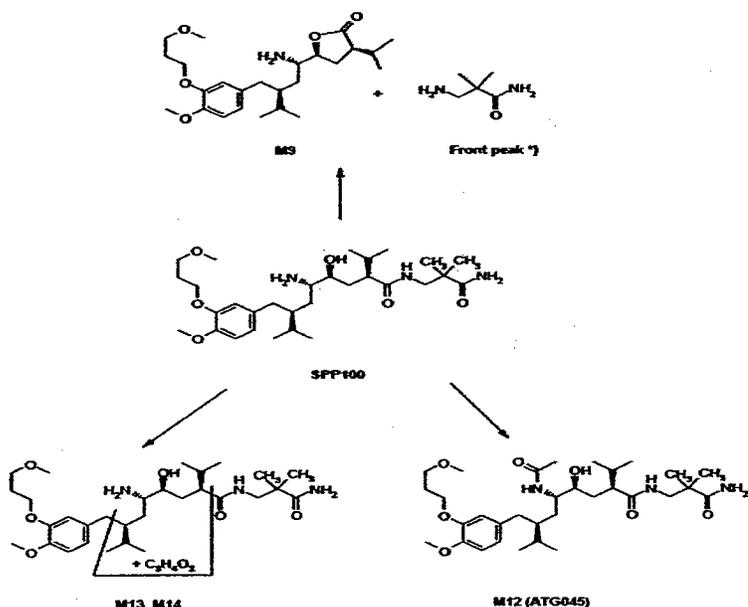


Continued



### CONCLUSIONS:

Following oral administration of the <sup>14</sup>C-radiolabelled aliskiren in an aqueous drink solution, the total urinary radioactivity and fecal metabolites amounted to about 3% of the dose administered.

- Pharmacokinetics:** The basic pharmacokinetic variables ( $C_{max}$ ,  $t_{max}$ , AUC) showed large interindividual variability. The concentration-time curves of radioactivity and SPP100 were approximately parallel. The difference between the curves was small, and was within the accuracy range of the analytical methods for <sup>14</sup>C (liquid scintillation counting and AMS) and for SPP100 (LC-MS/MS). After  $t_{max}$ , SPP100 declined rapidly with an initial apparent mean half-life of 2.1 hours. The terminal half-life of 49 hours in the period 48 - 144 hours was consistent with other clinical pharmacokinetics data and with the radioactivity half-life.
- Systemic Exposure:** The most abundant radiolabeled component in plasma was SPP100, accounting for 81% of the AUC of radioactivity (86% of AUC<sub>0-10h</sub>, means). The only notable, minor metabolites M3 and M2 were estimated to account for 3 % and 1 % of the radioactivity AUC, respectively.
- Distribution:** The radioactivity in blood was largely confined to plasma. A minor proportion of 11% (large interindividual variability) was estimated to be associated with RBC.
- Metabolism:** Part of the absorbed [<sup>14</sup>C]SPP100 was metabolized. Metabolism pathways observed were oxidative O-dealkylations at the phenolic moiety and the phenol moiety side chain, with formation of the oxidized metabolites M1 - M4. Traces were observed of a glucuronic acid conjugate (M6) and of a hydrolysis product. The same metabolites were found in human as observed previously in rat and rabbit. Additionally, the trace metabolites M12 (N-acetyl derivative), M13 and M14 were detected only in the feces (in peak P62). M13 and M14 were isomers and could be characterized only partially. These fecal metabolites appear to be artifacts formed from unabsorbed SPP100, possibly by microbial metabolism.
- Systemic Elimination:** The sum of oxidized metabolites in excreta amounted to approx. 1.4% of the dose. It appears that direct excretion of unchanged SPP100 in urine (0.4 %) and by the hepatobiliary/fecal route were relevant elimination processes.
- Excretion:** Excretion of radioactivity occurred largely in the first 2-4 days, and was fairly complete (91.5%) after 7 days. With a total renal excretion of 0.6 % of the radioactive dose, 91% were excreted via feces, whereof the largest part was unabsorbed drug. The major part of the absorbed dose fraction is concluded to be eliminated in unchanged form via the hepatobiliary route.

**REVIEWER'S COMMENT:**

1. No information was provided as to whether metabolites found were active.
2. One of the objectives was to determine the pharmacokinetics of aliskiren metabolites. However, no pharmacokinetic parameters seem to have been calculated.

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**STUDY (SPP100CRD15) SSP100A 0023 – A PHASE I, OPEN-LABEL, STUDY TO EVALUATE THE ABSORPTION, METABOLISM, KINETICS AND EXCRETION FOLLOWING A SINGLE ORAL DOSE OF [<sup>14</sup>C]-ALISKIREN TO HEALTHY MALE SUBJECTS.**

**STUDY INVESTIGATOR AND SITE:**

**REPORT # (SPP100CRD15) SSP100A 0023**

**VOLUME in EDR, Section 8**

**STUDY DATES: September 19 – November 2, 2001**

**Objectives:**

**Primary Objectives**

- 1) To evaluate the pharmacokinetics of total radioactivity in blood, plasma, urine and faeces and of Aliskiren in plasma following a single oral administration of a 150-mg dose of [<sup>14</sup>C]-Aliskiren to healthy male subjects.
- 2) To determine the urinary and faecal excretion of radioactivity following oral administration of [<sup>14</sup>C]-Aliskiren in healthy male subjects.
- 3) To examine the pattern of metabolites in plasma, urine and/or faeces following oral administration of [<sup>14</sup>C]-Aliskiren in healthy male subjects.
- 4) To characterize and possibly identify relevant metabolites if formed, and to determine their pharmacokinetics, if feasible.

**Secondary Objective**

- 5) To further determine the safety and tolerability of a single oral dose of [<sup>14</sup>C]-Aliskiren in healthy male subjects.

Note: Objectives 3 and 4 will be investigated by Novartis Pharma AG, Basel, Switzerland and reported separately.

**Investigational Products**

Investigational product	Batch number	Expiry date
Aliskiren (1500 mg) powder	S100B2001003	Aug 2002
[ <sup>14</sup> C]-Aliskiren (11.85 mg) powder	CFQ12601	NA

**STUDY DESIGN**

This was a single-site, open-label design. Four (4) normal healthy male subjects received a single oral dose of 150-mg Aliskiren containing a total of approximately 100 µCi ± 20% [<sup>14</sup>C]-Aliskiren. Test material was administered to overnight fasted subjects (i.e., at least 8 h). Subjects were confined at the clinical site from Check-in (Day -1) until study completion on Day 11 (i.e., 240 h post-dose).

The 150-mg dose level of [<sup>14</sup>C]-Aliskiren was selected, as this is the expected therapeutic dose.

Note: This study was not conducted in the fasted state whereas the prior mass balance study reviewed was conducted in the fasted state until four hours after study drug administration. Subjects received breakfast 30 minutes after the administration of study drug in this study.

Time	Food and fluid details
Evening of Day -1	Evening meal
From 21:00 on Day -1 until dosing	Fast from food and fluids, except water
At dosing	100 mL of sterile water with dissolved test material; and 2 x 50 mL of tap water to rinse dosing container
Approximately 0.5 h post-dose	Breakfast
Approximately 4 h post-dose	Lunch
Approximately 10 h post-dose	Evening meal
Approximately 13 h post-dose	Evening snack

Note: After Day 1, other meals were provided at appropriate times on each day.

## PK SAMPLE COLLECTION/CALCULATIONS AND STATISTICAL ANALYSIS:

### Blood samples

Whole blood and plasma PK profiles of Aliskiren-equivalent total radioactivity were evaluated using blood samples obtained at pre-dose (0 hr) and at post-dose times of: 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48 and 72 hours. Plasma PK profiles of unchanged Aliskiren were also evaluated through samples obtained at the time point listed above and additional times of 96, 120, 144, 168, 192, 216, and 240 hours post-dose. Sampling was however terminated at 72 hours based on negligible radioactive levels after 72 hours post-dose.

### Urine samples

Urine mass balance recovery of Aliskiren-equivalent total radioactivity was evaluated using samples obtained at pre-dose (-12 to 0 hour) and at post-dose intervals of: 0 to 6, 6 to 12, 12 to 24, 24 to 48, 48 to 72, 72 to 96, 96 to 120, 120 to 144, 144 to 168, 168 to 192, 192 to 216 and 216 to 240 hours.

### Fecal samples

Faecal recovery of Aliskiren-equivalent total radioactivity was evaluated using samples obtained at pre-dose (-24 to 0 hour) and at the post-dose intervals of: 0 to 24, 24 to 48, 48 to 72, 72 to 96, 96 to 120, 120 to 144, 144 to 168, 168 to 192, 192 to 216 and 216 to 240 hours.

Note: Metabolite profiling was not reported in these study results.

### Pharmacokinetic parameters calculated

Parameter	Definition
AUC(0-t <sub>z</sub> )	Area under the plasma drug concentration-time curve from time zero up to the time of the last quantifiable plasma drug concentration t <sub>z</sub> using the log-linear trapezoidal rule
AUC(0-∞)	Area under the plasma drug concentration-time curve from time zero to infinity AUC(0-∞) = AUC(0-t <sub>z</sub> ) + C <sub>t</sub> /λ <sub>z</sub>
%AUC <sub>ex</sub>	Percentage of AUC(0-∞) extrapolated from the time of the last quantifiable plasma drug concentration to infinity
C <sub>max</sub>	Maximum measured plasma drug concentration
t <sub>max</sub>	Time of maximum observed concentration
λ <sub>z</sub>	Apparent terminal phase rate constant
t <sub>½</sub>	Apparent terminal phase half-life = ln(2)/λ <sub>z</sub>
t <sub>z</sub>	Time of occurrence of the last plasma drug concentration above the lower limit of quantification

## RESULTS

Four subjects were recruited and entered the study. All subjects completed the study in accordance with the protocol.

**Mass balance and pharmacokinetic (PK) analysis results:**

**(i) Mass balance for Aliskiren-equivalent total radioactivity:**

The arithmetic mean 0- to 240-h post-dose recovery of total radioactivity was approximately 89%, with recovery in individual subjects ranging from 85.1 to 91.3%. The main route of excretion of Aliskiren-equivalent total radioactivity following oral administration was via the faeces. A mean of 88.1% of the dose was excreted in faeces and 1.06% was excreted in urine through 240 h post-dose.

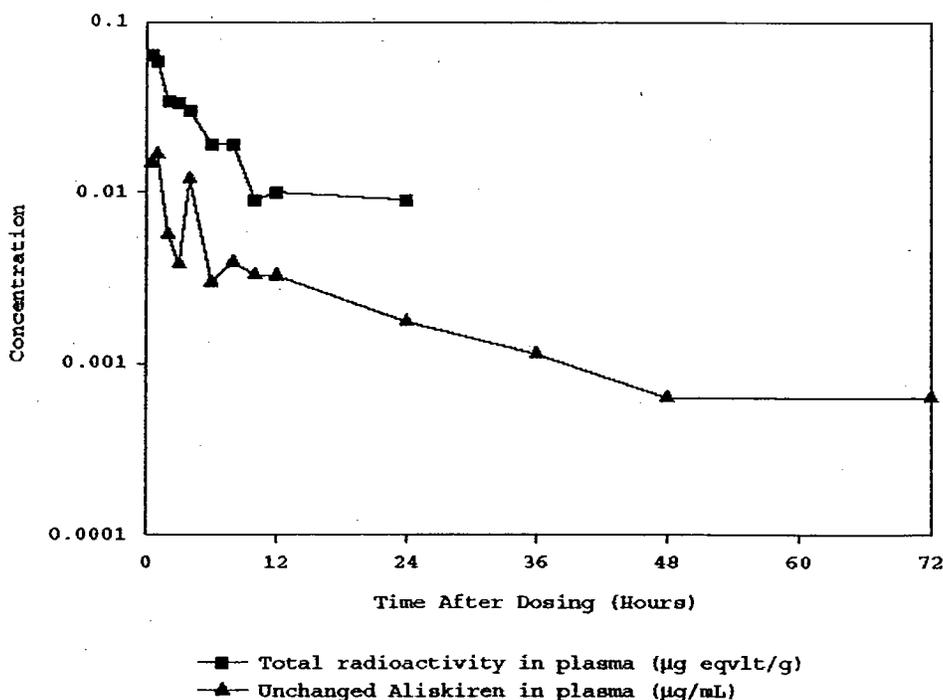
**(ii) Comparison of unchanged Aliskiren PK to Aliskiren-equivalent total radioactivity PK:**

Measurable levels of Aliskiren-equivalent total radioactivity were observed in plasma up to 24 h post-dose while measurable levels of unchanged Aliskiren were noted up to 72 h post-dose. Unchanged Aliskiren in plasma accounted for about 11 to 34% of Aliskiren-equivalent total radioactivity at the various time points up to 24 h post-dose, suggesting that a majority of circulating radioactivity is in the form(s) of metabolite(s). A summary comparison table of the arithmetic mean PK parameters of unchanged Aliskiren in plasma and Aliskiren-equivalent total radioactivity in plasma is shown in the table below:

