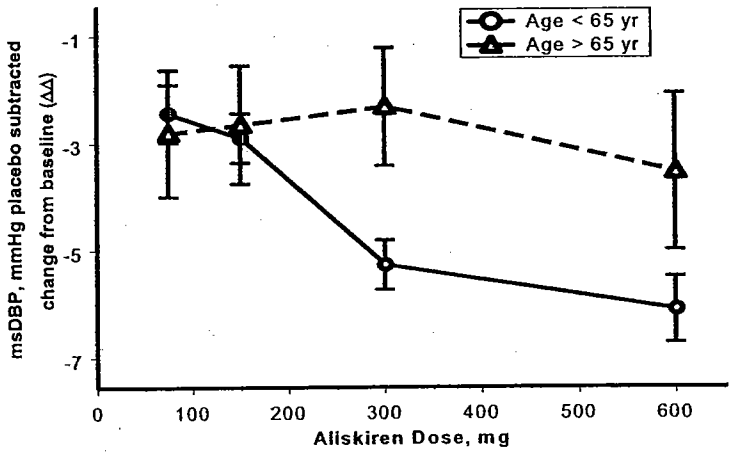
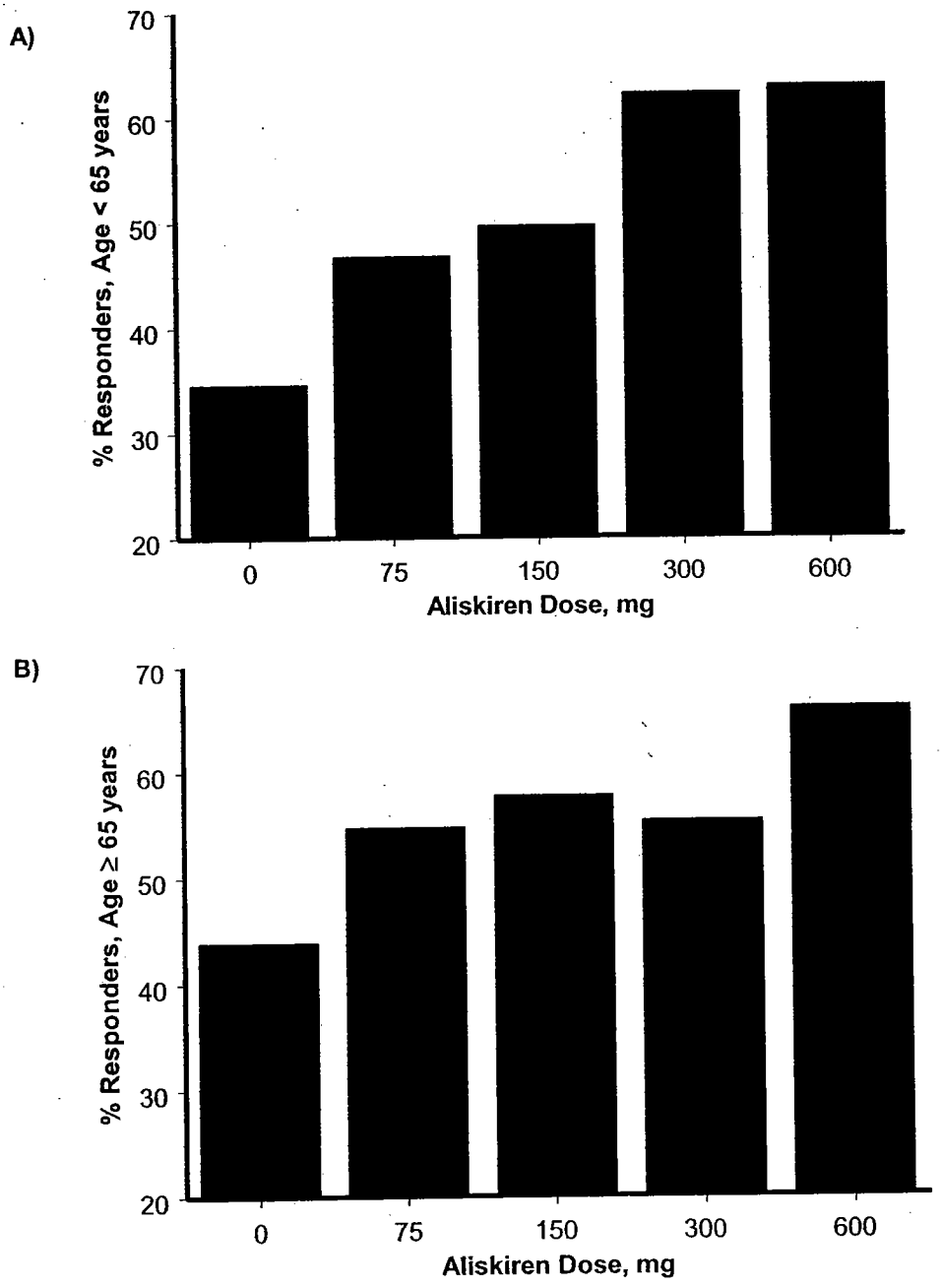


Figure 6: In elderly patients no dose-dependent increase in % responders is seen over 75 – 300 mg doses of Aliskiren.



D. WHAT ARE THE CHARACTERISTICS OF THE EXPOSURE-RESPONSE RELATIONSHIPS IN TERMS OF SAFETY?

Diarrhea was the most frequent adverse event seen in the placebo controlled clinical trials with aliskiren treatment (3.42%) compared to placebo (1.92%). A dose dependent response to diarrhea was observed with Aliskiren treatment as shown in Figure 1 below. The probability of diarrhea doubles when aliskiren dose increases from 75 mg to 300 mg, while an increase in aliskiren dose from 75 mg to 600 mg is associated with approximately a 6-fold increase in the probability of developing diarrhea. Gender and age (above and below 65 years) were not found to significantly predict diarrhea as shown in Figure 2A.

Figure 1: Percent of patients with diarrhea doubles with 300 mg Aliskiren.

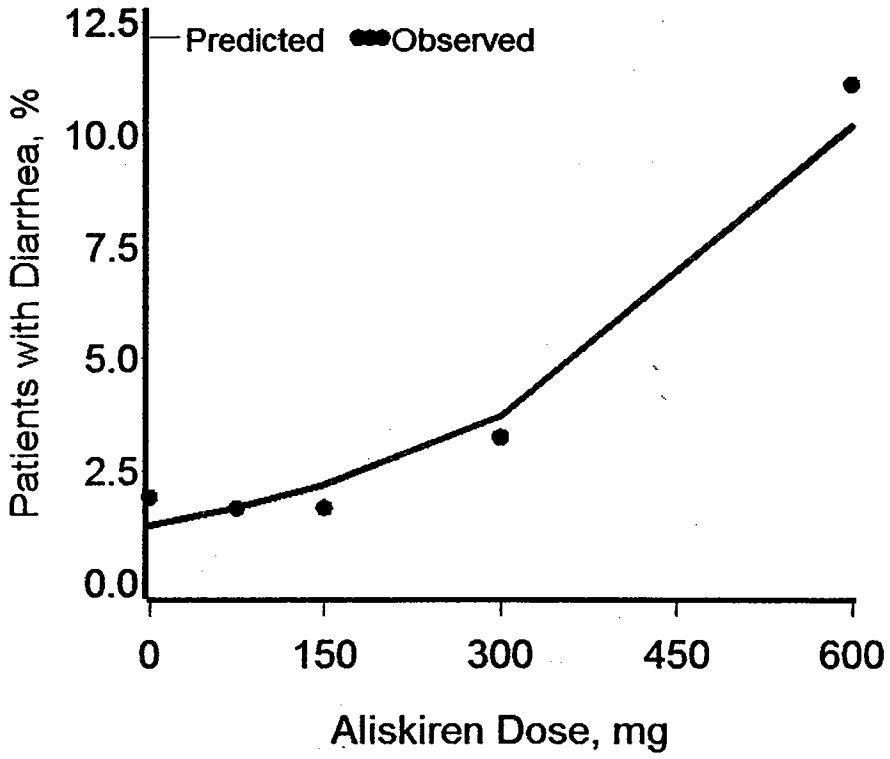
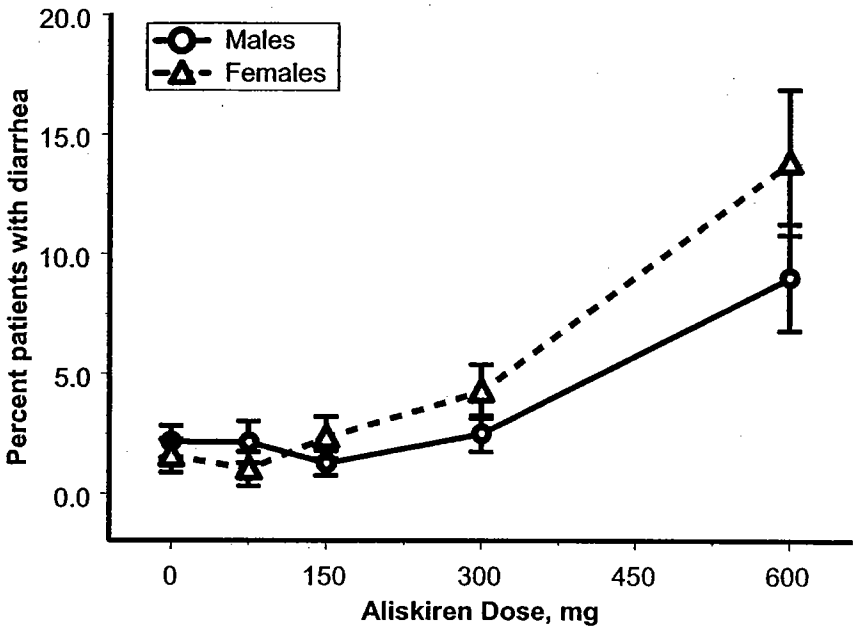
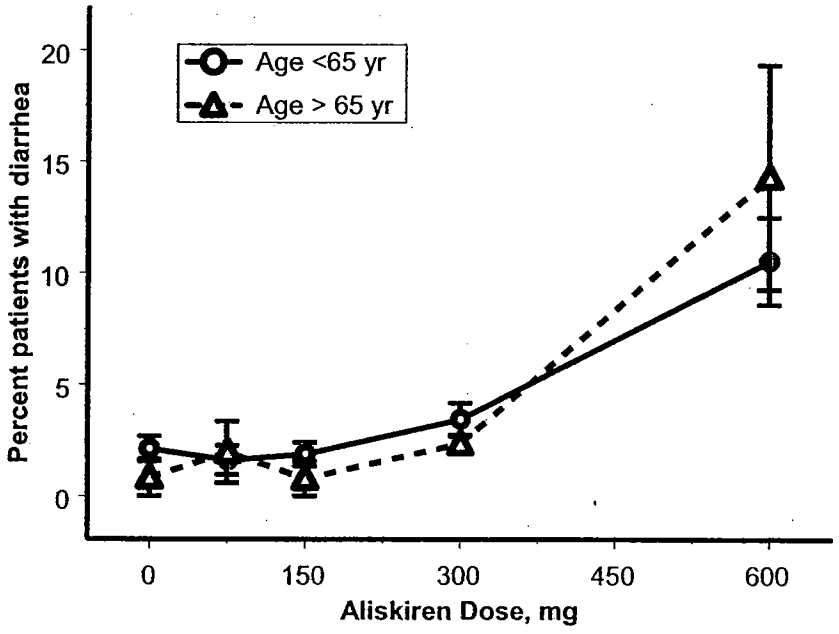


Figure 2: The risk for diarrhea is similar across the subgroups of gender (A) and age (B).

A



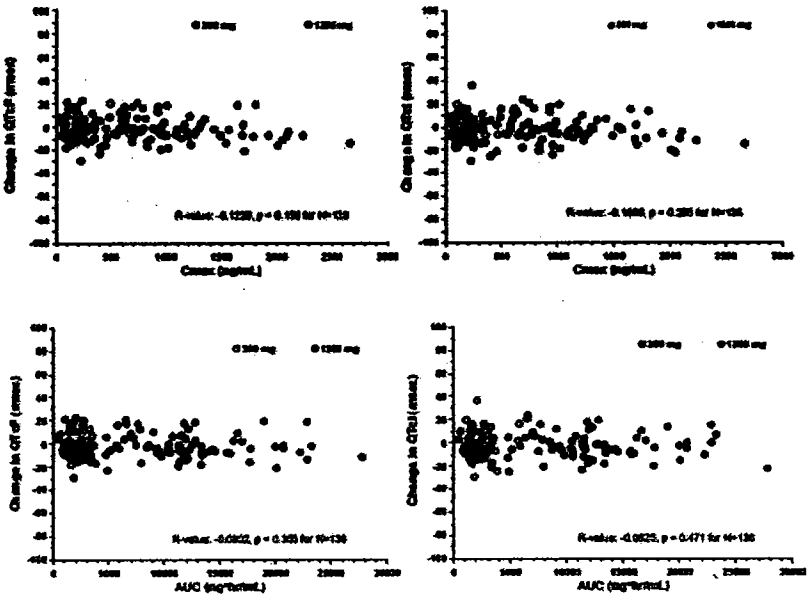
B



E. DOES ALISKIREN HAVE AN IMPACT ON QT/QTC INTERVAL?

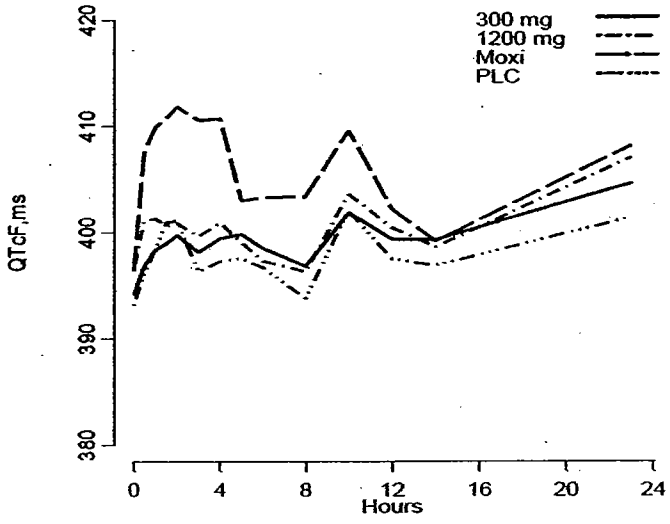
A study measuring the impact of Aliskiren on the QTc interval in humans was conducted. The findings made by the QT Review Team is preliminary in nature since the opportunity to review the ECGs was not possible. No ECGs were found in the NDA's ECG warehouse in order to verify the appropriateness of QT measurements made by the sponsor. However, based on the team's preliminary assessment, the QTc results did not cross the threshold of regulatory concern as demonstrated below:

. Change in QTc (at Tmax) as a Function of Aliskiren Cmax and AUC

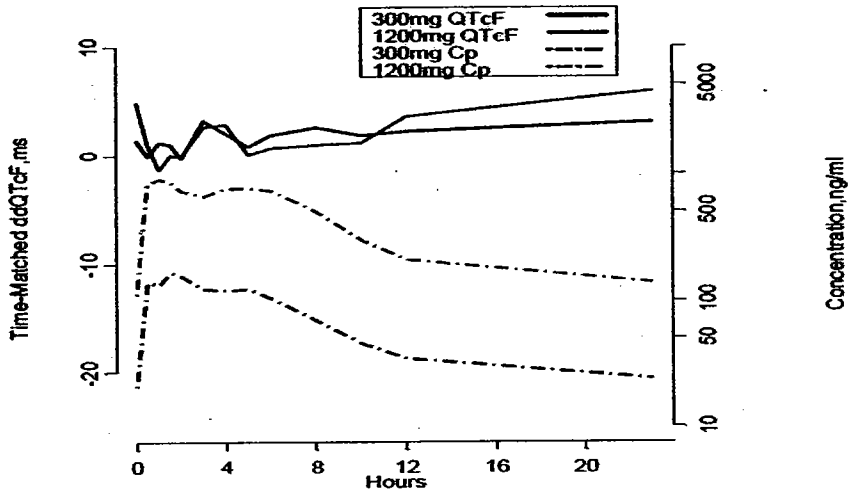


Time-Course of Mean QTcF Interval

(QTcF = QT corrected for RR interval on ECG by Friderica's method)



Time Course of Mean ddQTcF Intervals Overlaid with Mean Aliskiren Concentrations



Aliskiren does not appear to prolong the QTc interval.

F. DOES THE EXPOSURE-RESPONSE DATA SUPPORT THE PROPOSED DOSING REGIMEN?

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 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. Study 2324 is a study in elderly (age $\geq$ 65) hypertensives that included ABPM. The ABPM data do not show a pronounced peak effect for aliskiren but, after a plateau, gradual diminishing of BP reductions during the second half of the interdosing interval. Aliskiren 75 mg was comparable to or slightly better than 150 mg and little different than 300 mg. The ratios of mean daytime to mean nighttime ambulatory BP for aliskiren range from 0.59 to 0.90. The withdrawal studies show a gradual rise in BP over several weeks after withdrawal of aliskiren, suggesting a sustained effect not directly proportional to drug levels. Overall these data are weakly supportive of the proposed once daily dosing. More data, would be helpful to confirm that once daily dosing is good.

G. WHAT ARE THE SINGLE AND MULTIPLE DOSE PHARMACOKINETIC PARAMETERS FOR ALISKIREN AND ITS MAJOR METABOLITES?

Below are the single and multiple dose pharmacokinetic parameters for Aliskiren at the proposed doses in the fasted state:

	Route	Dose	Formul	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	t½ (h)	CL/F (L/h)
Single Dose	PO	150mg	capsule	72-148	0.5-2.5	530-663	570-720	27	230
Single Dose	PO	300mg	capsule	186-215	2-3	1124-1480	1274-2437	30-54	150-263
Multiple Dose	PO	300mg	capsule	321-403	2-4	2135-2519			

No multiple dose pharmacokinetic data was available with the 150 mg capsule in the fasted state.

Aliskiren's metabolite pharmacokinetic characteristics have not been evaluated since Aliskiren undergoes minimal metabolism.

H. How does the pharmacokinetics of Aliskiren in healthy volunteers compare to patients with hypertension?

No pharmacokinetic studies were conducted in hypertensive patients.

I. What is the bioavailability of Aliskiren?

A mass balance study was conducted where the bioavailability of 300 mg of [^{14}C]SPP100 and its metabolites in healthy male subjects was determined. Aliskiren was administered as an oral solution with the urinary and fecal excretion of Aliskiren and its metabolites determined. About 3% of the administered dose is actually absorbed when given as an oral solution. No other bioavailability data is available.

An open-label exploratory study was conducted in order to determine the concentrations of aliskiren in plasma, feces, and in rectal mucosa biopsy specimens at plasma steady-state after treatment with 300 mg daily. Correlations between fecal, rectal mucosal biopsy specimens, and plasma concentrations in humans as well as in the rat (250 mg/kg/d) were attempted. Unfortunately, no direct comparisons can be made between the results in rats and humans since mucosal aliskiren concentrations were not measured in rat rectum and that was the only sight biopsied and measured in humans. However, the colonic concentrations of Aliskiren in the rat (502 μg/g) are up to three times lower than the fecal Aliskiren concentrations in the rectum of humans (1527 μg/g).

J. What is the distribution characteristics of Aliskiren?

Protein binding of Aliskiren is about 40% and the blood to plasma ratio is about 0.61.

K. Was the metabolic pathway for Aliskiren characterized?

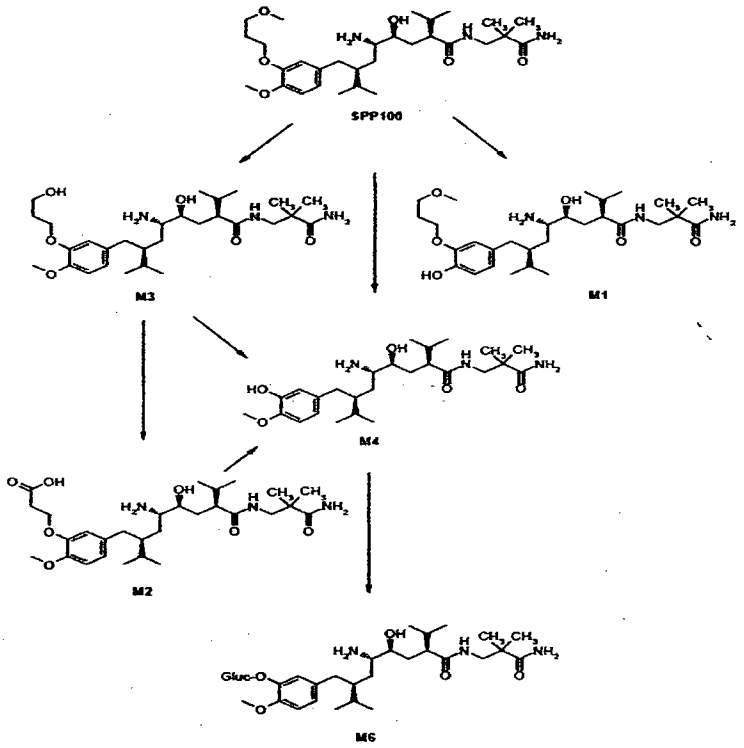
Yes. Metabolites M1 to M4 are formed by oxidation and account for about 1.4% of the dose administered. A trace of M4 was excreted in the form of a glucuronic acid conjugate M6. A further trace metabolite (front peak) was formed through hydrolysis of the amino-isobutyramide group. Trace metabolites (M12, M13, and M14) were detected only in feces (in peak 62). M13 and 14 are isomers and were characterized only partially. These fecal metabolites appear to be artifacts formed from unabsorbed SPP100, possibly by microbial metabolism.