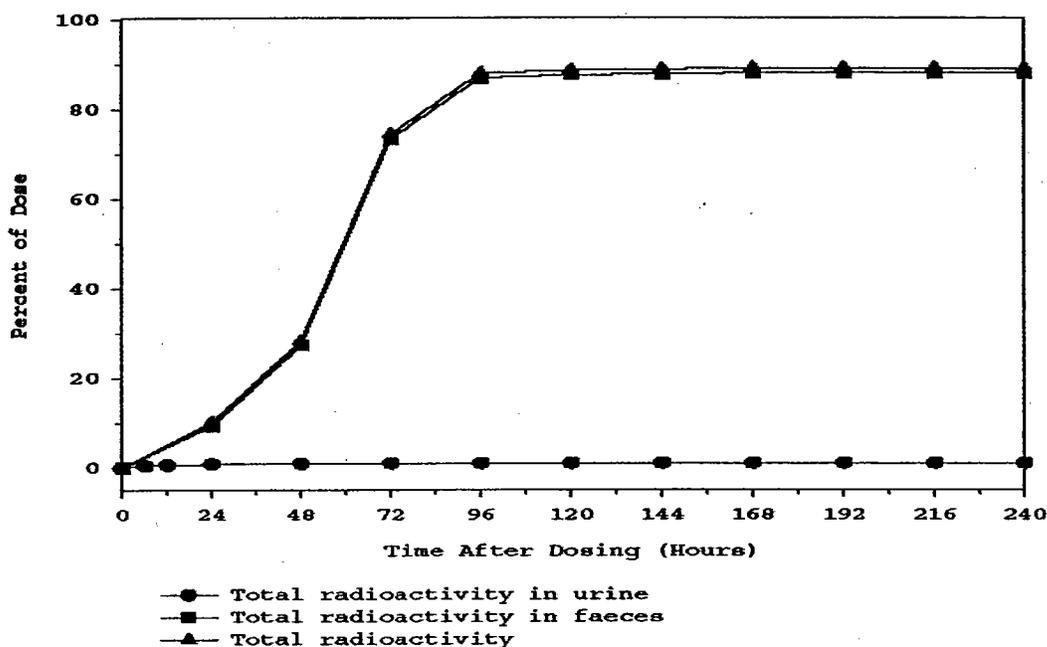
PK parameter*	Unchanged Aliskiren	Aliskiren equivalent total radioactivity
C <sub>max</sub>	22.9 ng/mL	63.5 ng-equivt/g
AUC <sub>0-∞</sub>	169 ng.hr/mL	604 ng-equivt.hr/g
t <sub>max</sub>	1 h	0.5 h
t <sub>1/2</sub>	32.7 h	ND

\*Arithmetic mean reported for C<sub>max</sub>, AUC<sub>0-∞</sub> and t<sub>1/2</sub>; median reported for t<sub>max</sub>

Arithmetic Mean Concentration of Total Radioactivity in Plasma and Unchanged Aliskiren in Plasma After Single Oral Dose of [<sup>14</sup>C]-Aliskiren to Healthy Male Subjects in the Log-linear Scale.



**Arithmetic Mean Cumulative Percent of Radioactivity in Urine and Faeces and of Aliskiren After Single Oral Dose of [<sup>14</sup>C]-Aliskiren to Healthy Male Subjects**



**SAFETY**

Two adverse events (mild in severity – GI disorder, retching) were reported with one thought to be due to study drug.

**CONCLUSIONS**

- The results indicate rapid oral absorption of Aliskiren and total radioactivity, with arithmetic mean 0- to 240-h post-dose recovery of total radioactivity being approximately 89% and recovery in individual subjects ranging from 85.1 to 91.3%. A mean terminal t<sub>1/2</sub> of 32.7 h was determined for unchanged Aliskiren in plasma.
- The main route of excretion of Aliskiren-equivalent total radioactivity following oral administration was via the faeces. A mean of 88.1% of the dose was excreted in faeces and 1.06% was excreted in urine through 240 h post-dose.
- Unchanged Aliskiren in plasma accounted for about 11 to 34% of Aliskiren-equivalent total radioactivity at the various time points up to 24 h post-dose, suggesting that a majority of circulating radioactivity is in the form(s) of metabolite(s).
- The C<sub>max</sub> and AUC<sub>(0-∞)</sub> ratios of unchanged Aliskiren to Aliskiren-equivalent total radioactivity in plasma were about 36% and 28%, respectively and similar to the ratios of unchanged Aliskiren to Aliskiren-equivalent total radioactivity concentrations in plasma.
- A single oral 150-mg dose of Aliskiren (including approximately 100 μCi ± 20% [<sup>14</sup>C] radioactivity) was well tolerated.

**REVIEWER’S COMMENT**

This study did not contribute to the prior results of study SPP100A 2223 conducted in the year 2005. This study was conducted earlier than most in-vitro studies were performed. As a result, some of the conclusions made in this study regarding the metabolism of Aliskiren (third bullet in conclusions section) are inaccurate since the drug is minimally metabolized and most of the drug is eliminated unchanged in the faeces due to poor drug absorption as demonstrated in the later study 2223.

**Study SPP100A 2105 – AN OPEN-LABEL, EXPLORATORY STUDY TO DETERMINE THE CONCENTRATION OF ALISKIREN IN FECES, RECTAL MUCOSA BIOPSY SPECIMENS, AND PLASMA STEADY STATE AFTER ORAL ADMINISTRATION OF 300 MG IN HEALTHY VOLUNTEERS**

**STUDY INVESTIGATOR AND SITE:**



**REPORT # 2105**

**EDR VOLUME** Submission dated November 7, 2006

**STUDY DATES:** August 14, 2006 – August 29, 2006

**Objectives:**

**Primary objective:**

- To quantify the concentrations of aliskiren in feces, rectal mucosal biopsy specimens, and plasma at plasma steady-state after treatment with 300 mg aliskiren daily

**Secondary objective:**

- To explore correlations between aliskiren concentrations in feces, rectal mucosal biopsy specimens, and plasma

**FORMULATION:**

Aliskiren 300 mg tablet (Batch# X299IA, KN# 6000937.006, Exp. Date 04/2006) by Novartis

**Design:** This was an open-label, single group study in healthy volunteers. Aliskiren concentrations in feces and rectal mucosal biopsy specimens were determined following daily administration of the highest anticipated therapeutic dose of aliskiren (300 mg p.o.) to achieve steady state plasma drug concentrations (study scheme depicted below).

Screening	Baseline	Treatment Period				
			Plasma, Fecal and Rectal Mucosal Drug Concentrations			End-of Study
Day -22 to Day -2	Day -1	Days 1-5	Days 6-7	Days 8-12*	Day 9, 10, 11, or 12**	Day 9, 10, 11, or 12
			Plasma samples obtained pre-dose and at the time of each natural bowel movement		Plasma sample obtained at the time of sigmoidoscopy	
			Fecal samples obtained pre-sigmoidoscopy - natural bowel movements		Fecal sample obtained during sigmoidoscopy and up to 4 hours post-sigmoidoscopy	
					Rectal mucosal biopsies obtained via flexible sigmoidoscopy	

\* - Collection of pre-sigmoidoscopy fecal samples began whenever subjects had their first natural bowel movement during this interval.

\*\* - Flexible sigmoidoscopy occurred the day after the first natural bowel movement, but no later than Day 12, by protocol.

**Duration of treatment:** One multiple dose treatment period of 9-12 days

**Drug concentration variables: schedule of assessments**

• **Fecal aliskiren concentrations**

- Pooled fecal samples: pre-sigmoidoscopy fecal collections after dosing on Day 8 until the time of flexible sigmoidoscopy (Day 9, 24-30 hours), a fecal sample (if visible) just prior to sigmoidoscopy (day 9), and post-sigmoidoscopy fecal collections up to 4 hours after sigmoidoscopy
- Individual bowel movements: after each natural bowel movement (during both pre- and post-sigmoidoscopy fecal collection) beginning after dosing on Day 8

- **Rectal mucosal biopsy aliskiren concentrations:** five (5) rectal mucosal biopsy samples obtained via flexible sigmoidoscopy approximately 2 to 4 hours after the final dose of aliskiren on Day 9 (four of the samples pooled for aliskiren concentration measurement)

• **Plasma aliskiren concentrations**

- Pre-dose (trough on Days 6, 7, 8, 9)
- At time of individual bowel movements (after drug administration on Day 8 until 4 hrs after sigmoidoscopy on Day 9)
- During sigmoidoscopy near time of biopsy (Day 9)

- **Aliskiren concentrations in isotonic saline rinses of biopsies:** approximately 1 mL aliquots of isotonic saline (approximately 5mL in each beaker) used to rinse the rectal mucosal biopsy specimens sampled for each of three rinses

**ANALYTICAL METHODS:**

**Analytes - media and methods:**

Plasma aliskiren concentration was determined by a LC-MS/MS method. The LLOQ is 0.5 ng/mL in plasma.

Fecal aliskiren, rectal mucosal aliskiren, and aliskiren in isotonic saline rinses of biopsy tissue were determined by LC-MS/MS methods. The LLOQs for each of the fecal samples, rectal mucosal biopsy specimens, and isotonic saline rinses were 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:**

**Statistical methods:** Descriptive statistics (including arithmetic mean, standard deviation, minimum, median, and maximum) are provided to summarize concentrations of aliskiren in feces, rectal mucosal biopsies, and plasma at various time points during and after treatment with aliskiren 300 mg daily. The average plasma trough steady state aliskiren concentration at ( $C_{PTSS}$ ) was calculated for each subject as the average pre-dose value of the plasma concentration on Days 8 and 9. Mean  $C_{PTSS}$  was calculated for the study population, as were mean plasma aliskiren concentrations at the time of natural bowel movements ( $C_{PBm}$ ) and at the time of sigmoidoscopy ( $C_{PSig}$ ).

Fecal aliskiren concentrations are summarized as the weighted average ( $C_{Fec\_Avg}$ ), minimum ( $C_{Fec\_Min}$ ), and maximum ( $C_{Fec\_Max}$ ) values calculated for each individual subject using data obtained from all fecal collections beginning after dosing on Day 8 and continuing until the last fecal collection after sigmoidoscopy. The weighted average thus includes the pre-sigmoidoscopy fecal collections, the sigmoidoscopy fecal sample (if obtained), and any post-sigmoidoscopy collections (if obtained). Mean  $C_{Fec\_Avg}$ ,  $C_{Fec\_Min}$ , and  $C_{Fec\_Max}$  were calculated for the population, as were fecal aliskiren concentrations specifically at the time of natural bowel movements ( $C_{Fec\_Bm}$ ) and at the time of sigmoidoscopy ( $C_{Fec\_Sig}$ ).

For rectal mucosal tissue, four biopsy specimens per subject (approximately 15 mg each) were pooled to obtain a single measurement for aliskiren concentration ( $C_{ReM}$ ) for each subject. Descriptive statistics were calculated for  $C_{ReM}$  for the population. Aliskiren concentrations are listed and a summary of descriptive statistics provided for each aliquot rinse in isotonic saline for each of the four rectal mucosal biopsies for each subject, as are the average aliskiren concentrations from each isotonic saline rinse over four rectal mucosal biopsies.

Data listings and a descriptive summary are provided for the following ratios of concentration data: ( $C_{ReM} / C_{PSig}$ ), ( $C_{ReM} / C_{PTSS}$ ), ( $C_{Fec\_Avg} / C_{ReM}$ ), ( $C_{Fec\_Max} / C_{ReM}$ ), ( $C_{Fec\_Sig} / C_{ReM}$ ), ( $C_{Fec\_Avg} / C_{PTSS}$ ), ( $C_{Fec\_Max} / C_{PTSS}$ ), ( $C_{Fec\_Sig} / C_{PSig}$ ), and ( $C_{Fec\_Bm} / C_{PBm}$ ).

Confirmation that aliskiren was at steady state after 6 days of treatment was determined by comparing pre-dose trough plasma drug concentrations on Days 6, 7, and 8. Log-transformed aliskiren plasma concentrations were analyzed using a mixed effect model with subject as a random effect and day as a fixed effect. The point estimates for the differences between days and the corresponding 90% confidence intervals on the log-scale were calculated. These values were back transformed to give point estimates and 90% confidence intervals for the ratios of means on the original scale.

Data were plotted and analyses performed to assess any correlations between the following parameters of aliskiren concentrations:

- Rectal mucosal concentration ( $C_{ReM}$ ; Y-axis) and plasma concentration at the time of sigmoidoscopy ( $C_{PSig}$ ; X-axis)
- Rectal mucosal concentration ( $C_{ReM}$ ; Y-axis) and plasma trough steady state concentration ( $C_{PTSS}$ ; X-axis)
- Rectal mucosal concentration ( $C_{ReM}$ ; Y-axis) and average fecal concentration ( $C_{Fec\_Avg}$ ; X-axis)
- Rectal mucosal concentration ( $C_{ReM}$ ; Y-axis) and maximum fecal concentration ( $C_{Fec\_Max}$ ; X-axis)
- Rectal mucosal concentration ( $C_{ReM}$ ; Y-axis) and fecal concentration at sigmoidoscopy ( $C_{Fec\_Sig}$ ; X-axis)
- Plasma trough steady state concentration ( $C_{PTSS}$ ; Y-axis) and average fecal concentration ( $C_{Fec\_Avg}$ ; X-axis)
- Plasma trough steady state concentration ( $C_{PTSS}$ ; Y-axis) and maximum fecal concentration ( $C_{Fec\_Max}$ ; X-axis)
- Plasma concentration at sigmoidoscopy ( $C_{PSig}$ ; Y-axis) and fecal concentration at sigmoidoscopy ( $C_{Fec\_Sig}$ ; X-axis)
- Plasma at the time of bowel movement ( $C_{PBm}$ ; Y-axis) and the corresponding fecal concentration at the time of bowel movement ( $C_{Fec\_Bm}$ ; X-axis)

## **RESULTS:**

### **Aliskiren concentrations in isotonic saline rinses of rectal mucosal biopsy samples**

The concentration of aliskiren in the final saline rinses of the rectal mucosal biopsy samples was 0.7 ng/mL. The aliskiren content of the final saline rinses was an average of only 4.3% of the total aliskiren recovered in the biopsy samples (range of 0.8% to 9.0%), with values less than 5% in 11 of 14 of the subjects. These data indicate that potential contamination of tissue samples from luminal content or feces was probably small. Therefore, aliskiren concentration measured in rectal mucosal biopsy samples is a reasonable estimate of aliskiren rectal mucosal tissue concentration.

### **Plasma aliskiren concentrations: assessment of steady state**

Plasma trough aliskiren concentrations on Days 6, 7, and 8 are summarized and compared in Table 1. There were no significant differences between concentrations on Day 6 or Day 7 compared to Day 8. The ratios of the geometric means between Day 6 and Day 8 and between Day 7 and Day 8 were approximately 1, with the 90% confidence intervals falling within 0.8 and 1.25, indicating that steady state aliskiren plasma concentration was achieved by Day 6.

**Table 1 Assessment of steady state**

Comparison	Day	n	Arithmetic mean	S.D.	Percent difference	P-value	Ratio geom. means	90% CI for ratio
Day 6 vs Day 8	Day 6	15	24.36	7.49	-4.30	0.59	0.97	(0.88, 1.07)
	Day 8	15	25.45	9.22				
Day 7 vs Day 8	Day 7	15	26.08	10.54	2.46	0.82	1.01	(0.92, 1.11)
	Day 8	15	25.45	9.22				

**Fecal, rectal mucosal, and plasma aliskiren concentrations**

Fecal, rectal mucosal, and plasma trough aliskiren concentrations are summarized in Table 2. The ratios of average aliskiren concentrations in feces to rectal mucosa, fecal to plasma concentrations, and rectal mucosa to plasma concentrations are summarized in Table 3.

As expected, the highest aliskiren concentrations were found in feces ( $C_{Fec\ Avg} = 1,526,923$  ng/g;  $C_{Fec\ Max} = 1,899,429$  ng/g;  $C_{Fec\ Sig} = 238,986$  ng/g), the average of which was approximately 90-fold higher than that in rectal mucosal tissue ( $C_{ReMi} = 22,192$  ng/g), which was approximately 1000 times higher than the average plasma steady state trough concentrations ( $C_{PTSS} = 24.9$  ng/mL) and approximately 150-fold higher than the plasma concentration at the time of biopsy ( $C_{PSig} = 216.9$  ng/mL).

**Table 2 Descriptive statistics for fecal, rectal mucosal, and plasma aliskiren concentrations**

	$C_{Fec\ Avg}^*$ (ng/g)	$C_{Fec\ Max}^*$ (ng/g)	$C_{Fec\ Sig}$ (ng/g)	$C_{Fec\ BM}$ (ng/g)	$C_{ReMi}^{**}$ (ng/g)	$C_{PTSS}^{***}$ (ng/mL)	$C_{PSig}$ (ng/mL)	$C_{PBM}$ (ng/mL)
n	14	14	7	14	14	15	13	14
Mean	1526923	1899429	238986	1534223	22192	24.9	216.9	154.1
SD	1315980	1467931	314644	1318553	15572	9.8	204.4	197.0
Min								
Median	1233961	1620000	69800	1240000	17850	24.1	130.0	85.9
Max								

$C_{PTSS}$  = average plasma trough steady state aliskiren concentration;  $C_{PBM}$  = mean plasma aliskiren concentrations at the time of natural bowel movements;  $C_{PSig}$  = mean plasma aliskiren concentrations at the time of sigmoidoscopy;  $C_{Fec\ Avg}$  = the mean weighted average fecal aliskiren concentration from all fecal samples (pre-, during, and post-sigmoidoscopy);  $C_{Fec\ Min}$  = the mean minimum fecal aliskiren concentration, and  $C_{Fec\ Max}$  = the mean maximum fecal aliskiren concentration;  $C_{Fec\ BM}$  = the mean fecal concentration at the time of natural bowel movements;  $C_{ReMi}$  = the mean aliskiren concentration in rectal mucosal biopsy samples.

\* - Average fecal aliskiren concentration = the weighted average fecal concentration calculated over all fecal samples beginning after dosing on Day 8 and continuing until the last fecal collection after sigmoidoscopy. The maximum fecal concentration and average fecal concentration were identical in three subjects for whom only one fecal sample was available.

\*\* - Rectal mucosal aliskiren concentration, based on pooled samples from four rectal mucosal biopsies. The sample weights at the one of the centers were much larger than at the other, but the drug concentrations were similar.

\*\*\* - Average pre-dose aliskiren plasma trough concentration calculated from Day 8 through the day of sigmoidoscopy (Day 9).

**Table 3 Ratios of rectal mucosal to plasma, fecal to plasma, and fecal to rectal mucosal aliskiren concentrations**

	$C_{ReM}/C_{PSig}$	$C_{ReM}/C_{PTSS}$	$C_{Fec\_Avg}/C_{ReM}$	$C_{Fec\_Max}/C_{ReM}$	$C_{Fec\_Sig}/C_{ReM}$	$C_{Fec\_Avg}/C_{PTSS}$	$C_{Fec\_Min}/C_{PTSS}$	$C_{Fec\_Sig}/C_{PSig}$	$C_{Fec\_Bm}/C_{PBm}$
<i>n</i>	13	14	14	14	7	14	14	6	14
<b>Mean</b>	163.2	984.9	88.5	115.2	9.93	72908	87786	1450	26039
<b>SD</b>	115.8	701.1	107.6	141.1	7.35	72018	76550	1418	34953
<b>Min</b>									
<b>Med</b>	141.1	810.6	54.3	71.4	7.83	49576	60740	1226	16010
<b>Max</b>									
<b>Correl Coeff (r)</b>	-0.042	0.122	0.152	0.061	0.934	-0.184	-0.086	-0.235	-0.385
<b>P-val</b>	0.892	0.677	0.604	0.836	0.002	0.528	0.771	0.653	0.174

$C_{PTSS}$  = average plasma trough steady state aliskiren concentration;  $C_{PBm}$  = mean plasma aliskiren concentrations at the time of natural bowel movements;  $C_{PSig}$  = mean plasma aliskiren concentrations at the time of sigmoidoscopy;  $C_{Fec\_Avg}$  = the mean weighted average fecal aliskiren concentration;  $C_{Fec\_Min}$  = the mean minimum fecal aliskiren concentration, and  $C_{Fec\_Max}$  = the mean maximum fecal aliskiren concentration;  $C_{Fec\_Bm}$  = the mean fecal concentration at the time of natural bowel movements;  $C_{ReM}$  = the mean aliskiren concentration in rectal mucosal biopsy samples.

**Table 4 Comparison of average fecal aliskiren concentrations in humans and rats**

	N	Fecal aliskiren concentration (µg/g) Mean (SD); Median	Ratio of Means (Rat: Human)	Ratio of Medians (Rat: Human)
Rat studies (TOX 057277 and TOX 0570299); Dose = 250 mg/kg/day*	10	13949 (3381); 14100	9.1	11.4
Human study (CSPP100A 2105); Dose = 300 mg/day	14	1527 (1316); 1234	-	-

\* These data represent the combined results of a 4-week and a 13-week study in which the dosage and route of administration (feed admixture) were identical. 250 mg/kg/day was the NOAEL dose.

**GI mucosal aliskiren concentrations in rats versus humans**

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

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

**SPONSOR'S CONCLUSIONS:**

- At steady state, following daily oral administration of 300 mg aliskiren:
  - Average fecal aliskiren concentration was  $1527 \pm 1316 \mu\text{g/g}$ .
  - The maximum fecal aliskiren concentration was  $1899 \pm 1468 \mu\text{g/g}$ .
  - The range for fecal aliskiren concentration (24-30 hrs) was 10.9 - 5010  $\mu\text{g/g}$ .
  - Rectal mucosal aliskiren concentration was  $22.2 \pm 15.6 \mu\text{g/g}$ .
  - Plasma aliskiren concentration at sigmoidoscopy was  $216.9 \pm 204.4 \text{ ng/mL}$ .
  - Plasma trough steady state aliskiren concentration was  $24.9 \pm 9.8 \text{ ng/mL}$ .
- Concentrations of aliskiren from sequential rinses of rectal mucosal biopsy samples indicated no significant contamination of tissue from luminal content/fecal matter.
- Both fecal and rectal drug concentrations showed high inter-subject variability.
- Average human fecal aliskiren concentration (over 24-36 hours) at a dose of 300 mg per day for 9 days was approximately 10-fold lower than rat fecal concentrations at the NOAEL dose (250 mg/kg/day in feed for 4 and 13 weeks).
- Human rectal mucosal aliskiren concentration was 6-fold lower than rat colonic mucosal aliskiren concentration at the NOAEL dose.
- Gastrointestinal tissue aliskiren concentrations may be determined by local luminal drug exposure as most of the variability in rectal mucosal drug concentrations could be explained by fecal drug concentration at the time of biopsy. This conclusion is based, however, on data from a very small number of subjects.

**REVIEWER'S COMMENT:**

1. The colonic concentrations of Aliskiren in the rat (502  $\mu\text{g/g}$ ) are up to three times lower than the fecal Aliskiren concentrations in the rectum of humans (1527  $\mu\text{g/g}$ ).

**APPEARS THIS WAY  
ON ORIGINAL**

**STUDY SSP100A 2207 – A RANDOMIZED, OPEN-LABEL, SINGLE-DOSE, TWO-PERIOD, CROSSOVER STUDY IN HEALTHY SUBJECTS TO EVALUATE THE EFFECT OF FOOD ON THE SPP FINAL MARKET IMAGE (FMI) TABLET.**

**STUDY INVESTIGATOR AND SITE:**

**REPORT # 2207  
EDR VOLUME 6**

**STUDY DATES: April 16 – August 12, 2005**

**Objective:**

To evaluate the effect of food on the bioavailability of the SPP100 300-mg FMI tablet

**Formulation:**

Aliskiren 300 mg, tablet, Novartis (Batch No: X316 1004 KN# 6000937.004; Exp Date: Not provided)

**Design:** Randomized, open-label, single-dose, two-period, crossover design. A total of 32 healthy male and/or female subjects were enrolled and received study drug; 30 subjects completed all treatments and procedures.

Each subject participated in a screening period (Day -21 to -2), a baseline evaluation in each treatment period (Day -1), two treatment periods with at least 10-day washout between the two treatment periods, and an end-of-study evaluation. Eligible subjects were randomized to one of two treatment sequences, with 15 subjects in each of the two sequences.

**Study design**

Screening (Day -21 to -2)	Period 1	10-day washout	Period 2	Study completion
	FMI tablet; Fasted (n=15)		FMI tablet; Fed (n=15)	
	FMI tablet; Fed (n=15)		FMI tablet; Fasted (n=15)	

On Day 1 of each treatment period, subjects received either a single, 300 mg oral dose of SPP100 (1 x 300 mg FMI tablet) in a fasted or fed state, depending on their assigned sequence. Subjects who were dosed in the fasted state received their dose of aliskiren (SPP100) after fasting for at least 10 hours and remained in the fasted state for the next 4 hours. Subjects who were dosed in the fed state consumed a FDA, standardized, high-fat breakfast after fasting for at least 10 hours and within 30 minutes prior to dosing.

For both treatment periods, subjects were admitted to the study center on Day -1, at least 12 hours prior to study drug administration. Safety assessments were performed and inclusion/exclusion criteria were reviewed to confirm subject eligibility. Subjects remained at the study center until 24 hours post dose for pharmacokinetic and safety assessments. Subjects were then discharged, but returned to the study center on an ambulatory basis on Days 3, 4, 5, 6 and 7 for additional pharmacokinetic assessments. The washout period between treatment periods was at least 10 days.

An end-of-study evaluation was performed on the last day of the last treatment period, after collection of the final PK blood sample.

Except for medication which was required to treat adverse events, no medication other than study drug was allowed from 14 days prior to the first dosing of study treatment until all of the end-of-study evaluations were conducted. Administration of concomitant medication may have required the subject to be replaced. Administration of acetaminophen was acceptable but had to be documented in the CRF. Decisions regarding replacements of subjects requiring concomitant medication were discussed with the sponsor on a case-by-case basis. The administration of any such medication (including over-the-counter medications) was documented on the Concomitant medications / Significant non-drug therapies CRF page.

Intake of xanthine (e.g., caffeine) containing food or beverages was discontinued 48 hours before dosing. Consumption of such foods and beverages (i.e., coffee, tea, soda, chocolate) was not permitted at any time while the subjects were domiciled.