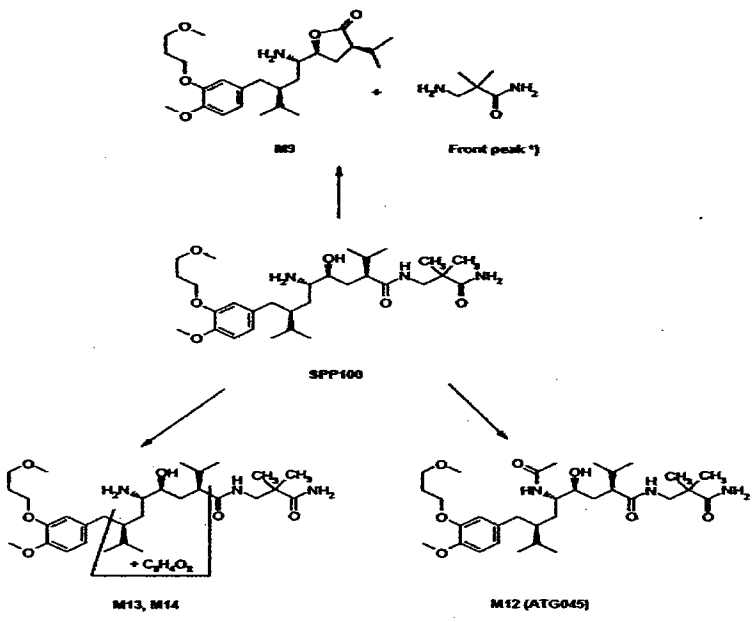
Table 4 **Metabolites in excreta [% dose] (means of N=4, SD)**

Metabolite		Urine	Feces	Total	SD
Front peak	not identified *	<0.1	0.1	0.1	0.1
M6	O-glucuronide of M4	<0.1		<0.1	
M2	carboxylic acid (oxidized side chain)	<0.1	0.5	0.6	0.5
M4	phenol, O-dealkylated	<0.1		<0.1	
M3	alcohol, O-demethylated	<0.1	0.6	<0.6	0.4
M1	phenol, O-demethylated		0.1	0.1	0.1
SPP100		0.4	77.5	79.8	3.0
P 62	M12: N-acetyl derivative; M13, M14: partly characterized (+$C_3H_4O_2$)		1.0	1.0	0.1
traces	unidentified	<0.1	1.5	1.6	0.7
not analysed			9.7	9.7	3.1
Total ^{14}C		0.6	90.9	91.5	4.5

* not unambiguously identified, possibly 3-amino-2,2-dimethylpropionamide, or a product of hydrolysis

Proposed main biotransformation pathways in man





L. What are the routes of elimination for Aliskiren?

Aliskiren is mainly eliminated via the fecal route since most of the drug is not absorbed (bioavailability of about 3%). About 0.6% of the dose is eliminated renally (23% of the amount absorbed) with the remainder via the biliary/fecal route.

M. Is Aliskiren dose proportional?

Aliskiren slightly deviated from being truly dose proportional. At doses ranging from 40 to 1800mg, the pharmacokinetics of Alsikiren can increase by as much as 2.6-fold. Three separate studies addressed the dose-proportionality of Aliskiren. The first study was a single dose, open-label, four-period, four-treatment, cross-over, randomized study in healthy subjects (2205) where a more recent assay methodology was utilized (HPLC):

Dose	T_{max} (hr)	C_{max} (ng/ml)	AUC_{0-t} (ng·h/mL)	$AUC_{0-\infty}$ (ng·h/mL)	$T_{1/2}$ (hr)	CL/F (L/h)
75	1	26 (31)	266 (235)	356 (217)[†]	54 (16)[†]	294 (178)[†]
150	2.5	72 (62)	530 (360)	627 (401)[‡]	41 (11)[‡]	321 (165)[‡]
300	3	202 (119)	1480 (806)	1620 (895)	37 (8)	254 (166)
600	2	420 (325)	3240 (1950)	3520 (2130)	34 (7)	222 (115)

[†]Median, [‡]n=23, [‡]n=29

The second study (CRD16) investigated higher doses of Aliskiren in sequential groups where doses of 850, 1200, and 1800 mg of Aliskiren were investigated administered as single as well as multiple doses in male subjects utilizing an earlier assay (RIA) methodology:

Parameter	Dose of Aliskiren					
	850 mg		1200 mg		1800 mg	
	Day 1 (N=6)	Day 11 (N=6)	Day 1 (N=6)	Day 11 (N=6)	Day 1 (N=6)	Day 11 (N=5#)
$AUC(0-t_z)$	2141	NC	4397	NC	5561	NC
(ng.h/mL)	(25.2)		(43.3)		(78.9)	
$AUC(0-\tau)$	1580	5609	3368	9576	4245	10625
(ng.h/mL)	(26.2)	(50.9)	(47.0)	(66.7)	(77.4)	(28.5)
$AUC(0-\infty)$	2523	NC	4765	NC	6037	NC
(ng.h/mL)	(30.6)		(42.7)		(79.8)	
C_{max}	207	652	357	931	543	1053
(ng/mL)	(57.3)	(35.9)	(68.2)	(67.6)	(41.7)	(41.0)
t_{max} †	3.00	3.50	3.00	3.00	0.750	3.07
(h)	(1.00-6.00)	(0.500-6.00)	(0.500-6.00)	(1.00-6.00)	(0.500-10.0)	(1.00-6.00)
C_{min}	19.2	106	42.2	188	53.0	170
(ng/mL)	(32.6)	(60.1)	(39.9)	(78.7)	(86.9)	(25.9)
$AUC(0-t_z)$	211	NC	300	NC	238	NC
(norm)	(16.9)		(35.9)		(94.3)	
$AUC(0-\tau)$	156	553	230	653	181	441
(norm)	(18.8)	(42.4)	(39.2)	(57.2)	(94.0)	(36.9)
$AUC(0-\infty)$	249	NC	325	NC	258	NC
(norm)	(24.2)		(35.1)		(94.6)	
C_{max}	20.4	64.3	24.3	63.4	23.2	43.7
(norm)	(55.1)	(34.0)	(58.4)	(58.9)	(57.7)	(43.1)
C_{min}	1.89	10.4	2.88	12.6	2.27	7.07
(norm)	(27.7)	(53.9)	(34.6)	(71.0)	(107)	(35.2)
$t_{\frac{1}{2}}$	32.3	30.0	24.1	31.2	23.9	27.1
(h)	(64.2)	(68.4)	(15.1)	(27.2)	(31.8)	(28.6)
MRT	31.6	26.1	23.0	28.6	22.7	25.6
(h)	(54.6)	(34.2)	(12.3)	(13.6)	(28.9)	(9.19)
RA_1	1.60 (14.8)[a]	3.55 (50.2)	1.41 (5.62)[a]	2.84 (39.2)	1.44 (10.2)[a]	2.84 (45.2)
RA_2		3.16 (93.4)		2.61 (14.7)		2.02 (55.0)
RL		2.22 (49.1)		2.01 (39.0)		1.97 (48.3)

Source: Section 10.3 (Table 3)
Geometric mean (CV%) data are presented
† Median (min-max)
N= Number of subjects studied
# Subject 19 withdrawn from study (received his last dose on Day 7)
(norm) = Normalised for dose and body weight (ng/kg)
NC = Not calculated
τ = 24 h
[a] = predicted value

The third study (02 MD) investigated dose proportionality at doses ranging from 40 mg to 600 mg administered as both single and multiple doses in male subjects utilizing the same assay (RIA) as study CRD16 above:

Dose (mg)	Pharmacokinetic Parameters		
	C_{max} (ng/ml)	t_{max} (h)	AUC (ng/ml*h)
	Single Dose (Day 1)		
40	5.1 ± 2.1	1.6 ± 1.8	28.5 ± 13.5
80	11.0 ± 3.6	2.8 ± 2.5	96.4 ± 31.6
160	21.5 ± 9.6	2.7 ± 2.1	214.8 ± 73.5
640	146.2 ± 61.6	2.1 ± 1.1	1193.4 ± 588.6
	Multiple Dose (Day 8)		
40	6.2 ± 2.9	2.1 ± 3.1	46.7 ± 29.2
80	12.7 ± 4.0	1.8 ± 2.4	136.9 ± 54.0
160	39.1 ± 24.6	4.1 ± 2.4	362.7 ± 146.5
640	335.1 ± 196.2	3.2 ± 1.8	2972.5 ± 1263.2

N. WHAT IS THE INTRA AND INTER-SUBJECT VARIABILITY FOR ALISKIREN?

The pharmacokinetic intra- and inter-subject variability of Aliskiren was explored in two drug interactions studies (Study 2211 and 2214). Study 2211 involved coadministration of Aliskiren with Furosemide and study 2214 involved coadministration of Aliskiren with digoxin. In both studies either the MF (market image) or FMI (final market image) formulation was given. As depicted below, the inter-subject variability was higher than the intra-subject variability.

Inter-subject variability (%) of C_{max} and AUC for aliskiren

Study No.	C_{max}^{ss}	$AUC_{0-\tau}$
2211	50, 75	46, 50
2214	36, 48	29, 31

Intra-subject variability (%) of C_{max} and AUC for aliskiren

Study No.	C_{max}	$AUC_{0-\tau}$
2211	39	21
2214	37	18

O. INTRINSIC FACTORS

1. AGE

Pharmacokinetics: The primary pharmacokinetic variables for aliskiren for the different age groups are summarized in the table below.