A physician was present for at least the first 4 hours after dosing on Day 1 in each treatment period and available by pager at all other times throughout the study.

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

- No strenuous physical exercise (e.g., weight training, aerobics, football) for 7 days before dosing until after the end of study evaluation,
- No alcohol for 72 hours before dosing until after the end-of-study evaluation, and
- No intake of fruit juices, including grapefruit juice, due to pH modifying effects.

#### ANALYTICAL METHODS:

Analytes, media and methods: parent drug in plasma by HPLC/MS/MS method; LOQ at 0.5 ng/ml  
Analytical methods acceptable and validated.

#### PK SAMPLE COLLECTION/CALCULATIONS AND STATISTICAL ANALYSIS:

Blood collection (5 ml blood per sample in lithium heparin tubes (plasma)): pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120 and 144 h post dose

PK parameters:  $AUC_{0-\infty}$ ,  $AUC_{0-t}$ ,  $AUC_{0-t_{max}}$ ,  $C_{max}$ ,  $t_{max}$ ,  $Cl_{ff}$ ,  $Vd_{ff}$ ,  $t_{1/2}$  from plasma concentration-time data

PK evaluations for food effect: All subjects who had complete pharmacokinetics profiles are included in the pharmacokinetic analysis. Descriptive statistics are provided for the derived PK parameters from different treatments.  $AUC_{0-\infty}$  and  $C_{max}$  are considered as the primary pharmacokinetic parameters in the evaluation of food effect.

Statistical methods: Statistical analysis of effect of food on SPP100 was performed by comparing the pharmacokinetic parameters  $AUC_{0-\infty}$ ,  $AUC_{0-t}$ ,  $AUC_{0-t_{max}}$ ,  $C_{max}$  and  $t_{max}$  during fasted and fed conditions.

Analysis of variance (ANOVA) was performed on log-transformed AUCs and  $C_{max}$  data using the PROC MIXED SAS procedure to generate results for inference tables. The sources of variation in the analysis model include sequence, period and treatment as fixed effects, and with subject (sequence) as a random effect. Appropriate ESTIMATE statements and 90% confidence intervals for the test-reference ratios (fed/fasted) were constructed.

Statistical analysis for  $t_{max}$  was performed by a non-parametric method.

The study was powered to detect a food effect on mean PK parameter of aliskiren by a magnitude of 50% or more. Aliskiren has a CV value in the range of 0.40 to 0.70. For a sample size of 30 subjects, the power of detecting a significant food effect was evaluated for various combinations of CV and true mean difference (range 30% to 60%), in the table below. It can be seen, for instance, that when CV = 0.60, the power will reach at least 84% or higher when the true difference in mean PK parameters is 50% or more.

#### RESULTS:

**Safety and tolerability:** There were no deaths or serious adverse events reported in this study. Aliskiren was well tolerated in both the fasted and fed states. Seventeen (17) subjects experienced a total of 18 adverse events (AEs). A total of 7 subjects in the fasted treatment experienced 9 adverse events (9/18, 50%). In the fed treatment, a total of 11 subjects experienced 9 adverse events (9/18, 50%). The majority of AEs were mild (16/18, 88.9%) and resolved spontaneously without treatment. Two AEs were moderate in severity (2/18, 11.1%); both were incidences of headache and Tylenol was administered as treatment. Only one adverse event, nausea (Subject 5124, fasted state, two incidences), was suspected to be related to study drug.

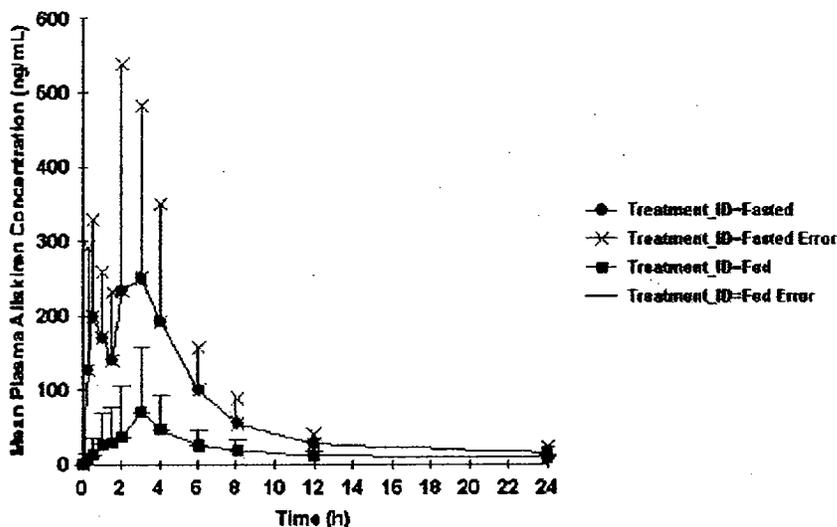
There were no clinically significant ECG abnormalities. Laboratory values slightly outside the normal range were not considered clinically significant.

### Pharmacokinetics

Pharmacokinetic parameters calculated are listed below:

Treatment ID	C <sub>max</sub> (ng/mL)	t <sub>max</sub> (h)	AUC <sub>(0-t)</sub> (ng x h/ml)	t <sub>1/2</sub> (h)	AUC <sub>(0-∞)</sub> (ng x h/ml)	Vd/f (mL)	CL/f (mL/h)	AUC <sub>(0-tmax)</sub> (ng x h/ml)
<b>Fasted</b>								
N	32	32	32	32	32	32	32	32
Mean	453.2	2.1	2315	54	2437	12051345	150550	355
SD	308.5	1.3	1165	14	1194	6078837	65941	266
Min								
Median	386.5	2.0	2008	52	2122	11312449	141488	348
Max								
CV%	68.1	60.8	50.3	26.4	49.0	50.4	43.8	75.0
<b>Fed</b>								
N	31	31	31	31	31	31	31	31
Mean	92.4	3.2	707	46	767	32842810	577002	92
SD	95.2	1.7	434	15	464	15060301	378042	79
Min								
Median	46.4	3.0	654	46	709	30622330	423088	80
Max								
CV%	103.0	51.6	61.4	32.6	60.5	45.9	65.5	85.4

Mean Aliskiren concentrations under fed and fasted state in healthy volunteers



**Ratios of the geometric means and the corresponding 90% confidence intervals in fed subjects relative to fasted subjects**

Parameter	Ratio of geometric means (A:B)	90% CI for ratio
AUC <sub>0-∞</sub> (ng x h/mL)	0.29	(0.24, 0.34)
AUC <sub>0-4</sub> (ng x h/mL)	0.28	(0.24, 0.34)
AUC <sub>0-4max</sub> (ng x h/mL)	0.26	(0.18, 0.38)
C <sub>max</sub> (ng/mL)	0.15	(0.11, 0.20)

Treatment A = Aliskiren 300mg Fed

Treatment B = Aliskiren 300mg Fasted

The summary of the analysis results of t<sub>max</sub> for aliskiren is presented in table below. The median increase in t<sub>max</sub> was one hour when aliskiren was administered with food compared to in the fasted state.

**The effect of food on aliskiren FMI tablet bioavailability based on t<sub>max</sub>**

Parameter	Median difference (A - B)	p-value
t <sub>max</sub> (ng/mL)	1.0	0.001

Treatment A = Aliskiren 300mg Fed

Treatment B = Aliskiren 300mg Fasted

**CONCLUSIONS:**

- Ingestion of a high-fat meal 30 minutes prior to oral administration of aliskiren reduces drug exposure (AUC and C<sub>max</sub> decreased by 71% and 85%, respectively) and delays drug absorption (median t<sub>max</sub> increased by 1 hour).
- Aliskiren was safe and well tolerated in healthy subjects during fasted and fed conditions.

**REVIEWER'S COMMENT:**

1. Reviewer concurs.
2. Aliskiren should be taken without food since the changes in rate and extent of absorption are remarkable and may influence what is already a shallow dose-response curve.

**APPEARS THIS WAY  
ON ORIGINAL**

**STUDY SPP100A 2217 – AN OPEN-LABEL SINGLE DOSE STUDY ASSESSING THE EFFECT OF AGE ON THE PHARMACOKINETICS OF SPP100.**

**STUDY INVESTIGATORS AND SITES:**

**REPORT # 2217**

**EDR VOLUME 6**

**STUDY DATES: June 22 – October 16, 2005**

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**OBJECTIVES:**

**Primary Objective**

- To investigate the effect of age on the pharmacokinetic (PK) parameters of SPP100 (aliskiren)

**Secondary Objective**

- To evaluate the safety and tolerability after a single oral dose of aliskiren in young and elderly healthy subjects

**FORMULATION:**

Aliskiren 300 mg tablets (Batch No: X2991A, KN#6000937.006; Exp Date: Not Provided)

**STUDY DESIGN:**

**Design:** This was an open-label, non-randomized, multiple-center, parallel-group, single-dose study in healthy subjects.

A total of 60 healthy subjects between the ages of 18 to 45 years inclusive (n=30) and ≥65 years (n=30) (65 to 74 years, n=15 and ≥75 years, n=15) were to be enrolled and matched by gender, weight, and race. At least 28 subjects from each group, young and elderly, were required to complete all study treatments and procedures.

Each subject participated in a 21-day screening period, a baseline period (Day -1), one treatment period (dose on Day 1), and a study completion evaluation 168 hours after dosing.

Once eligibility was confirmed, each subject received a single, oral dose of 300 mg aliskiren (SPP100) on Day 1 after a 10-hour fast, with blood samples obtained for up to 168 hours after dosing.

Subjects were admitted to the study center at least 24 hours prior to dosing and stayed until at least the 48-hour PK sample was collected. Subjects returned to the study center on an ambulatory basis for the remainder of the PK samples collection. Subjects had an end-of-study evaluation after the 168-hour PK sample was collected, prior to leaving the study center.

**Criteria for inclusion:** Male and female subjects from 18 to 45 years (inclusive) and ≥65 years of age who were in good health as determined by past medical history, physical examination, vital signs, ECG, and laboratory tests performed at screening. Female subjects of child bearing potential were surgically sterilized, using a double-barrier local contraception, or postmenopausal. In addition, all subjects provided written informed consent prior to participation in the study.

Subjects were excluded if they were smokers, used any prescription or over-the-counter (OTC) drugs within 2 weeks prior to dosing (however acetaminophen was acceptable), had a past medical history of clinically significant ECG abnormalities or a family history of a prolonged QT-interval syndrome, a history of autonomic dysfunction, a history of acute or chronic bronchospastic disease (including asthma and chronic obstructive pulmonary disease, treated or not treated), or had any surgical or medical condition that might significantly alter the absorption, distribution, metabolism or excretion of drugs or which may jeopardize the subject in case of participation in the study.

During recruitment, informed consent review and baseline period, the subjects observed the following restrictions:

- No strenuous physical exercise (e.g., weight training, aerobics, football) for 7 days before dosing until after the end-of-study evaluation.
- No alcohol for 72 hours before dosing until after the end-of-study evaluation.
- No grapefruit or grapefruit juice for 72 hours before dosing until after the end-of-study evaluation.
- Intake of xanthine (e.g., caffeine) containing food or beverages were to be discontinued 48 hours before dosing. Consumption of such foods and beverages (i.e., coffee, tea, soda, chocolate) was not permitted at any time while the subjects were domiciled.

**ANALYTICAL METHODS:**

Plasma levels for aliskiren were assayed by LC/MS/MS detection with an LOQ of 0.5 ng/mL. assay validation was performed and is acceptable.

**PK SAMPLE COLLECTION/CALCULATIONS, PD ASSESSMENTS/CALCULATIONS AND STATISTICAL ANALYSIS:**

At each time of aliskiren determination in plasma, 5 mL of venous blood was drawn from a forearm vein into lithium-heparin tubes. Samples were taken at the following time points: pre-dose, and 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, 144 and 168 hours post dose.

**Pharmacokinetic calculations**

Pharmacokinetic evaluations: Aliskiren PK parameters calculated or observed in this study included  $AUC_{0-t}$ ,  $AUC_{0-\infty}$ ,  $C_{max}$ ,  $t_{max}$ ,  $t_{1/2}$ ,  $C_{max}/AUC$ ,  $CL/F$ , and  $Vd/F$ . Parameter calculations were performed using non-compartmental analysis. Statistical methods were used to evaluate differences in AUC and  $C_{max}$ .

**Statistical Analysis**

Aliskiren was highly variable with CV of AUC and  $C_{max}$  in the range of 0.50 to 0.70. For the selected sample size of 28 subjects per group, the power of detecting a statistical difference between the two groups will reach 80% or higher when the true difference in mean PK parameters is as high as 40% or 50% depending upon the true value of CV.

**Power of detecting a difference with N=28 subjects per group**

CV	Probability that 90% CI for ratio of means does not contain value 1		
	Difference in means = 30%	Difference in means = 40%	Difference in means = 50%
0.50	65%	83%	93%
0.60	54%	72%	85%
0.70	45%	62%	76%

**Statistical methods:** The pharmacokinetic parameters of aliskiren were compared between the two age groups ( $\geq 65$  years versus  $\leq 45$  years) based on log-transformed data using a linear model with age group (elderly or young) as a fixed factor. Point estimate and the corresponding 90% confidence interval for the ratio of means (elderly/young) were calculated for  $AUC_{0-4}$ ,  $AUC_{0-\infty}$  and  $C_{max}$ .