Primary Pharmacokinetic Variables for the Evaluation of Age on Aliskiren Pharmacokinetics

Age Group 18-45 years	C_{max} (ng/mL)	t_{max} (h)	$AUC_{(0-t)}$ (ng•h/mL)	$AUC_{(0-\infty)}$ (ng•h/mL)	$t_{½}$ (h)
N	28	28	28	28	28
Arithmetic Mean	374.5	1.8	1560	1649	60.6
Geometric Mean	290.2	1.5	1312	1399	58.4
Median	273.5	2.0	1300	1415	60.9
CV%	77.6	47.7	62.6	60.9	26.3

Age Group 65-74 years	C_{max} (ng/mL)	t_{max} (h)	$AUC_{(0-t)}$ (ng•h/mL)	$AUC_{(0-\infty)}$ (ng•h/mL)	$t_{½}$ (h)
N	16	16	16	16	16
Arithmetic Mean	451.8	1.9	2410	2583	69.6
Geometric Mean	351.0	1.4	2056	2204	68.7
Median	356.0	2.0	1984	2120	66.7
CV%	90.2	67.1	69.5	68.9	17.9

Age Group ≥75 years	C_{max} (ng/mL)	t_{max} (h)	$AUC_{(0-t)}$ (ng•h/mL)	$AUC_{(0-\infty)}$ (ng•h/mL)	$t_{½}$ (h)
N	13	13	13	13	13
Arithmetic Mean	604.1	2.0	2611	2814	69.7
Geometric Mean	395.2	1.5	2020	2184	68.9
Median	277.0	1.5	1995	2117	71.1

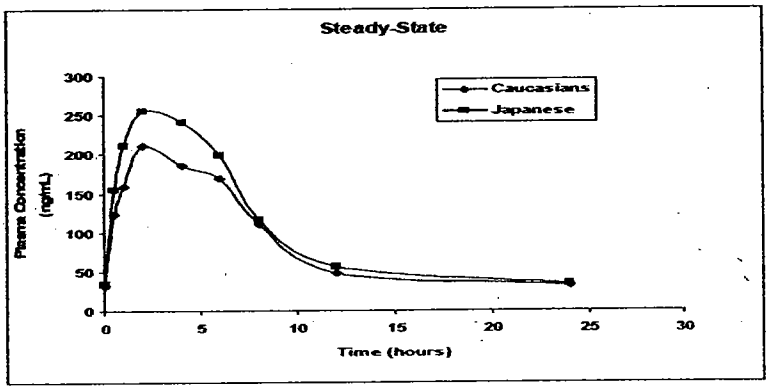
Aliskiren exposures increased by 55% in the 65 to 74 year age group and by 67% in the ≥ 75 year age group; which is clinically significant.

2. GENDER

The sponsor pooled data from 7 studies in order to explore pharmacokinetic differences between genders (78 females, 107 males). All the data used was from multiple-dose, drug-drug interaction studies. After performing weight-adjustments to all the data, no pharmacokinetic differences were observed between the two groups.

3. RACE

A study investigating the pharmacokinetics between Japanese and Caucasian subjects was explored. Japanese subjects tended to have greater exposures than Caucasians by 18%, not clinically significant. The sponsor claims that all subjects were at steady state when the analysis was performed. However, upon reviewing the raw data, 12 of the 19 (63%) Japanese subjects' trough concentrations as well as the groups mean values indicate that steady-state had not been reached. Only seven of the 19 Caucasian subjects (37%) reached steady-state. These findings could affect the pharmacokinetics of Aliskiren when compared to the Japanese versus the Caucasian population since multiple dosing pharmacokinetics seem to indicate drug accumulation making the disparity in the pharmacokinetic findings possibly even greater. A multiple dose plasma concentration-time profile is depicted below for both races.



A cross-study analysis on the same studies used for a gender analysis above was performed in order assess any pharmacokinetic differences between Caucasians, Blacks, Hispanics, and Orientals. Definition of Oriental was not provided and it is not clear if all subjects in the "Other" category are of Hispanic origin. A definition for Hispanics was not provided. Below are the results:

	Caucasians	Blacks	Oriental	Other
C_{max} (ng/mL) [CV%]	268 [68%]	289 [62%]	250 [42%]	351 [56%]
AUC_{0-t} (ng.h/mL) [CV%]	1889 [49%]	2253 [53%]	1566 [29%]	1986 [44%]

The labeling

4. HEPATIC IMPAIRMENT

No Pharmacokinetic differences of clinical significance were observed when hepatically impaired patients were compared to healthy subjects grouped according to matched hepatic impairment group after the administration of a single dose of 300 mg of Aliskiren.

Table 1 **Descriptive statistics for Aliskiren pharmacokinetic parameters in healthy subjects (grouped according to matched hepatically impairment group)**

Subject Group (Healthy)		Cmax (ng/mL)	Tmax (h)	t1/2 (h)	$AUC_{(0-144)}$ (ng x h/mL)	$AUC_{(0-\infty)}$ (ng x h/mL)	CL/F (ml/h)	Vd/F (mL)
Mild	N	6	6	6	6	6	6	6
	Mean	258.2	0.6	46.6	1349	1415	244714	17557659
	SD	133.8	0.2	11.4	600	619	95271	11185870
	Median	263.5	0.5	41.3	1219	1274	239936	13994622
Moderate	N	6	6	6	6	6	6	6
	Mean	190.4	1.3	48.4	1203	1274	248038	17658556
	SD	97.4	1.3	10.1	323	324	60242	6327247
	Median	174.0	1.0	45.3	1116	1196	252278	17833046
Severe	N	4	4	4	4	4	4	4
	Mean	220.7	2.8	57.9	1336	1425	263340	21882168
	SD	174.2	1.5	2.7	588	611	170190	13738461
	Median	191.5	3.0	57.6	1429	1543	194817	16829632

Table 2 **Mean and descriptive statistics for Aliskiren pharmacokinetic parameters in hepatic impaired subjects**

Subject Group (Hepatic Impairment)		Cmax (ng/mL)	Tmax (h)	t1/2 (h)	$AUC_{(0-144)}$ (ng x h/mL)	$AUC_{(0-\infty)}$ (ng x h/mL)	CL/F (ml/h)	Vd/F (mL)
Mild	N	6	6	6	6	6	6	6
	Mean	267.0	1.2	52.2	1438	1547	267916	19645338
	SD	111.3	1.4	11.5	1166	1237	125541	8943536
	Median	247.5	0.5	56.6	1014	1114	269302	19789946
Moderate	N	6	6	6	6	6	6	6
	Mean	291.6	1.1	64.9	1506	1675	235869	22561745
	SD	252.0	1.0	12.0	944	1025	127663	15880639
	Median	245.0	0.8	62.9	1358	1512	206305	18101817
Severe	N	4	4	4	4	4	4	4
	Mean	222.8	1.1	86.1	1371	1646	191951	23096450
	SD	121.2	1.3	18.5	356	447	48431	4520559
	Median	179.5	0.5	92.9	1262	1561	193833	21809195

For all pharmacokinetic parameters, the differences in geometric means were around 20% or less when the data was pooled across all subgroups of subjects with hepatic impairment. There was no correlation between the pharmacokinetic parameters and the Child-Pugh scores.

Table 3 **Ratios of Geometric Mean Aliskiren Pharmacokinetic Parameters on Day 1 in Hepatic Impaired Subjects Relative to Healthy Subjects**

Parameter	Stratum	Ratio of geometric means (Hepatic vs. Healthy)	90% CI for ratio	P-value
$AUC_{0-\infty}$ (ng.h/mL)	Mild	0.97	(0.63, 1.51)	0.912
	Moderate	1.17	(0.75, 1.82)	0.541
	Severe	1.24	(0.72, 2.13)	0.496
	All	1.12	(0.85, 1.48)	0.476
AUC_{0-144} (ng.h/mL)	Mild	0.95	(0.60, 1.49)	0.843
	Moderate	1.10	(0.70, 1.74)	0.703
	Severe	1.11	(0.64, 1.93)	0.749
	All	1.05	(0.79, 1.39)	0.759
C_{max} (ng/mL)	Mild	1.10	(0.63, 1.91)	0.767
	Moderate	1.23	(0.71, 2.14)	0.515
	Severe	1.24	(0.63, 2.45)	0.577
	All	1.19	(0.84, 1.68)	0.388

The confidence intervals for the pharmacokinetic parameters were wide due to the variability of the data and the small numbers of subjects.

5. Renal Impairment

Patients with renal impairment were compared pharmacokinetically to matched-healthy control subjects (Study 2209). Aliskiren AUC was 290% greater in the moderate renal impairment group (713.6 versus 2068.7 ng·h/mL) and 80% in the severe renally impaired group (543.7 versus 982.4 ng·h/mL) when compared to age and weight-matched healthy subjects on day 1 of treatment.

After multiple dosing, exposures were 2.5-fold in the mild group (1109.4 versus 2799.0 ng·h/mL), 2.1-fold in the moderate group (1165.8 versus 2449.3 ng·h/mL) and virtually no difference between groups in the severe group. However, a 4.4-fold increase in Cmin in the severe group (7.8 versus 34.1 ng/mL) and a 27% decrease in oral clearance (357204 versus 262254 mL/h) was observed in the severe group. Increases in exposures did not seem to correlate with severity of renal impairment. However, when Cmin was compared across all groups of renal impairment, a 2-fold increase was observed regardless of level of renal impairment when compared to their matched-healthy control subjects.

6. Type II Diabetes

No pharmacokinetic differences of clinical significance were observed when Type II Diabetic patients were compared to healthy subjects.

Mean and descriptive statistics for Aliskiren primary pharmacokinetic parameters in healthy subjects following administration of a single dose of 300 mg Aliskiren

	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng x h/mL)	$AUC_{0-\infty}$ (ng x h/mL)	CL/F (mL/h)	$t_{1/2}$ (h)	Vd/F (mL)
N	30	30	30	30	30	30	30
Mean	348	1.97	1642	1783	234063	39.9	13118481
SD	236	1.77	1031	1114	137080	8.1	7699801
Min							
Median	278	1.25	1255	1338	224178	39.0	11363105

Max							
CV%	68.0	89.7	62.8	62.5	58.6	20.2	58.7
Geometric Mean	283	1.32	1382	1505	199316	39.1	11242866

Mean and descriptive statistics for Aliskiren in type 2 diabetic patients following administration of a single dose of 300 mg Aliskiren

	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng x h/mL)	$AUC_{0-\infty}$ (ng x h/mL)	CL/F (mL/h)	$t_{1/2}$ (h)	Vd/F (mL)
N	30	30	30	30	30	30	30
Mean	394	1.62	1859	2037	205284	44.0	12330453
SD	288	1.21	1106	1198	136706	11.4	6981790
Min							
Median	328	1.00	1614	1899	158080	40.7	9800120
Max							
CV%	73.3	75.1	59.5	58.8	66.6	25.9	56.6
Geometric Mean	322	1.22	1587	1739	172485	42.7	10625840

There were no statistical differences noted in the primary pharmacokinetic parameters (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$) of Aliskiren in healthy subjects and type 2 diabetic patients. The analysis of SPP100 pharmacokinetic parameters AUCs and C_{max} indicated that, in terms of geometric means, type 2 diabetic patients had about 14-16% higher values in AUC and C_{max} than the healthy volunteers. These observed differences between two groups were not statistically significant (p-values all greater than 0.30).

Ratio of geometric means and the corresponding 90% confidence intervals are summarized in the below.

Statistical analysis results of the SPP100 pharmacokinetic parameters between Type 2 diabetic patients and healthy volunteers

Parameter	P-value of difference	Ratio of geometric means (test/ref)	90% CI for the ratio
$AUC_{0-\infty}$	0.349	1.16	(0.89, 1.50)
AUC_{0-t}	0.347	1.15	(0.89, 1.49)
C_{max}	0.455	1.14	(0.85, 1.51)

Test group = Type 2 diabetic patients, Reference group = Healthy volunteers

P. EXTRINSIC FACTORS

1. WERE ANY DRUG INTERACTIONS EXPLORED?

Yes. Seventeen drug interaction studies were reviewed with results listed below. Study designs were either single or multiple doses.

Study Number	Drug and Dose Study Design	Results
2209	**Single Dose** **Irbesartan** 300 mg **Aliskiren** 300 mg **Multiple Dose**	**Aliskiren data only** **Mild (healthy)** 30% reduction Cmax, 15% reduction in AUC, Tmax reduced by 66%, 20% increase in CL/F **Moderate (healthy)** 15% increase Cmax, 10% reduction AUC, Tmax reduced by 55%, 38% increase in CL/F **Mild (renal)** 55% reduction Cmax, 28% reduction in AUC, 156% increase in Tmax, no change in CL/F **Moderate (renal)** 9% reduction Cmax, No change in AUC, no change in Tmax or AUC

		Note: When comparing the healthy group to the renal impairment group after Irbesartan administration, Aliskiren exposures in the renal impairment group (mild and moderate) increase by 130%. Labeling recommendations regarding dosage adjustments not necessary.
2211	**Furosemide** 20 mg (max initial dose 80 mg) **Aliskiren** 300 mg **Multiple Dose**	**Furosemide** 46% reduction in Cmax, 26% reduction in AUC, 55% increase in Tmax. **Aliskiren** 12% reduction in Cmax, 5% reduction in AUC, Tmax unchanged
2214	**Digoxin** 0.25 mg **Aliskiren** 300 mg **Multiple Dose**	**No interaction - both medications**
2216	**Valsartan** 320 mg **Aliskiren** 300 mg **Multiple Dose**	**Valsartan** No change in Cmax, AUC, and Tmax of clinical significance **Aliskiren** 28% reduction in Cmax, 26% reduction in AUC, 45% reduction in Tmax
2218	**Amlodipine** 10 mg **Aliskiren** 300 mg **Multiple Dose**	**Amlodipine** No change in Cmax, AUC, and Tmax **Aliskiren** 18% increase in Cmax, 29% increase in AUC, 127% increase in Tmax, 22% decrease CL/F
2220	**Metformin** 1100 mg (max dose; 1000 – 2550 mg/D) **Aliskiren** 300 mg **Multiple Dose**	**Metformin** No change in Cmax and AUC of clinical significance **Aliskiren** 29% reduction in Cmax, 27% reduction in AUC, Tmax unchanged
2221	**Ramipril** 10 mg **Aliskiren** 300 mg **Multiple Dose**	**Ramipril** No change of clinical significance **Ramiprilat** No change of clinical significance **Aliskiren** 31% increase in Cmax, 12% increase in AUC, 29% increase in Tmax
2228	**HCTZ** 25 mg **Aliskiren** 300 mg **Multiple Dose**	**HCTZ** 26% decrease in Cmax, AUC unchanged **Aliskiren** 22% decrease in Cmax, AUC unchanged Assay Missing
2334	**Ketoconazole** 200mg Q12h **Aliskiren** 300 mg **Multiple Dose**	**Ketoconazole** not assessed **Aliskiren** 81% increase in Cmax, 76% increase in AUC, 57% decrease in CL/F No labeling recommendation on dose reduction is necessary;
SPP100CRD10 **SPP100 011**	**Cimetidine** 800 mg **Aliskiren** 150 mg (max dose-300 mg) **Single Dose**	**Cimetidine** not assessed **Aliskiren** 19% increase in Cmax, 14% increase in AUC, half-life increased by 4 hrs, CL/F dropped by 15%
SPP100CRD11 **SPP100 0019**	**Warfarin** 25 mg **Aliskiren** 150 mg (max dose –300 mg) **Alisk MD/War SD**	**R-Warfarin** no change (Aliskiren dose low) **S-Warfarin** no change (Aliskiren dose low) **INR** no change of clinical significance-trend toward lower INR **Aliskiren** no change
SPP100CRD12 **SPP100 0020**	**Celecoxib** 200 mg (max dose-400mg) **Aliskiren** 150 mg (max dose-300mg) **Single Dose**	**Celecoxib** trend towards decrease in Cmax and AUC **Aliskiren** Cmax increase of 250-600% in 20% patients with increase in AUC of 90-200%. Overall trend toward increase in Cmax and AUC in summary data.
SPP100A 2235	**Celecoxib** 200 mg	**Celecoxib** No clinically significant change

	BID **Aliskiren** 300mg **Multiple Dose**	**Aliskiren** Cmax no change, AUC 14% decrease
SPP100CRD13 **SPP100 0021**	**Atenolol** 100 mg (max HTN dose 100 mg) **Aliskiren** 150 mg (max dose 300 mg) **Single Dose**	**Atenolol** No clinically significant change **Aliskiren** No clinically significant change
CSPP100A 2230	**Atenolol** 100 mg (max HTN dose 100 mg) **Aliskiren** 300 mg **Multiple Dose**	**Atenolol** No clinically significant change **Aliskiren** No clinically significant change
SPP100CRD14 **SPP100 0022**	**Lovastatin** 40 mg (Max dose 80 mg) **Aliskiren** 150 mg (max dose 300 mg) **Single Dose**	**Lovastatin** Change not clinically significant **Hydroxyacid** Change not clinically significant **Aliskiren** Change not clinically significant, trend toward increase in Cmax and AUC with decrease CL/F
CSPP100A 2234	**Atorvastatin** 80 mg **Aliskiren** 300 mg **Multiple Dose**	**Atorvastatin** changes not clinically significant **o-hydroxy** Changes not clinically significant **p-hydroxy** Changes not clinically significant **Aliskiren 50% increase in Cmax, 47% increase in AUC** Labeling recommendation on dose reduction not necessary.

2. **WERE ANY IN-VITRO METABOLIC OR TRANSPORTER PATHWAY STUDIES PERFORMED?**

In total, twelve in-vitro studies were performed by the sponsor addressing these issues. Based on in-vitro data, Aliskiren is about 30% metabolized with the rest of the drug remaining intact. Human CYP3A4 (99.6 %) and CYP2D6 (0.4 %) were the major contributors toward the metabolism of aliskiren through oxidative metabolism when incubated with human liver microsomes. Aliskiren does not inhibit CYP3A4/5 at clinical concentrations. Ketoconazole and monoclonal antibody effectively inhibit aliskiren metabolism by CYP3A4. PSC833 has a concentration-dependent influence on Aliskiren's permeability via an inhibition interaction at the efflux transporter level. Transport capability of aliskiren is concentration and direction dependent. Basolateral to apical transport is greater than that of apical to basolateral transport possibly due to the existence of a potential efflux pump on the apical membrane. Results seem to support the conclusion that aliskiren is a substrate for and is actively transported by MDR1. Study results are summarized below:

STUDY	DESCRIPTION/OBJECTIVE	RESULTS
DMPK R0500660	Effect of excipient material (backfill material) and external pH on Aliskiren permeability was examined since some clinical studies used overencapsulated Aliskiren for blinding purposes thereby creating a new formulation. Apical to basolateral transport experiments were conducted.	Aliskiren absorption not affected by filler material; but increased when pH of apical chamber was lower than the basolateral chamber (pH 6.5 to 7.4).
DMPK R100670	To determine the predictive absorption on the involvement of active transporters of	Aliskiren was moderately permeable and transported both from the apical-basolateral and

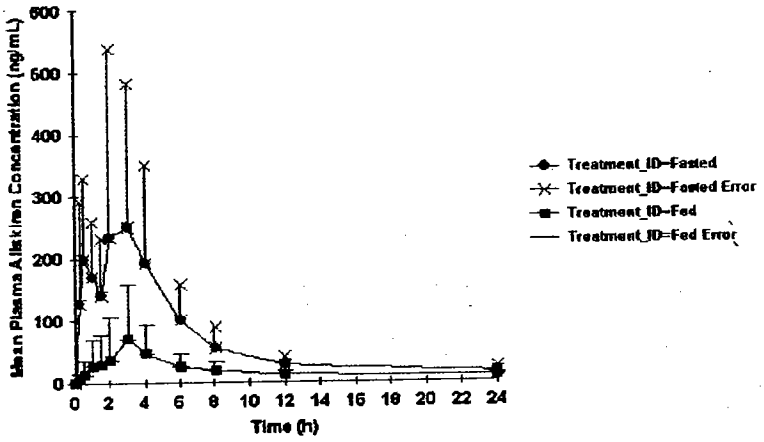
	aliskiren across the intestinal barrier using Caco-2 mono layer cells. To determine the direction of aliskiren transport.	basolateral-apical direction evenly. **NOTE:** Results differ from study R0200734. May be due to using free base form of Aliskiren and the to-be-marketed formulation will be the hemifumarate form. According to results from study R0200734 using hemifumarate had extremely low absorption (less than mannitol).
DMPK R0400107	Determination of the interaction with the human MDR1, MRP2 and BCRP (MXR) transporters using the ATPase assay in order to determine the types of ABC transporters involved in Aliskiren transportation.	Aliskiren was a substrate for MDR1 (Conc. Range 1 - 10μM); but not for MRP2 and MXR. Inhibitory effect of aliskiren on MXR was observed, however, it was < 20 % , not clinically relevant.
PCS(EU) R0400151	To determine the effect of the potential efflux pump modulator PSC833 on the permeation potential of SPP100. Caco-2 cells were cultured on permeable polyethylene terephthalate membranes. Apical to basolateral transportation (upper chamber to lower chamber), basolateral to apical transportation and effect of transport inhibitor on SPP100 (1μM) were determined in the presence of the potential efflux pump inhibitor PSC833 (0, 0.2, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, and 2μM).	SPP100 is a moderate affinity, moderate capacity substrate for the efflux pump involved in its transport. The inhibition kinetics of PSC833, revealed an IC_{50} value of about 0.1μM, indicative of a high inhibitor potential for PSC833. PSC833 is likely to have a conc.-dependent influence on SPP100 permeability by an inhibition interaction at the efflux transporter level.
DM(EU) 18/1994	To investigate metabolic stability of Aliskiren in postmitochondrial liver fraction (S12) from man. Aliskiren was incubated with human liver post mitochondrial fraction and analyzed.	Aliskiren was metabolized in postmitochondrial fraction of human liver with 2/3 remaining intact after 120 min of incubation. Three metabolites (P3, P4 and P5) were found. Molecular structure of metabolites was not determined. Aliskiren is considered to be metabolically stable in human liver postmitochondrial fractions.
DMPK R0101129	Identification of human cytochrome P450 enzymes involved in the oxidative metabolism of SPP100 was investigated.	CYP3A4 (99.6 %) and CYP2D6 (0.4 %) were the major contributors toward the metabolism of aliskiren when incubated with human liver microsomes. Chemical (ketoconazole) and biological (monoclonal antibody) inhibitors effectively inhibit aliskiren metabolism by CYP3A4.
DMPK 1997/452	In vitro biotransformation of Aliskiren by human liver microsomes was investigated. Aliskiren was incubated with human liver microsomes containing an NADPH generating system. Formed metabolites were analyzed.	Aliskiren was metabolized to its derivative without the metoxyproply side chain and demethylated further to other compounds. The precise molecular structures were not completely determined. More than 95 % of aliskiren in supernatant fraction was converted to metabolites after 120 min of incubation in conc < 10 μM. Since the sponsor used purified human liver microsomes, the metabolite proportions were higher in comparison to study #18-1994. Even if the protein conc in the reaction mixture were the same, the exact amounts of enzymes were not equal.
PCS(EU) R0101128	The inhibition capacity of SPP100 on specific CYP450 enzymes in human liver microsomes was determined. Pooled human liver microsomes (HIV1, 2, HTLV1, 2 and Hepatitis B, C negative) were used. Inhibition capacity of aliskiren on CYP subtypes was investigated using a specific	**Aliskiren does not inhibit CYP2C9, 2C19, and 2D6 at clinical concentrations.** Significant inhibition on 2C9, 2C19 and 2D6 were observed. However, the in vitro concentration range required to achieve inhibition (200μM) is beyond clinically achievable blood concentrations since Aliskiren's C_{max} when administered at a dose of 150 mg to