**RESULTS:**

**Number of subjects:** A total of 57 healthy volunteers enrolled and 57 subjects completed the study (28 young subjects (18 to  $\leq 45$  years) and 29 elderly subjects (16 subjects 65-74 and 13 subjects  $\geq 75$  years)).

**Summary of Demographic Information**

<b>Parameter</b>	<b>Young Subjects n=28</b>	<b>Elderly Subjects n=29</b>	<b>Total N=57</b>
<b>Age (years)</b>			
Range	24 -44	65 - 83	24 - 83
Mean (SD)	34.3 (6.62)	73.2 (5.69)	54.1 (20.59)
<b>Gender (n, %)</b>			
Male	9 (32.1%)	9 (31.0%)	18 (31.6%)
Female	19 (67.9%)	20 (69.0%)	39 (68.4%)
<b>Race (n, %)</b>			
Caucasian	13 (46.4%)	15 (51.7%)	28 (49.1%)
Oriental	9 (32.1%)	11 (37.9%)	20 (35.1%)
Other	6 (21.4%)	3 (10.3%)	9 (15.8%)
<b>Weight (kg)</b>			
Mean (SD)	65.16 (9.878)	64.37(11.141)	64.76 (10.453)
<b>Height (cm)</b>			
Mean (SD)	165.7 (8.68)	160.8 (8.56)	163.2 (8.89)
<b>BMI (kg/m<sup>2</sup>)</b>			
Mean (SD)	23.749 (3.2330)	24.833 (3.1979)	24.300 (3.2281)

**APPEARS THIS WAY  
ON ORIGINAL**

## Pharmacokinetics

**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	$C_{max}$ (ng/mL)	$t_{max}$ (h)	$AUC_{(0-4)}$ (ng•h/mL)	$AUC_{(0-\infty)}$ (ng•h/mL)	$t_{1/2}$ (h)
<b>18-45 years</b>					
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
<b>65-74 years</b>					
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
<b>≥75 years</b>					
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
CV%	100.2	78.1	73.2	72.7	16.3

Relative to the age group of 18-45 years, the ratio of the arithmetic means for  $C_{max}$  was 1.2 for the 65-74 years group and 1.6 for the  $\geq 75$  years group. Relative to the age group of 18-45 years, the ratio of the arithmetic means for  $AUC_{0-\infty}$  was 1.6 for the 65-74 years group and 1.7 for the  $\geq 75$  years group. An increase in Aliskiren half-life of about 9 hours was observed in the 65-74 year and the  $\geq 75$  year age group when compared to the 18-45 year age group.

Relative to the age group of 18-45 years, the ratio of the geometric means for  $C_{max}$  was 1.2 for the 65-74 years group and 1.4 for the  $\geq 75$  years group. Relative to the age group of 18-45 years, the ratio of the geometric means for  $AUC_{(0-\infty)}$  was 1.6 for both the 65-74 years group and the  $\geq 75$  years group.

Inferential assessments were performed on elderly ( $\geq 65$  years) versus young ( $\leq 45$  years) groups. The summary of the analysis results of  $AUC_{0-4}$ ,  $AUC_{0-\infty}$  and  $C_{max}$  for aliskiren is presented in the table below. Aliskiren  $AUC_{0-4}$  values were 55% higher,  $AUC_{0-\infty}$  values were 57% higher, and  $C_{max}$  values were 28% (in geometric means) higher for elderly subjects compared to younger subjects, although the increase for  $C_{max}$  was not statistically significant.

**Summary statistical analysis results of aliskiren pharmacokinetic parameters**

Pharmacokinetic Parameter	Ratio of Geometric Means (Elderly:Young)	90% CI for Ratio
AUC <sub>0-t</sub> (ng•h/mL)	1.55	(1.18, 2.05)
AUC <sub>0-∞</sub> (ng•h/mL)	1.57	(1.19, 2.06)
C <sub>max</sub> (ng/mL)	1.28	(0.91, 1.79)

Young = Aliskiren 300 mg (age group 18-45 years), Elderly = Aliskiren 300 mg (age group ≥65 years)

**SAFETY:**

**Safety and tolerability:** No serious adverse events (SAEs) were reported. A total of 13 subjects (13/57, 22.8%), 8 young subjects and 5 elderly subjects experienced adverse events (AEs). The majority of AEs were mild in severity, and only five AEs were suspected to be related to study drug, as follows: Subject 5106 (diarrhea), Subject 5122 (high lipase), Subject 5152 (high amylase), Subject 5153 (metallic taste in mouth), and Subject 5158 (lightheadedness).

No subjects had clinically significant ECG abnormalities. Several subjects had vital signs that were out of the normal range, however deviations did not warrant study discontinuation. All clinical laboratory values that were slightly outside of the reference range were reported as not clinically significant.

**CONCLUSIONS:**

- There was a 1.2 to 1.6 fold increase in the C<sub>max</sub> and a 1.6 to 1.7 fold increase in AUC<sub>0-∞</sub> in elderly subjects ≥ 65 years of age.
- An increase in half-life of 9 hours (15%) was observed in the elderly group ≥ 65 year age in comparison to the younger population (18-45 years of age).
- There was a 1.3 fold increase in C<sub>max</sub> when the elderly groups were compared to each other and half-lives remained unchanged.

**REVIEWER'S COMMENT:**

1. /
2. The reviewer concurs.

**APPEARS THIS WAY  
ON ORIGINAL**

**STUDY SPP100A 2229** – AN OPEN-LABEL, PARALLEL GROUP STUDY TO COMPARE THE PHARMACOKINETICS AND PHARMACODYNAMICS OF A SINGLE DOSE OF SPP100 (ALISKIREN) BETWEEN HEALTHY SUBJECTS AND TYPE 2 DIABETIC PATIENTS.

STUDY INVESTIGATOR AND SITE:

**REPORT # 2229**

**EDR VOLUME 6**

**STUDY DATES: June 4 – August 19, 2004**

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**OBJECTIVES:**

**Primary Objective**

- To compare the single dose pharmacokinetics of Aliskiren between healthy subjects and type 2 diabetic patients.

**Secondary Objectives**

- To compare single dose pharmacodynamics of Aliskiren between healthy subjects and type 2 diabetic patients
- To evaluate safety and tolerability after single oral doses of Aliskiren in healthy subjects and type 2 diabetic patients.

**FORMULATION:**

Aliskiren                      300 mg tablets (Batch No: X199FA, KN#6000937.006; Exp Date: Not Provided)

**STUDY DESIGN:**

This was an open-label, non-randomized, single-center, and parallel-group single-dose study in healthy and type 2 diabetic subjects.

Two parallel groups, one healthy (n = 30), the other type 2 diabetics (n = 30), (age, weight and race matched) were enrolled in this study.

Each subject participated in a 21-day screening period, a baseline period (Day -1), one day treatment period (Day 1) and a study completion evaluation 96 hours after the treatment.

Once eligibility had been confirmed each subject received a single oral dose of SPP100 300 mg (aliskiren) on Day 1 with 96 h PK sampling. The study drug, SPP100, was given following a 10 hour fast.

Subjects were admitted to the study site at least 12 hours prior to the dosing and were confined to the clinic for at least 48 h samples and were advised to come back for the rest of the PK samples collection. Subjects underwent a study completion evaluation at 96 h post-dose prior to discharge from the study site.

Except for medication which may be required to treat adverse events, no medication other than study drug was allowed from 14 days prior to the first dosing of study treatment until the entire end of study evaluations had been conducted. Administration of concomitant medication may require the subject to be replaced. Administration of acetaminophen was acceptable but had to be documented in the eCRF. Decisions regarding replacements of subjects requiring concomitant medication were discussed with the sponsor on a case-by-case basis. The administration of any such medication (including over-the-counter medications) was clearly documented on the Concomitant medications / Significant non-drug therapies eCRF page.

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

- No strenuous physical exercise (e.g., weight training, aerobics, football) for 7 days before the first dose in each phase until after the end of study evaluation.
- No alcohol for 72 hours before the first dose in each phase until after the end-of-study evaluation.
- No grapefruit or grapefruit juice for 72 hours before the first dose in each phase until after the end-of-study evaluation.
- Intake of xanthine (e.g., caffeine) containing food or beverages must be discontinued 48 hours before the first dose in each period. Consumption of such foods and beverages (i.e., coffee, tea, soda, chocolate) is not permitted at any time while the subjects are domiciled. If a deviation occurs during the domicile period, it must be noted as appropriate in the eCRF as a comment.

**Criteria for Inclusion:**

Healthy (group 1) and type 2 diabetic patients (group 2), male or female non-smoking subjects between 30 and 75 years of age having provided a written informed consent before entering the study. At screening, the subjects must be in good health as determined by past medical history, physical examination, electrocardiogram, laboratory tests and urinalysis.

**ANALYTICAL METHODS:**

Analytes, media and methods: Plasma SPP100 was determined by a HPLC/MS/MS method. The detection threshold of the assay is approximately 0.5 ng/mL.

Within-study assay validation was performed by analysis of QC samples together with the study samples and seems acceptable.

**PK SAMPLE COLLECTION/CALCULATIONS, PD ASSESSMENTS/CALCULATIONS AND STATISTICAL ANALYSIS:**

Blood collection Blood sample of 5 mL was collected at each of the following time points into lithium heparin tubes ( plasma in two tubes after centrifugations)

PK parameters:  $AUC_{0-t}$ ,  $AUC_{0-\infty}$ ,  $C_{max}$ ,  $t_{max}$ ,  $t_{1/2}$ ,  $C_{max}/AUC$ ,  $CL/F$  and  $Vd/F$ . The primary pharmacokinetic assessments were performed on  $C_{max}$ ,  $AUC_{0-t}$  and  $AUC_{0-\infty}$ .

PK evaluations: Non-compartmental analysis.

**Pharmacodynamic Assessments**

The following pharmacodynamic assessments were assessed: active renin, plasma renin activity (PRA), plasma angiotensin I and II and serum aldosterone on Day 1.

**Statistical Analysis –**

**APPEARS THIS WAY  
ON ORIGINAL**

The pharmacokinetic parameters of aliskiren were compared between the two groups based on log-transformed data using a linear model with group as a fixed factor and matched pair as a random factor. Point estimate and the corresponding 90% confidence interval for the ratio of means (diabetic patients/healthy) were calculated for AUC and  $C_{max}$ .

The pharmacodynamic variables and parameters were summarized by descriptive statistics. Graphical methods were used to examine the trend over time.

Aliskiren is highly variable with a CV of AUC and  $C_{max}$  in the range of 0.50 to 0.70. For the selected sample size of 28 subjects per group, the power of detecting a statistical difference between the two groups were to reach 80% or higher when the true difference in mean PK parameters was as high as 40% or 50% depending upon the true value of CV.

**Power of detecting a difference with N = 28 subjects per group**

CV	Probability that 90% CI for ratio of means does not contain value 1		
	Difference in means = 30%	Difference in means = 40%	Difference in means = 50%
0.50	65%	83%	93%
0.60	54%	72%	85%
0.70	45%	62%	76%

**RESULTS:**

**Summary of demographic information**

Demographic variable		Type 2 Diabetic Patients (N=30)	Healthy Volunteers (N=30)
Age (years)	mean	57.9 ± 9.26	57.2 ± 8.5
	range	34 - 73	34 - 74
Height (cm)	mean	162.4 ± 7.3	163.2 ± 9.04
	range	149-180	147-183
Weight (kg)	mean	74.69 ± 11.9	73.11 ± 10.8
	range	56.4-108.6	55-110
Elbow breadth (cm)	mean	6.9 ± 0.53	6.79 ± 0.6
	range	5.7-7.9	5.7-8.3
Sex	Male	16 (53.3 %)	13 (43.3 %)
	Female	14 (46.7 %)	17 (56.7 %)
Race	Caucasian	6 (20.0 %)	6 (20.0 %)
	Black	4 (13.3 %)	4 (13.3 %)
	Other	20 (66.7 %)	20 (66.7 %)
Body frame	Medium	17 (56.7 %)	18 (60.0 %)
	Large	13 (43.3 %)	12 (40.0 %)

**According to the sponsor:**

All type II diabetic patients have taken one of the following medications listed below prior to the study and continued this medication at a constant dose throughout the study for glucose control:

Glipizide, Pioglitazone, Metformin, Glibomet, Glibenclamide, Metaglip, Gemfibrozil and Rosiglitazone Maleate.

**Note:** Glibomet is a glyburide/metformin combination formulation and Metaglip is a glipizide/metformin combination formulation. Neither medication is approved in the U.S. Gemfibrozil is listed as a medication for glucose control; but is approved in the US to treat hyperlipidemia.

### Safety and tolerability:

All subjects who received at least one treatment were included in the safety and tolerability evaluation.

Sixty (60) subjects were enrolled in the study and 60 (100%) subjects completed the study. There were no serious adverse events reported. In total, 7 of the 60 (12%) subjects reported a total of 17 adverse events. Two (3%) subjects reported multiple adverse events (12/17, 70%). All adverse events were mild. Fifteen (88%) of the adverse events were determined by the investigator to be related to study treatment. The adverse events of headache and diarrhea occurred with the highest frequency.