	substrate for each subtype.	healthy volunteer is observed to be about 0.03 μM. The maximum concentration of aliskiren used in CYP3A4/5 was 10 μM whereas 200 μM was used in other subtypes. Higher concentrations were re-examined for the inhibition of CYP3A4/5 in study DMPK R0101128-01.
DMPK R0 101128-01	The inhibition capacity of SPP100 on CYP3A4/5 using two different substrates specific for CYP3A4/5 was determined.	**Aliskiren does not inhibit CYP3A4/5 at clinical concentrations.** Significant inhibition on CYP3A4 was observed for both substrates. However, the concentration range required to achieve inhibition (IC_{50} - testosterone 6β-hydroxylation 71 μM, midazolam 1'-hydroxylation 251 μM) were higher than clinically achievable
DMPK R0400734	To determine the possible involvement of Organic Cation Transporter (OCT) on aliskiren transportation.	The affinity of aliskiren to hOCT1 was low and almost no affinity to hOTC3. Thus, transport of aliskiren is not likely to occur through this transporter. However, the incubation time for the uptake was only 1 second; which is sufficient for binding but not enough time for uptake. As a result, it's not possible to evaluate this study thoroughly.
DMPK R0200734	The predictive absorption, particularly the involvement of a non-passive diffusion system in the transport of SPP100 across the intestinal barrier was determined. Transporter identification for SPP100 in the presence of potent efflux system inhibitors CsA (10μM) and Verapamil (100μM) was investigated. Caco-2 cells were cultured on permeable polyethylene terephthalate membranes. Apical to basolateral transportation (upper chamber to lower chamber) or basolateral to apical transportation and effect of transport inhibitor were determined.	Aliskiren transportation from apical to basolateral was concentration dependent within the range of 1 to 50 μM while basolateral to apical transportation was saturated at a concentration of 1 μM. Transport capability of aliskiren was dependent on direction. Basolateral to apical transport was significantly greater than that of apical to basolateral transport. **This could be explained by the existence of a potential efflux pump on the apical membrane, such as MDR 1. The results support the conclusions that the efflux system involved in Aliskiren transport is MDR1.** Potential transporter inhibitor cyclosporine A (CsA) increased apical to basolateral aliskiren transportation. However, Verapamil, another transporter inhibitor had no effect on aliskiren transportation from the apical to basolateral direction.
DMPK R0500381	Determination of the hepatic uptake clearance of SPP100 using primary human hepatocytes was conducted and the identification of the involved transporters using cRNA injected Xenopus laevis oocytes was also determined.	PSC833 did not influence the uptake of Aliskiren into human hepatocytes. This study was conducted for the clarification of the possible hepatic uptake mechanism in human. Human OATP1 is a candidate for hepatic uptake of aliskiren. However, it expressed mainly in brain and hepatic expression was relatively low. Thus, the precise mechanism of hepatic uptake of aliskiren is still controversial. **Note:** The labeled test compound in this study was the —— salt whereas hemifumarate was used in other Studies (DMPK R0500660, DMPK R0101129, DMPK 1997/452, DMPK R0400734, and DMPK R0200734).

3. WHAT IS THE EFFECT OF FOOD ON THE BIOAVAILABILITY OF THE DRUG FROM THE DOSAGE FORM?

As demonstrated in study 2207, food had a significant impact on the rate and extent of absorption of Aliskiren. This was a randomized, open-label, single-dose, two-period, cross-over design in 30 healthy volunteers. Aliskiren C_{max} fasted versus fed was 80% lower (453.2 and 92.4 ng/mL, respectively) with a CV% of 68 and 103%. T_{max} was delayed by one hour (2.1 versus 3.2 hours, fasted to fed with a CV% of 60.8 and 51.6%, respectively) and Aliskiren AUC_{0-t} dropped by 70% (2315 versus 707 ng·h/mL with a CV% 50.3 and 61.4%). The $AUC_{0-\infty}$ also dropped by 69% (from 2437 to 767 ng·h/mL) when food was given. The CV% was 49 and 60.5%, respectively. Aliskiren's half-life decreased from 54 to 46 (15%) hours when food was given and the clearance increased from 150550 mL/h under fasted to 577002 mL/h under fed conditions (280%) indicating that the small amount absorbed upon drug administration with food underwent increased oral clearance. All pharmacokinetic variables had a high CV%. However, the clinical impact of the variability would be negligible with results such as these.

Mean Aliskiren concentrations under fed and fasted conditions in healthy volunteers



III. GENERAL BIOPHARMACEUTICS

A. WERE THE CORRECT MOIETIES IDENTIFIED AND PROPERLY MEASURED TO ASSESS THE CLINICAL PHARMACOLOGY?

Aliskiren was identified and measured in all pharmacokinetic studies and several of the clinical studies as listed above in the summary tables addressing the design features of the clinical pharmacology and the clinical studies that were used to support dosing or claims. No other moieties were measured since Aliskiren undergoes minimal metabolism.

B. WHERE DIFFERENT FORMULATIONS USED THROUGHOUT THE DEVELOPMENT PROGRAM OF ALISKIREN?

Several formulations were used in clinical trials submitted. In an effort to blind medications used for some of the clinical studies, the sponsor inadvertently created a new formulation according to SUPAC Guidance since backfill material was used as filler when aliskiren was over-encapsulated.

Novartis SPP100 formulations used in Clinical Studies: 75mg dosage strength

Component	75mg tablet in capsule (uncoated MF) 6001149.001 (mg/capsule)	75mg film-coated tablet in capsule (MF) 6001149.002 (mg/capsule)	75mg film-coated tablet (FMI) 3764313.004 and 3764313.007 (mg/tablet)	Function
Tablet / Film-coated tablet				
SPP100 hemifumarate				Active substance
Cellulose microcrystalline (Ph. Eur./NF)				
Crospovidone (Ph. Eur. / NF)				
Povidone (Ph. Eur./ USP)				
Magnesium stearate (Ph. Eur./NF)				
Colloidal silicon				
Tablet target weight				
Film coating				
Total weight of the film coated tablet				
Capsule backfill				
Total capsule backfill				
Weight of shell			—	
Total weight of capsule			—	

MF: market formulation, FMI: final market image

For the 75 mg strengths, formulation number 6001149.001 (first column) was used in phase II study 2203 and formulation number 6001149.002 (second column) was used for phase II study 2204 both considered to be pivotal by the Clinical Division for assessment of approvability.

Novartis Aliskiren Formulations used in Clinical Studies: 150mg dosage strength

Component	150mg tablet in capsule (uncoated MF) 3768785.002 (mg/capsule)	150mg film-coated tablet in capsule (MF) 3768785.004 (mg/capsule)	150mg film-coated tablet (FMI) 3765070.005 3765070.008 and 3765070.010 (mg/tablet)	Function
Tablet / film-coated tablet				
SPP100 hemifumarate				Active substance
Cellulose microcrystalline (Ph. Eur./NF)				
Crospovidone (Ph. Eur. / NF)				
Povidone (Ph. Eur./ USP)				
Magnesium stearate (Ph. Eur./NF)				
Colloidal silicon				
Tablet target weight				
Film coating	—			
Total weight of the film coated tablet	—		357.00	
Capsule backfill			—	
			—	
			—	
Total capsule backfill				
Weight of shell			—	
Total weight of capsule			—	

MF: market formulation, FMI: final market image

For the 150 mg strengths, formulation number 3768785.002 (first column) was used in phase II study 2201 and formulation number 3768785.004 (second column) was used

for phase II studies 2203 and 2204 both considered to be pivotal by the Clinical Division for assessment of approvability. The later formulation was also used for bioequivalence study 2343 in order to establish bioequivalence between the MF and FMI formulation. Formulation number 3765070.008 (third column) was used in phase III study 2308.

Novartis Aliskiren Formulations used in Clinical Studies: 300mg dosage strength

Component	300mg tablet in capsule (uncoated MF) 3768801.002 (mg/capsule)	300mg film-coated tablet (MF) 6000937.001 and 6000937.005 (mg/tablet)	300mg film-coated tablet (FMI) 6000937.004, 6000937.006 and 6000937.007 (mg/tablet)	Function
Tablet / film-coated tablet				
SPP100 hemifumarate				Active substance
Cellulose microcrystalline (Ph. Eur./NF)				
Crospovidone (Ph. Eur. / NF)				
Povidone (Ph. Eur./ USP)				
Magnesium stearate (Ph. Eur./NF)				
Colloidal silicon				
Tablet target weight				
Film coating				
Total weight of the film coated tablet			**706.00**	
Capsule backfill				
Total capsule backfill				
Weight of shell				
Total weight of capsule				

MF: market formulation, FMI: final market image

Formulation number 3768801.002 (first column) was used for phase II study 2201 while formulation number 6000937.001 and 6000937.005 (second column) were used for phase II studies 2203 and 2204, respectively. Formulation number 6000937.006 (third column) was used in phase III study 2308.

C. WAS AN ADEQUATE LINK ESTABLISHED BETWEEN THE CLINICAL AND TO-BE-MARKETED FORMULATIONS?

The sponsor conducted several of their Phase III clinical trials (Studies 2203 and 2204.) with a market image formulation of the 150 mg strength that was over-encapsulated in order to blind their studies. In so doing, they created another formulation since the backfill material constituted a SUPAC IR level-3 change in the formulation's components and composition. As a result, demonstration of bioequivalence between the clinical trial formulation and the to-be-marketed formulation (Final Market Image-FMI) was required for the 150 mg strength.