Maximum incidence (13/17, 76%) of adverse events was observed in the healthy volunteer group. The type 2 diabetic patients group reported 4 (23%) adverse events and the healthy volunteer group reported 13 (76%) adverse events. No adverse event required study drug discontinuation.

### ECG

No clinically relevant ECG changes were observed in any subjects during the study.

### Laboratory parameters

All 60 subjects had an out-of-range clinical laboratory test result (blood chemistry, hematology, and/or urinalysis) at some point during the study. The investigator did not consider any of these values to be clinically significant, nor did the results prevent any subjects from continuing in the study.

### Vital signs

Of the 60 subjects enrolled, 20 subjects (14 of 30 diabetic patients and 6 of 30 healthy volunteers) had an out-of-range vital sign at some point during the study. The investigator did not consider any of these values to be clinically significant, nor did the results prevent any subjects from continuing in the study.

### Pharmacokinetics

Comparison of the arithmetic means indicated a slight difference in CL/F between healthy subjects and type 2 diabetic patients. Healthy subjects had a 14% higher clearance than type 2 diabetic patients. The increase in CL/F led to slight increases in  $C_{max}$  (13%),  $AUC_{0-t}$  (13%) and  $t_{1/2}$  (10%) in type 2 diabetic patients relative to healthy subjects. All differences observed were 15% or less. The Vd/F was virtually identical between healthy subjects and type 2 diabetic patients. A similar observation was evident for the median  $t_{max}$ . All differences observed were 15% or less. The Vd/F was virtually identical between healthy subjects and type 2 diabetic patients. A similar observation was evident for the median  $t_{max}$ . The primary pharmacokinetic parameters for statistical assessment were  $C_{max}$ ,  $AUC_{0-t}$  and  $AUC_{0-\infty}$ . The table below contains the mean and descriptive statistics for the primary Aliskiren pharmacokinetic parameters statistically assessed in healthy subjects and type 2 diabetic patients following administration of a single dose of 300 mg Aliskiren.

#### 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)
<b>N</b>	30	30	30	30	30	30	30
<b>Mean</b>	394	1.62	1859	2037	205284	44.0	12330453
<b>SD</b>	288	1.21	1106	1198	136706	11.4	6981790
<b>Min</b>							
<b>Median</b>	328	1.00	1614	1899	158080	40.7	9800120
<b>Max</b>							
<b>CV%</b>	73.3	75.1	59.5	58.8	66.6	25.9	56.6
<b>Geometric Mean</b>	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)

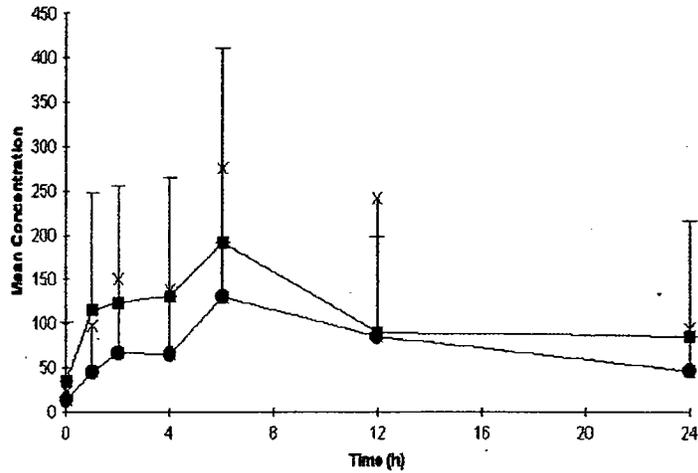
Test group = Type 2 diabetic patients, Reference group = Healthy volunteers

#### Pharmacodynamics:

Both healthy subjects and type 2 diabetic patients showed an increase in plasma active renin following administration of a single dose of 300 mg Aliskiren with a trend back towards baseline at the 24 hour observation. The effect appeared more prominent in type 2 diabetic patients compared to healthy subjects. In contrast to plasma active renin, following the administration of 300 mg Aliskiren, both healthy subjects and type 2 diabetic patients showed a decrease from baseline for PRA. This decrease stayed virtually constant over the entire 24 hour post-dosing assessment. Angiotensin I remained stable relative to baseline for both healthy subjects and type 2 diabetic patients over the 24 hour assessment period following the administration of 300 mg Aliskiren. Angiotensin II remained stable relative to baseline for healthy subjects and type 2 diabetic patients over a 12 hour period following the administration of 300 mg Aliskiren. In healthy subjects the angiotensin II stayed constant over the remaining 12 hour period of assessment. In type 2 diabetic patients angiotensin II rose to be 55% greater than baseline at the 24 hour assessment period. Both healthy subjects and type 2 diabetic patients showed a decrease from baseline for serum aldosterone.

The mean arithmetic  $AUC_{0-24}$  of the plasma active renin was 45% higher in type 2 diabetic patients compared to healthy subjects. The mean  $AUC_{0-24}$  in healthy subjects was 1835 (mu/L) compared to 2664 (mu/L) for type 2 diabetic patients. The CV of the  $AUC_{0-24}$  mean values was high for both healthy subjects (136.6%) and type 2 diabetic patients (115.4%).

Mean plasma active rennin in healthy and type 2 diabetic volunteers following administration of a single 300 mg dose of aliskiren



Plasma active renin (mu/L) in healthy subjects (mean = □, SD = X) and type 2 diabetic patients (mean = ●, SD = -)

Following the administration of 300 mg Aliskiren, both healthy subjects and type 2 diabetic patients showed a decrease from baseline for serum aldosterone. In both healthy subjects and type 2 diabetic patients, the greatest decrease was noted at 12 hours. At 12 hours, the mean serum aldosterone was 37% of the baseline value in healthy subjects and 46% in type 2 diabetic patients. At 24 hours, the serum aldosterone had risen and was 73% of baseline value and 76% in type 2 diabetic patients. The mean serum aldosterone was identical between healthy subjects and type 2 diabetic patients at 24 h post-dosing of Aliskiren. There were no major differences noted between healthy subjects and type 2 diabetic patients.

**CONCLUSIONS:**

- There are no major differences noted in the pharmacokinetics of Aliskiren in healthy subjects and type 2 diabetic patients.
- A single 300 mg dose of aliskiren was safe and well tolerated by both healthy subjects and type 2 diabetic patients.
- Both healthy subjects and type 2 diabetic patients show an increase in plasma active renin following administration of a single dose of 300 mg Aliskiren.
- There is no difference noted between healthy subjects and type 2 diabetic patients with respect to PRA, angiotensin I, or serum aldosterone behavior.
- Both healthy subjects and type 2 diabetic patients show a decrease from baseline for plasma PRA and serum aldosterone. Angiotensin I remains stable relative to baseline.
- In healthy subjects, the angiotensin II stayed constant over the 24 hour assessment period while in type 2 diabetic patients, it increased from the 12 to 24-hour period.

**REVIEWER’S COMMENT:**

1. Reviewer concurs.

**STUDY SPP100A 2210** – AN OPEN-LABEL, SINGLE DOSE, PARALLEL-GROUP STUDY TO ASSESS THE PHARMACOKINETICS OF SPP100A IN SUBJECTS WITH IMPAIRED HEPATIC FUNCTION IN COMPARISON WITH HEALTHY CONTROLS.

STUDY INVESTIGATOR AND SITE:

**REPORT # 2210**

VOLUMES in EDR, Section 6

STUDY DATES: July 6 – October 7, 2005

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**OBJECTIVES:**

Primary objective

- To characterize the single-dose pharmacokinetics of 300 mg of aliskiren in subjects with stable chronic liver disease in comparison to healthy controls with normal liver function.

Secondary objective

- To evaluate the safety and tolerability of a single 300 mg oral dose of aliskiren in subjects with chronic liver disease.

**FORMULATION:**

Aliskiren 300 mg tablets (Batch No: X199FA, KN#6000937.006; Exp Date: Not Provided)

**STUDY DESIGN:**

**Design:** This was a single center, open-label, parallel group, single-dose design in subjects with stable chronic liver disease and healthy controls. Each subject participated in a screening period, single treatment period and an end of study evaluation.

Hepatic impairment was defined by the Child-Pugh Clinical Assessment score: mild (score=5-6); moderate (score= 7-9); and severe (score=10-15). The healthy control group for each group of subjects with hepatic impairment was matched by age, gender race and weight. Healthy subjects with normal liver function and were matched 1:1 with each patient from each of the three groups of patients with hepatic impairment by gender, race, age ( $\pm 5$  years) and weight ( $\pm 10$  kg).

Subjects who satisfied all inclusion and exclusion criteria entered the study center on the evening of Day -1 for verification of inclusion/exclusion criteria. Blood samples for evaluation of routine laboratory tests were collected that evening. On Day 1 following a 10 hour fast, subjects received a 300 mg dose of Aliskiren in the morning (0700-0830 h) and continued fasting for an additional 4 hours. A low sodium breakfast was provided immediately following the 4 hr. blood sample. Subjects remained on the low salt (low sodium) diet during the first day of the study. Standardized meals were resumed 24 hours following the single dose of Aliskiren.

During recruitment, informed consent review, and baseline period, the subjects had to observe the following restrictions:

- No strenuous physical exercise (e.g., weight training, aerobics, football) for 7 days before dosing until after the study completion evaluation.
- No alcohol for 72 hours before dosing until after the study completion evaluation.
- Low salt (low sodium) dietary restriction should be strictly observed for 5 days prior to the single dose of aliskiren.

Intake of xanthine (e.g., caffeine) containing food or beverages had to be discontinued 48 hours before dosing. Consumption of these foods and beverages (i.e., coffee, tea, soda and chocolate) was not permitted at any time while the subjects were domiciled. If a deviation occurred during the domicile period, it had to be noted on the Comments CRF page.

There were no medication restrictions for subjects with hepatic impairment with respect to prior prescription medications, OTCs, or vitamins.

Criteria for inclusion: Males or females between 18 and 70 years of age. Group 2, 3, 4 consisted of patients with clinically diagnosed hepatic impairment and with a Child-Pugh Clinical Assessment score of 5-6 (Group 2 - mild), 7-9 (Group 3 - moderate), 10-12 (Group 4 - severe). Group 1 consisted of healthy subjects with normal liver function and were matched 1:1 with each patient from each of the three groups of patients with hepatic impairment by gender, race, age ( $\pm$  5 years) and weight ( $\pm$  10 kg).

#### ANALYTICAL METHODS:

Plasma levels for aliskiren were assayed by LC/MS/MS detection with an LOQ of 0.5 ng/mL. assay validation was performed and is acceptable.

#### PK SAMPLE COLLECTION/CALCULATIONS, PD ASSESSMENTS/CALCULATIONS AND STATISTICAL ANALYSIS:

**Pharmacokinetic evaluations:** Blood collections for plasma Aliskiren determinations were collected pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96, 120 and 144 hours post-dose. Plasma levels of Aliskiren were determined using LC-MS/MS, LOQ at 0.5 ng/mL. Pharmacokinetic parameters were calculated using non-compartmental methods and included  $AUC_{0-\infty}$ ,  $AUC_{0-t}$ ,  $C_{max}$ ,  $t_{max}$ ,  $t_{1/2}$ , CL/F,  $V_d/F$

#### Statistical Analysis –

The comparison between the subjects in the hepatically impaired groups (Group 2, 3, and 4) and the corresponding healthy controls was made for the pharmacokinetic parameters  $AUC_{0-\infty}$ ,  $AUC_{0-t}$  and  $C_{max}$  of aliskiren. A mixed effect linear model including Group (mild, moderate, and severe), and Status (impaired, healthy) as fixed factors and Matched Pair (nested in group) as a random factor was used for analysis. A 90% confidence interval for the ratio of the diseased over healthy for  $AUC_{0-\infty}$ ,  $AUC_{0-t}$  and  $C_{max}$  was provided for each group separately and for the pooled data, if appropriate.

Correlation between Child-Pugh score and PK parameters was explored graphically.

Aliskiren has a CV of approximately 0.60 ( $C_{max}$ ). With a total of 18 subjects in each group, there is an 80% power to detect a statistically significant difference between two group means that differ by 80% or more.

**RESULTS:****Summary of demographic data:**

Number of subject dosed: 32	Hepatic Impaired (N=16)	Healthy Subjects (N=16)
<b>Age (years)</b>		
Mean	52.3	51.3
(SD)	6.60	8.93
<b>Weight (kg)</b>		
Mean	84.51	83.03
(SD)	17.189	14.193
<b>Height (cm)</b>		
Mean	172.4	172.6
(SD)	9.63	8.47
<b>Gender</b>		
Male	11	11
Female	5	5
<b>Race</b>		
Caucasian	12	12
Black	0	0
Other	4	4

**Pharmacokinetics**

**Pharmacokinetics:** Table 1 and Table 2 contain the descriptive statistics of primary pharmacokinetics obtained in healthy subjects and those with hepatic impairment.

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

Subject Group (Healthy)		C <sub>max</sub> (ng/mL)	T <sub>max</sub> (h)	t <sub>1/2</sub> (h)	AUC <sub>(0-144)</sub> (ng x h/mL)	AUC <sub>(0-∞)</sub> (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

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

Subject Group (Hepatic Impairment)		C <sub>max</sub> (ng/mL)	T <sub>max</sub> (h)	t <sub>1/2</sub> (h)	AUC <sub>0-144</sub> (ng x h/mL)	AUC <sub>(0-∞)</sub> (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

**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 <sub>0-∞</sub> (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 <sub>0-144</sub> (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 <sub>max</sub> (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 ratios of the geometric means of exposure (C<sub>max</sub> and AUC) in subjects with mild, moderate and severe hepatic impairment groups were all approximately equal to unity. For all PK parameters, the differences in geometric means were less than 20% when pooled across all subgroups of subjects with hepatic impairment. In addition, there was no correlation between PK parameters and Child-Pugh

score. Confidence intervals for PK parameters were wide due to the variability of the data and the small number of subjects.

**SAFETY:**

**Safety and tolerability:** Aliskiren was well tolerated in subjects with hepatic impairment and in healthy subjects. There were no deaths or serious adverse events reported. Headache was the most commonly reported adverse event. There were no subjects who had ECG tracings with clinically significant abnormalities. Aliskiren tended to decrease blood pressure 1-4 h after administration although no patients/subjects developed symptomatic hypotension. Abnormal laboratory values at baseline were consistent with hepatic disease and did not change following drug administration.

**CONCLUSIONS:**

- Hepatic impairment has no significant effect on the pharmacokinetics of aliskiren following single dose administration.
- Aliskiren is well tolerated in subjects with hepatic impairment and in healthy subjects without signs of hepatic disease when administered as a single 300 mg dose.

**REVIEWER'S COMMENT:**

1. Reviewer concurs.
2. Note: Many drug abusers were identified in this study (pg 24 of study report where they have positive testing for cocaine, amphetamine, benzos).
3. No Exp date for Aliskiren.

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ON ORIGINAL**

**RACE - DESCRIPTIVE STATISTICS**

**EDR VOLUME** Submission date March 31, 2006 (Appendix 3)

Various studies' raw data were pooled together in order to obtain the pharmacokinetic statements/conclusions All data submitted  
will be illustrated below.

**FORMULATION:**

Aliskiren 150 and 300 mg tablets (Batch No: vary; Exp Date: vary)

**STUDY DESIGN:**

Different studies with different designs were used to obtain the information required for a particular race's analysis. However, all studies used for the analysis were drug-drug interaction studies. All subjects were in the fasted state. Reason for not using any other studies was not provided.

**ANALYTICAL METHODS:**

Plasma levels for aliskiren were assayed by HPLC/MS/MS detection.

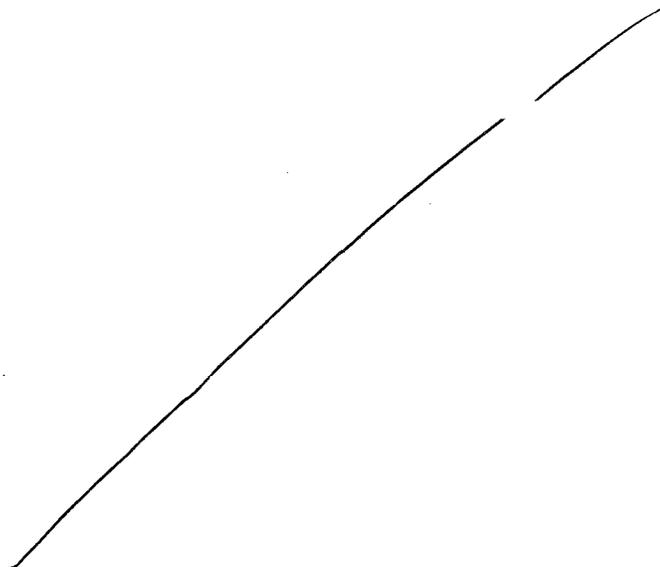
**STATISTICAL ANALYSIS** – The sponsor calculated mean Aliskiren  $C_{max}$  and  $AUC_{(0-t)}$ .

**DATA SUBMITTED:**

***Pooled Mean AUC and CMAX for SPP100 Studies***

Caucasian=1  
Black=2  
Oriental=3  
Other=4

<u>Study</u>	<u>Race</u>	<u>Subject_ID</u>	<u>Cmax</u>	<u>AUC(0-t)</u>	<u>Study</u>	<u>Race</u>	<u>Subject_ID</u>	<u>Cmax</u>	<u>AUC(0-t)</u>
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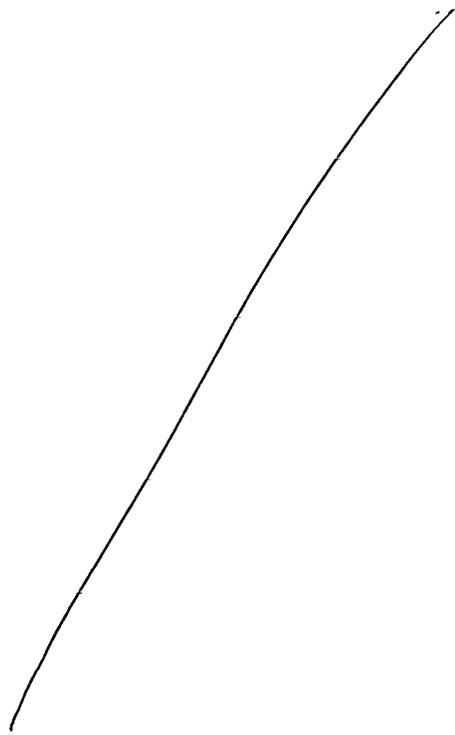
	2	47	47
N		289	2263
Mean		179	1228
SD		243	2064.1
Min			
Med			
Max		62%	54%
%CV		248	1968
Geo Mean			

	1	69	89
N		268	1889
Mean		181	926
SD			
Min		217	1783.62
Med			
Max		68%	49%
%CV		213	1691
Geo Mean			

Study      Race      Subject ID Cmax      AUC(0-t)

	3	5	5
N		250	1658
Mean		106	480
SD			
Min		275	1495.04
Med			
Max		42%	29%
%CV		231	1607
Geo Mean			

Study      Race      Subject ID Cmax      AUC(0-t)



N	4	64	64
Mean		351	1986
SD		198	876
Min		████	████
Med		301	1960.595
Max		████	████
%CV		56%	44%
Geo Mean		302	1786

Race	Cmax (range) CV%	AUC <sub>0-t</sub> (range) CV%
Caucasian N=69	268 ( — ) 68%	1889 ( — ) 49%
Black N=47	289 ( — ) 62%	2253 ( — ) 54%
Oriental N=5	250 ( — ) 42%	1566 ( — ) 29%
Other N=64	351 ( — ) 56%	1986 ( — ) 44%

**CONCLUSIONS:**

The sponsor's conclusion is that the pharmacokinetics of aliskiren does not differ significantly among different races and ethnicities (Blacks, Caucasian, Hispanics, and Japanese).

**REVIEWER'S COMMENT:**

1. No statistical analysis was applied to the data collected in order to determine equivalence between the groups.
2. The collection of the submitted data and the analysis performed was retrospective in nature.
3. Rationale was not provided for the use of some studies versus other studies.
4. The reviewer does not concur with the conclusions made from the data generated in this study regarding no PK differences between all four groups.
5. The "Other" category was later described as Hispanic; but no definition was provided for that category.
6. The "Oriental" category was not defined either.
7. As a result, the only conclusions that can be made is that there's no PK differences between Caucasian and Black subjects only.

**APPEARS THIS WAY  
ON ORIGINAL**

**GENDER - DESCRIPTIVE STATISTICS**

**EDR VOLUME** Submission date March 31, 2006 (Appendix 2)

Various studies' raw data were pooled together in order to obtain the pharmacokinetic statements/conclusions. All data submitted will be illustrated below.

**FORMULATION:**

Aliskiren 300 mg tablets (Batch No: vary; Exp Date: vary)

**STUDY DESIGN:**

All studies were multiple dose drug-drug interaction studies. All subjects were in the fasted state.

**ANALYTICAL METHODS:**

Plasma levels for aliskiren were assayed by HPLC/MS/MS detection.

**STATISTICAL ANALYSIS** – The sponsor calculated mean Aliskiren  $C_{max}$  and  $AUC_{(0-t)}$ .

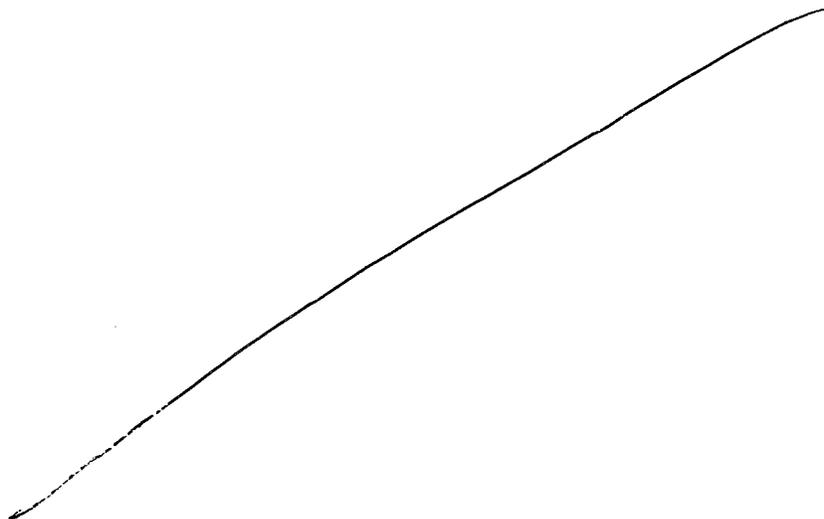
**DATA SUBMITTED:**

Male=1

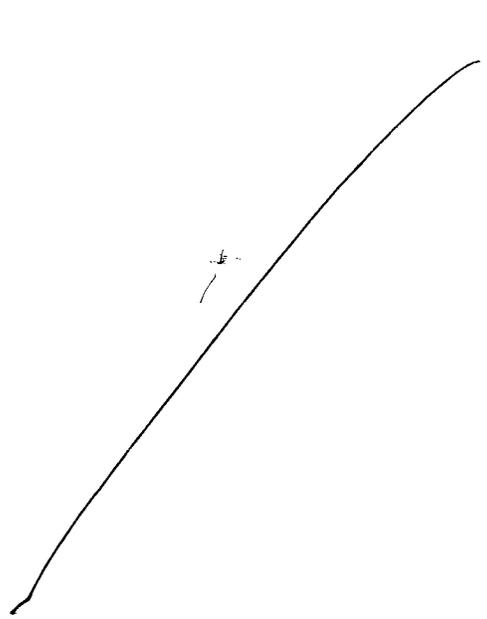
Female=2

**Study Gender Subject ID Cmax AUC(0-t)**

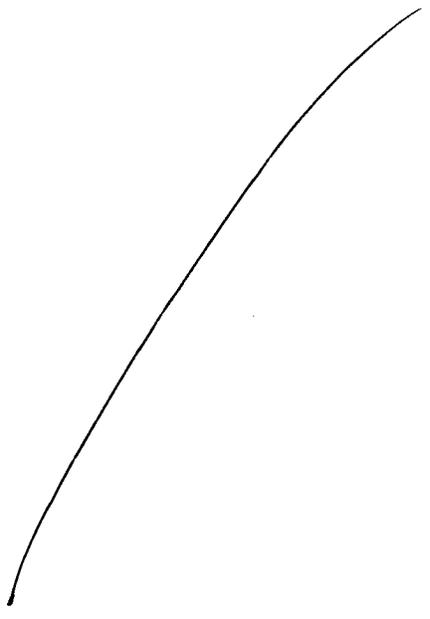
**Study Gender Subject ID Cmax AUC(0-t)**



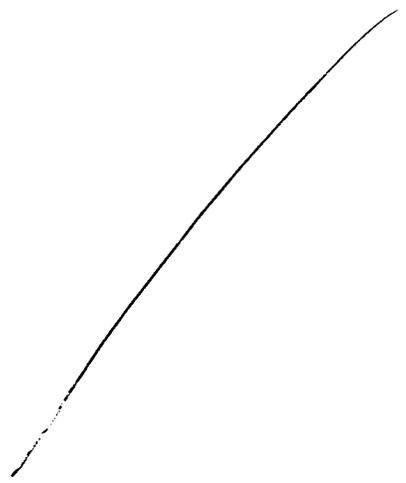
Male=1  
 Female=2  
 Study Gender Subject\_ID Cmax AUC(0-t)



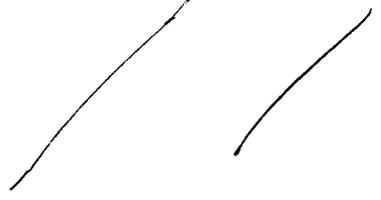
Study Gender Subject\_ID Cmax AUC(0-t)



Male=1  
 Female=2  
 Study Gender Subject\_ID Cmax AUC(0-t)



Study Gender Subject\_ID Cmax AUC(0-t)



N	2	78	78
Mean		368	2330
SD		218	1122
Min		█	█
Median		305	2183
Max		█	█
CV%		59%	48%

Mean Ratio% (MF) -45% -31%

Male=1  
Female=2  
Study Gender Subject\_ID Cmax AUC(0-t)

N	107	107
Mean	253	1775
SD	145	818
Min		
Median	231	1501.19
Max		
CV%	57%	46%

PK parameter	Females (n=78)	Males (n=107)
C <sub>max</sub> (range)	368	253
CV%	59%	57%
AUC <sub>0-t</sub> (range)	2330	1775
CV%	48%	46%

**CONCLUSIONS:**

The AUC of Aliskiren is 24% lower in males when compared to females.