Study 2343 was a single-dose, randomized, open-label, 4-period, replicate, cross-over, fasted study in 48 healthy volunteers (58 enrolled and 48 completed all treatment periods). Results below seem to indicate a lack of bioequivalence between the blinded/over-encapsulated clinical trial formulation and the FMI in regards to extent of exposure:

Treatment	t_{max} (h) Median (min; max)	C_{max} (ng/mL) Mean ± SD (CV %)	$AUC_{(0-t)}$ (ng-h/mL) Mean ± SD (CV%)	$AUC_{(0-\infty)}$ (ng-h/mL) Mean ± SD (CV %)	$AUC_{(0-tmax)}$ (ng-h/mL) Mean ± SD (CV %)
Overencapsulated Tablet	1.5 (0.28; 6.0)	98.2 ± 85.5 (87.0%)	598.3 ± 425.1 (71.0%)	663.8 ± 467.8 (70.5%)	75.1± 82.3 (109.6%)
FMI Tablet	1.0 (0.25; 6.2)	119.6 ± 91.1 (76.1%)	654.6 ± 351.4 (53.7%)	719.8 ± 389.4 (54.1%)	71.7 ± 80.2 (112%)
Geometric Mean Ratio – Overencapsulated Tablet : FMI Tablet (90% CI)	–	0.80 (0.70, 0.90)	0.88 (0.82, 0.96)	0.89 (0.83, 0.97)	1.07 (0.85, 1.36)

Aliskiren C_{max} of the over-encapsulated tablet was 82% of the FMI tablet (18% less than the reference). The 90% CI was 70 to 90% with a Geometric mean ratio of 0.80, which is within the 90% CI. The difference in Aliskiren C_{max} is of no clinical significance.

The CI for AUC_{0-t} was 82 to 96% and for $AUC_{0-\infty}$ 83 to 97%, demonstrating bioequivalence. The AUC_{0-tmax} was 5% greater for the over-encapsulated in comparison to the FMI formulation. Again, not of any clinical significance even though the 90% CI was 85 to 136% and the Geometric mean ratio was 1.07.

Aliskiren 300 mg was not over-encapsulated and did not require a bioequivalence study.

D. WAS ALISKIREN CLASSIFIED UNDER THE BCS CLASSIFICATION SYSTEM?

Aliskiren drug substance is highly soluble in water according to the Biopharmaceutics Classification System (highest dose strength soluble in ≤ 250 ml water over a pH range of 1 to 7.5). Aliskiren drug substance is a low permeability drug and is therefore categorized as a class 3 compound according to the Biopharmaceutics Classification System (BCS).

Table 1-1 Solubility of SPP100

Solvent	Temperature (°C)	Solubility
Water (Millipore filtered)	23 °C	> 350 g/l, pH 6.0
0.1N HCl	23 °C	> 350 g/l, pH 4.3
Phosphate buffer USP, pH = 7.6	23 °C	> 350 g/l, pH 7.0
Phthalate Buffer USP, pH = 4.5	23°C	> 350 g/l, pH 5.2

IV. DISSOLUTION

A. ARE THE PROPOSED DISSOLUTION METHOD AND SPECIFICATIONS ACCEPTABLE?

The sponsor's proposed dissolution methods and specifications for Aliskiren are acceptable and described below:

Apparatus	USP Apparatus I (Basket
Medium	0.01N HCL
Volume	500 mL
Temperature	37° C ± 0.5° C
Q	~ of label claim after 30 minutes

V. ASSAY AND VALIDATION

A. WERE ALL ASSAYS VALIDATED?

Aliskiren concentrations were analyzed in most studies by a validated HPLC-MS/MS or a LC-MS/MS method with a LOQ of 0.5 ng/mL in plasma and 5 ng/mL for urine.

For dose proportionality study 0024, Aliskiren was analyzed by a solid phase RIA method and validated in the range of 0.1358 to 905 ng/mL in plasma and 113.125 to 13575 ng/mL in urine.

The bioanalytical assay for study 2228 is missing. It remains unclear whether Aliskiren was measured by LC/MS/MS or by LC/UV since the assay methodology is reported differently in the synopsis than in the study report. The sponsor should submit the assay since there's unusually high inter-subject variability in this study. Reliability of study results is dependent on the validated assay results. Demonstration of consistency, linearity and accuracy of the assay is pivotal in assessing the study results.

VI. LABELING

A. IS THE PROPOSED LABELING FOR ALISKIREN ACCEPTABLE?

The proposed labeling is acceptable provided the Reviewer Labeling Comments described in the Recommendations section are addressed by the sponsor. A copy of the proposed package insert is included in Appendix I.

74 Page(s) Withheld

_____ Trade Secret / Confidential

7 Draft Labeling

_____ Deliberative Process

STUDY DMPK R0500660– EFFECT OF EXCIPIENTS AND PH ON [^{14}C]SPP100 ABSORPTIVE PERMEABILITY ACROSS CACO-2 CELL MONOLAYERS

INVESTIGATORS: Hanna I, Alexander N
SITE: Novartis Pharmaceuticals Corporation
Drug Metabolism and Pharmacokinetics
Absorption, Distribution, Metabolism and
Excretion (ADME) Section
East Hanover, New Jersey, USA

REPORT # DMPK R0500660
EDR VOLUME 6
RELEASE DATE: December 21, 2005

FORMULATION:

Radio labeled drug	[^{14}C]aliskiren hemifumarate (Batch No.RSE229-12 Ch.E- 15087-39-35, specific activity of 73.39 µCi/mg (120.34 mCi/mmol) and a radiochemical purity > —
Non-radio labeled	Aliskiren 75 mg tablets (batch No. Med# D47032 Ch-B- drug 03-1453CH)

The effect of excipient material and external pH on the permeability of SPP100 was examined in the Caco-2 monolayer model. Apical-to-basolateral transport experiments were conducted either with dispersed tablets or [^{14}C]SPP100.

The average permeability values for SPP100 estimated at a nominal concentration of 544 µM (dispersed tablets) or 11 µM ([^{14}C]SPP100) in the apical-to-basolateral direction were compared to those obtained in the presence of either back-fill material found in overencapsulated tablets or known efflux transport protein inhibitors. In all cases, the permeability of SPP100 was lower than that of the low permeability marker mannitol, and was not appreciably affected by the presence of back-fill material or the transport protein inhibitors

Back-fill material found in over-encapsulated tablets of SPP100 had no meaningful effects on absorptive permeability of this compound. SPP100 permeability was modestly higher when the pH of the apical chamber was lower than that of the basolateral chamber. Overall the observed poor *in vitro* cellular permeability is consistent with *in vivo* observations of low to modest absorption of SPP100.

Table1 **Ingredients of the excipient material for SPP100 tablets, and the back-fill material**
A 75 mg tablet of Aliskiren (SPP100) was sonicated in 250 mL of HBSS buffer (final SPP100 concentration approximately 544 µM). The ingredients of the 75 mg tablet and those of the back-fill material are listed in the table below

Component	Tablet (mg)	Backfill (mg)	Function
SPP100 hemifumarate			Active substance
Cellulose microcrystralline			
Cropovidone			
Povidone			
Magnesium Streate			
Colloidal silicon			
Total weight			

Table 2 Effect of capsule back-fill material on SPP100 absorptive permeability across Caco-2 monolayers

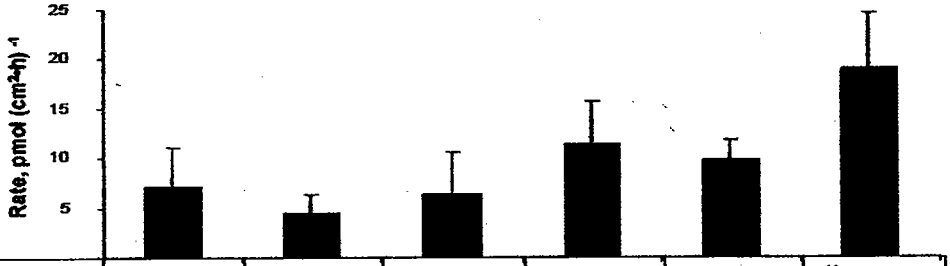
Substrate	Description, concentration	Additive, concentration	Average (± SD) Absorptive permeability [a] ($cm \cdot min^{-1}$) × 10^{-5}
SPP100	Dispersed tablet, 544 µM	none	3.2 ± 1.8 (n=6)
SPP100	Dispersed tablet, 544 µM	Back-fill material, 2.3 $mg \cdot mL^{-1}$	2.2 ± 1.3 (n=5)[b]
[^{14}C]SPP100	Radio-labeled compound, 11 µM	none	1.0 ± 0.4 (n=6)
[^{14}C]SPP100	Radio-labeled compound, 11 µM	Back-fill material, 0.74 $mg \cdot mL^{-1}$	0.8 ± 0.3 (n=6)
[^{14}C]SPP100	Radio-labeled compound, 11 µM	GF120918, 2.0 µM	1.8 ± 0.6 (n=6)
[^{14}C]SPP100	Radio labeled compound, 11 µM	LY335979, 1.0 µM	1.7 ± 0.3 (n=6)
Mannitol	Radio-labeled low permeability marker	none	7.3 ± 1.2 (n=6)

[a] Absorptive permeability calculated by measuring the concentration of test substance in the basolateral compartment at the end of the 2 h incubation period.

[b] One of the observed values was eliminated from the calculation since it was shown to be an outlier using the Grubbs test (extreme studentized deviate) using the GraphPad Software.

Figure 1 Effect of filler material on the rate of [^{14}C]SPP100 movement across Caco-2 monolayers

The effect of capsule filler material and the known transport-protein inhibitors (LY335979 and GF120918) on the rate of [^{14}C]SPP100 (11 µM) movement in the apical-to-basolateral direction across Caco-2 monolayers was estimated as described in Section 2.3.3. The rate of [^{14}C]mannitol (3.9 µM) movement is included for comparison purposes.



Test Compound	[^{14}C]SPP100	[^{14}C]SPP100	[^{14}C]SPP100	[^{14}C]SPP100	[^{14}C]SPP100	[^{14}C]mannitol 3.9 µM
Additive	none	Filler	Filler	GF120918	LY335973	none
Concentration	-	0.74 mg/mL	1.5 mg/mL	2 µM	1 µM	-

Table 3 Effect of the pH of the donor chamber on SPP100 absorptive permeability

Compound	Nominal concentration	Average (± SD) Absorptive permeability [a] ($cm \cdot min^{-1}$) × 10^{-5} Apical chamber pH 6.5	Average (± SD) Absorptive permeability [a] ($cm \cdot min^{-1}$) × 10^{-5} Apical chamber pH 7.4
[^{14}C]SPP100	10 µM	0.5 ± 0.1	0.2 ± 0.0
[^{14}C]SPP100	30 µM	0.5 ± 0.1	0.2 ± 0.1
[^{14}C]SPP100	75 µM	0.5 ± 0.1	0.2 ± 0.1
[^{14}C]SPP100	150 µM	0.6 ± 0.3	0.3 ± 0.2
[^{14}C]mannitol	4.0 µM	7.6 ± 2.2	5.8 ± 0.9
[^{14}C]propranolol	6.0 µM	73.3 ± 4.5	129 ± 6.3

CONCLUSIONS:
Absorption of aliskiren was not affected by filler material but increased when pH was shifted to acidic conditions (7.4 to 6.5).

REVIEWER'S COMMENT:
1. The reviewer concurs.

APPEARS THIS WAY
ON ORIGINAL

STUDY DMPK R0100670–PERMEABILITY STUDY ACROSS CACO-2 CELL MONOLAYERS

INVESTIGATOR: —
SITE: Not provided

REPORT # DMPK R0100670
EDR VOLUME 6
RELEASE DATE: July 31, 2001

OBJECTIVES:
1. To determine the predictive absorption especially on the involvement of active transporters of aliskiren across the intestinal barrier using Caco-2 mono layer cells.
2. To determine the direction of aliskiren transport.

MATERIALS:
Aliskiren (free base) Batch No. NE-5810-Batch-02-01, purity —

ABBREVIATIONS:
AP	apical (luminal side)
AP-BL / BL-AP	apical to basolateral / basolateral to apical
BL	basolateral (blood side)

RESULTS:
From the results presented, aliskiren was efficiently transported in comparison to mannitol. Aliskiren was transported in either direction with about the same efficiency.

Table 1 Permeability across Caco-2 cell monolayers
Permeability coefficients P_{app} of SPP100

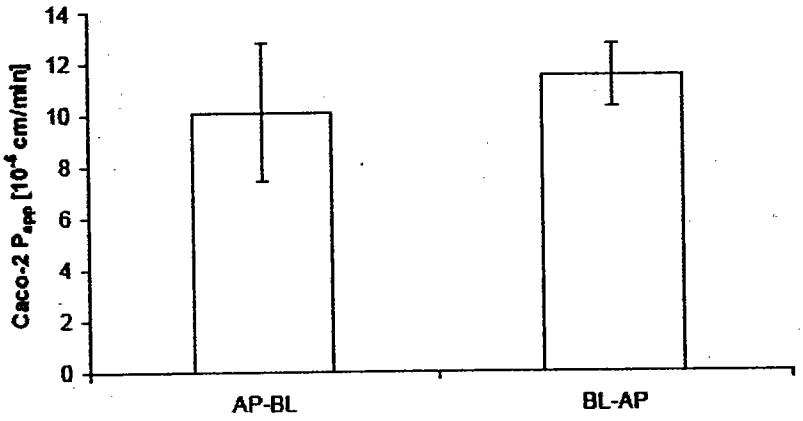
Compound	Conc. [µM]	Caco-2 permeability					
		$P_{app(AP-BL)}$ [10^{-5} cm/min]	SD		$P_{app(BL-AP)}$ [10^{-5} cm/min]	SD	
SPP100	5	10.1	2.7	(-)	11.5	1.2	(-)
[^{3}H] Mannitol	0.01	0.8	0.2	(-)	-	-	(-)
[^{3}H] Propranolol	0.01	37.6	2.5	(-)	-	-	(-)

() = recovery values in %
- = not measured

APPEARS THIS WAY
ON ORIGINAL

Figure 1 Bi-directional transport

Transport of SPP100 across Caco-2 cell monolayers measured in the AP-to-BL and BL-to-AP direction



CONCLUSIONS:

Aliskiren was moderately permeable. This was based upon its observed permeability coefficient being in the middle, between highly permeable propranolol and less permeable mannitol (Table 1). Aliskiren was transported both apical to basolateral and basolateral to apical direction evenly.

REVIEWER'S COMMENT:

1. Laboratory site was not provided.
2. These study results are different from study R0200734 even though the same experimental system was used. This could be due to the fact that in this study they used the free base form of Aliskiren and the to-be-marketed formulation will be the hemifumarate form of aliskiren. According to the results from study R0200734 using hemifumarate had an extremely low absorption (less than the low absorption model compound mannitol).

APPEARS THIS WAY
ON ORIGINAL

STUDY DMPK R0400107–DETERMINATION OF THE INTERACTION WITH THE HUMAN MDR1, MRP2 AND BCRP (MXR) TRANSPORTERS USING THE ATPASE ASSAY

INVESTIGATOR: —
SITE: Not provided

REPORT # DMPK R0400107
VOLUMES in EDR, Section 6
RELEASE DATE: September 02, 2004
STUDY DATE: June 20, 2004 – July 25, 2004

OBJECTIVES:

To determine the type(s) of ABC transporter involved in aliskiren transportation.

MATERIALS AND METHODS:

Aliskiren CGP060536-NX-1: 551.77 g/mol, purity: >

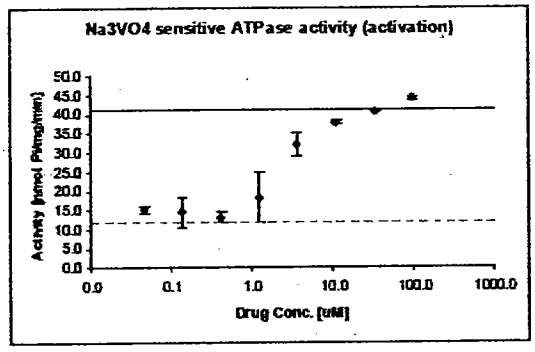
Commercially available membrane vesicles expressing different human ABC transporters (MDR1, MRP2 and MXR) were used. Formed inorganic phosphate (Pi) through consumed ATP during transportation of aliskiren measured by an Ammonium Molybdate/Zinc Acetate colorimetric method was employed. Inhibitory effect of aliskiren on ABC transporters was measured in the presence of specific activation agents.

RESULTS:

Aliskiren stimulated MDR1 with its maximum stimulating effects reached at a concentration range of 1 to 10 µM. However, it did not stimulate MRP2 and MXR. Aliskiren had a minimal (< 20%) inhibitory effect on MXR at very low concentrations (< 0.1 µM).

Figure 1 Concentration-dependency of MDR1 ATPase activity

MDR1-dependent Na_3VO_4 sensitive transporter ATPase activity. Transported substrates increase the baseline ATPase activity (dotted line), while inhibitors inhibit the maximal possible ATPase activity measured in the presence of the stimulating agent Verapamil [50 µM] (solid line).



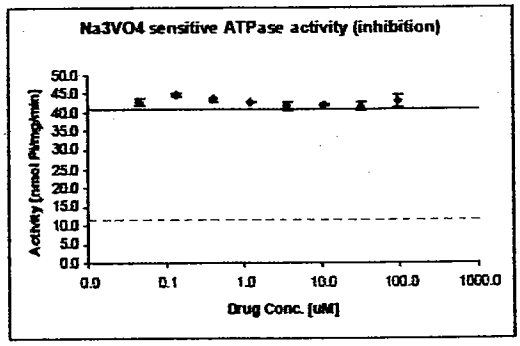


Figure 2 Concentration-dependency of MRX ATPase activity

MXR-dependent Na_3VO_4 sensitive transporter ATPase activity. Transported substrates increase the baseline ATPase activity (dotted line), while inhibitors inhibit the maximal possible ATPase activity measured in the presence of the stimulating agent Sulfasalazine [10 µM] (solid line).

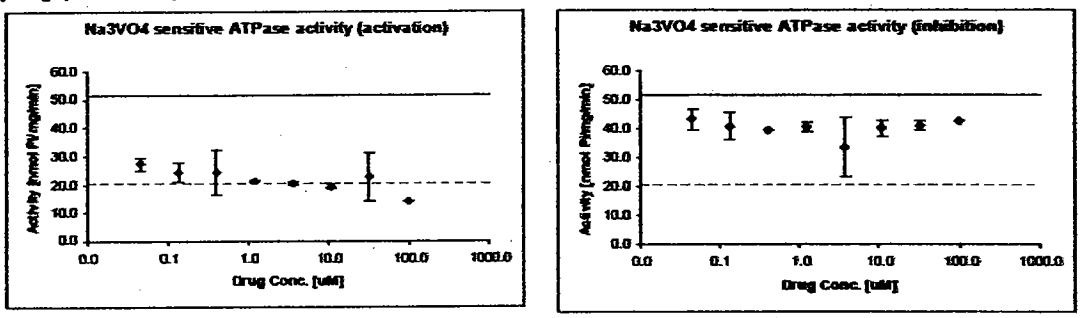
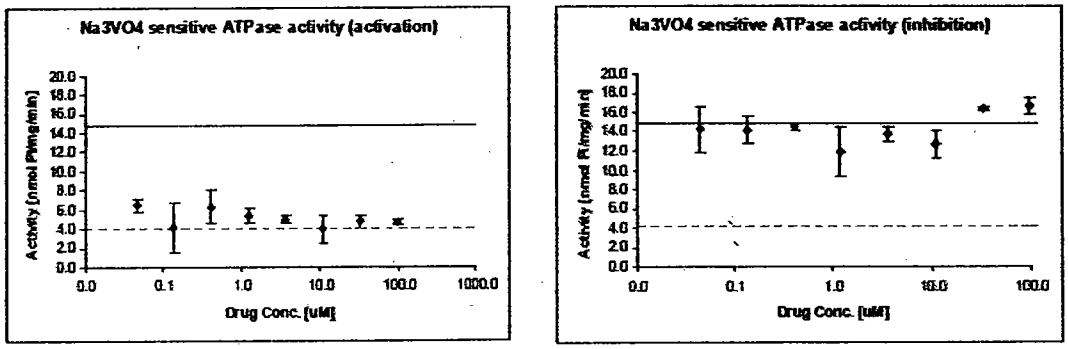


Figure 3 Concentration-dependency of MRP2 ATPase activity

MRP2-dependent Na_3VO_4 sensitive transporter ATPase activity (in the absence of GSH). Transported substrates increase the baseline ATPase activity (dotted line), while inhibitors inhibit the maximal possible ATPase activity measured in the presence of the stimulating agent Probenecid [10 mM] (solid line).



CONCLUSIONS:

Based upon presented results, aliskiren was a substrate for MDR1 but not for MRP2 and MXR. Inhibitory effect of aliskiren on MXR was observed, however, it was < 20 % and this effect was not clinically relevant.

REVIEWER'S COMMENT:

1. Laboratory site was not provided.
2. Test compound's characteristics (i.e., free bas, salt) and batch number and expiration information were not provided.