**REVIEWER'S COMMENT:**

1. Weight adjustments did not seem to be made and no mention was made to that effect. However, females seemed to have a C<sub>max</sub> that was 45% greater than the males and an AUC that is 31% greater than males.
2. The collection of the submitted data and the analysis performed was retrospective in nature.
3. Rationale was not provided for the use of some studies versus other studies.
4. Not all subjects in the above studies were utilized for this analysis and no rationale was provided for not utilizing all the data available in these studies.
5. Subsequent e-mail (November 20, 2006) sent by the sponsor verifies that no weight adjustments had been made in this analysis. Upon re-analyzing the data, the sponsor found that no pharmacokinetic differences were observed between groups (see below).

SPP100A  
Assessment of gender difference on PK parameters  
(comparison results include both unadjustment and adjustment for weight)

Parameters	Treatment	N	Arithmetic mean	Standard deviation	Percent difference	Geometric mean	Ratio of geometric means	90% CI for ratio
AUCUnadj (ng.h/mL)	Male	107	1774.8	815.6	-23.82	1602.8	0.77	(0.69, 0.87)
	Female	78	2329.6	1122.1				
C <sub>max</sub> Unadj (ng/mL)	Male	107	253.4	144.9	-31.15	213.7	0.69	(0.59, 0.80)
	Female	78	368.1	218.4				
AUCAdj (ng.h/mL)	Male	107	459.6	210.1	-10.46	415.5	0.92	(0.81, 1.03)
	Female	77	513.4	259.6				
C <sub>max</sub> Adj (ng/mL)	Male	107	65.2	36.9	-19.75	55.4	0.82	(0.70, 0.95)
	Female	77	81.3	49.8				

Note:

1. Female is the Reference treatment. Male is the Test treatment being compared to Female.
2. Adjusted data analyzed above are weight adjusted dose normalized PK parameter: (PK parameter)/(300/weight).
3. Percent difference = 100\*(Test treatment mean - Reference treatment mean)/Reference treatment mean.
4. Geometric means, ratio of geometric means, and 90% confidence interval for ratio of population means are determined from an ANOVA model for the log transformed values with Treatment as fixed effect.

**STUDY SPP100A 2343** – AN OPEN-LABEL, RANDOMIZED, SINGLE-DOSE, CROSSOVER, REPLICATE STUDY TO DEMONSTRATE THE BIOEQUIVALENCE BETWEEN THE FINAL MARKET IMAGE (FMI) TABLET OF ALISKIREN AND OVER-ENCAPSULATED TABLETS OF ALISKIREN.

STUDY INVESTIGATOR AND SITE:

**REPORT # 2343**

**EDR VOLUME 6**

**STUDY DATES:** October 5 – December 21, 2005

**OBJECTIVES:**

Primary objective:

- To demonstrate the bioequivalence between the final market image (FMI) aliskiren tablet and overencapsulated aliskiren tablets

Secondary objective:

- To assess the safety and tolerability of a single oral dose of aliskiren in healthy subjects

**FORMULATION:**

Test Aliskiren 150 mg FMI tablet (Batch No: 3765070.010/X101CB;  
Batch size: — Manufacture Date: 03/14/05) by Novartis

Reference Aliskiren 150 mg over-encapsulated tablet (Batch No:  
3768785.004/X239 0903; Batch size: — Manufacture Date:  
06/19/03) by Novartis

Note: Biobatches are defined by the sponsor as the drug batches used in a definitive bioavailability or bioequivalence trial.

**STUDY DESIGN:**

**Design:** This study employed an open-label, randomized, single-dose, four-period, replicate, crossover design. Each subject participated in a 21-day screening period (Day -22 to Day -2), four baseline periods (Days -1, 15, 29, and 43), four single-oral-dose treatment periods, and an end-of-study evaluation. Each treatment period was 14 days in duration, comprised of a 7-day pharmacokinetics (PK) assessment period and a 7-day study drug washout period. Subjects were domiciled from baseline of each treatment period through 168h post-dose.

At baseline (Day -1) for Period 1, each eligible subject was randomized to receive, under fasting conditions, a single oral dose of 150 mg aliskiren either in the test formulation (overencapsulated tablet) or the reference formulation (final market image [FMI] tablet) according to the randomization scheme. Subjects received the alternate treatment during Period 2, and the sequence for Periods 1 and 2 was repeated for Periods 3 and 4.

Each treatment period was 14 days in duration, which represented the interval in between each study drug administration, including a 7-day PK assessment period and a 7-day washout period. Subjects were domiciled from baseline of each treatment period through 168 hours post-dose, totaling 32 domiciled days during the study (8 domiciled days/study period).

During the study, all subjects received each of the following treatments twice under fasting conditions:

**Treatment 1:** Single dose of 150 mg SPP100 (aliskiren) FMI tablet [Reference]

**Treatment 2:** Single dose of 150 mg SPP 100 (aliskiren) overencapsulated tablets [Test]

Subjects who received the FMI tablet in Period 1 then received the overencapsulated tablet in Period 2 and vice versa; Periods 3 and 4 merely repeated the sequence from Periods 1 and 2 (see table below).

Treatment Sequence	Period 1	Period 2	Period 3	Period 4
A	1	2	1	2
B	2	1	2	1

Pharmacokinetic assessments began prior to administration of study drug (pre-dose, 0h), and continued post-dose at the following timepoints: 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, 144 and 168 hours post-dose.

For Periods 1–3, subjects were discharged from the study clinic for a 7-day study drug washout following the last PK assessment, after which they returned to the study clinic for the next baseline period. For Period 4, following the last PK assessment, subjects underwent a routine end-of-study safety evaluation and were then discharged from the study.

**Duration of treatment:** There were four single-dose treatment periods each comprising approximately seven (7) days each (dosing and PK assessment period), followed by an additional seven (7) day wash-out period (14 day interval between each drug administration).

**Criteria for inclusion:** Non-smoking male and female subjects, between 18 and 45 years of age (inclusive), and in good health as determined by past medical history, physical examination, and screening and baseline evaluations. Each subject had to give written informed consent prior to participating, and female subjects must have been either surgically sterile, using double-barrier local contraception, or post-menopausal.

Except for medication required to treat adverse events, no medication other than study drug was allowed from 14 days prior to the first dose of study drug until all final study evaluations had been completed. Administration of acetaminophen was acceptable, if necessary, but was to be documented in the CRF. Decisions regarding replacements of subjects requiring concomitant medication were to be discussed with the sponsor on a case-by-case basis. The administration of any such medication (including over-the-counter medications and vitamins) was to be clearly documented in the CRF.

- No strenuous physical exercise (e.g., weight training, aerobics, football) for 7 days before dosing until after the study completion evaluation.
- No alcohol for 72 hours before dosing until after the study completion evaluation.

All subjects had to fast for at least 10 hours prior to dosing and they were to continue fasting for at least 5 hours thereafter on dosing days. No fluid was to be consumed from 2 hours pre-dose until 2 hours post-dose on dosing days; thereafter, in addition to the fluid taken with study drug, at least 200 mL fluid was to be consumed every 4 hours during waking hours on dosing (and non-dosing) days. On dosing days, lunch and dinner were served at ~1200 and 1800, respectively, and a large snack was served at 2100; on non-dosing days, breakfast was served in addition at 0800. Subjects followed a standard weight-maintaining diet while domiciled and were to consume the entire contents of each meal. Meals were similar in caloric content and distribution for all subjects on the days of dosing. On non-dosing washout days, subjects were to follow similar guidelines with respect to meals as much as possible.

Intake of xanthine (e.g., caffeine) containing food or beverages had to be discontinued 48 hours before dosing. Consumption of these foods and beverages (i.e., coffee, tea, soda, chocolate) was not permitted at any time while the subjects were domiciled.

#### **ANALYTICAL METHODS:**

Plasma levels for aliskiren were assayed using LC/MS/MS detection. The lower limit of quantification (LOQ) was 0.5 ng/mL.

#### **PK SAMPLE COLLECTION/CALCULATIONS, PD ASSESSMENTS/CALCULATIONS AND STATISTICAL ANALYSIS:**

##### **Blood samples**

Blood collection for aliskiren determination: 3 mL sodium heparin tubes were used for whole blood sampling at the following time points: pre-dose, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, 144 and 168 hours post-dose during each treatment period.

**Pharmacokinetic evaluations:**  $AUC_{0-t}$ ,  $AUC_{0-\infty}$ ,  $AUC_{0-t_{max}}$ ,  $C_{max}$ ,  $t_{1/2}$  and  $t_{max}$  were evaluated. PK parameters were determined using non-compartmental method(s) using WinNonlin Enterprise (Version 4.0).

Note: Three subjects (#5133, 5145, and 5147) had pre-dose Aliskiren concentrations (a total of seven periods). The concentrations were below 5% of  $C_{max}$  according to the sponsor and included in the PK analysis.

##### **Statistical Analysis**

The statistical data analysis method for a replicate design is similar to that of a standard two period crossover design in that information from the intra-subject comparison between two formulations is combined for all subjects. With a replicate design, however, more precise information on formulation comparison is available from each subject as a result of the replicate dosing, and thus, fewer subjects are required for the study.

Log-transformed AUC and  $C_{max}$  were analyzed by a linear mixed effects model, with fixed effects from sequence, treatment, and period, and random effects from subject nested in sequence. The resulting 90% confidence intervals of the appropriate treatment mean ratios were used to evaluate the bioequivalence between the FMI tablet (reference formulation) and the overencapsulated tablets (test formulation). According to established guidelines, bioequivalence between formulations can be concluded for a PK parameter if the 90% confidence interval for the ratio of means is contained within the range (0.80, 1.25).

## **RESULTS:**

**Number of subjects:** Planned: 56 subjects enrolled to complete with a minimum of 46; Actual: 58 subjects enrolled and 48 completed all four study periods.

All screening and first period baseline tests for smoking, alcohol, drugs of abuse, pregnancy, Hepatitis B & C, and HIV were negative. Baseline tests at Periods 2-4 revealed a positive pregnancy test for Subject #5119 (Period 4), and positive drug or urine cotinine screens for Subjects #5117, #5130, and #5132. As a result, each of these four subjects was discontinued from the study prior to full completion.

Subject 5124 was dropped from the study on day 32 due to neck pain not considered to be due to study drug.

Subject #5102 was dropped from study at baseline Period 4 due to low hemoglobin (10.0 g/dL) and hematocrit (29.5%). The subject's hematology parameters indicated a repeat pattern of abnormalities noted at baseline Period 3, so the subject was discontinued from the study.

Subject #5114 was dropped prior to dosing in Period 2 due to the presence of urinary RBCs, which were present at baseline and even slightly more elevated (5/HPF) the next day. This subject was discontinued from the study and referred to his primary care physician.

Subject #5129 was discontinued from the study at baseline Period 2 due to elevated liver enzymes (SGPT was 118 U/L; upper normal limit = 60 U/L). The repeat measurement the following day was still elevated (112 U/L), and the subject was discontinued.

Subjects #5108 and #5137 withdrew consent (both did not show at baseline Period 3).

Two replacement subjects (#6114 and 6129) were enrolled into the study and were assigned to their corresponding treatment as per the randomization list.

### **Protocol deviations included:**

Several subjects (#5107, #5120, #5121, #5126, #5128, #5129, and #6114) had participated in prior investigational studies within 4 weeks of dosing, which was an exclusion criterion for the present study. However, the date of last dose of drug in the other studies either met the washout requirement or was very close to meeting study requirements (whereas the official date of "last participation" may have been later due to follow up procedures, including follow up phone calls and/or physical exams). The sponsor approved these subjects for enrollment.

Four subjects (#5125, #5127, #5148, and #5152) were screened outside the screening time window (screening physical exams were combined with the physical exam required at baseline), but were approved by the sponsor to enroll in the study.

Subjects #5129 and #5152 were taking a multi-vitamins within 2 weeks of first study drug administration (both subjects discontinued taking these 4 days prior to the first dose), and the sponsor approved both subjects for study participation.

## **Pharmacokinetics**

A summary of PK parameters of aliskiren after single doses of the 150-mg overencapsulated tablet and of the 150-mg FMI tablet is given in the following table:

Treatment	$t_{max}$ (h) Median (min; max)	$C_{max}$ (ng/mL) Mean $\pm$ SD (CV %)	$AUC_{(0-t)}$ (ng-h/mL) Mean $\pm$ SD (CV%)	$AUC_{(0-\infty)}$ (ng-h/mL) Mean $\pm$ SD (CV %)	$AUC_{(0-t_{max})}$ (ng-h/mL) Mean $\pm$ SD (CV %)
Overencapsulated Tablet	1.5 (0.28; 6.0)	98.2 $\pm$ 85.5 (87.0%)	598.3 $\pm$ 425.1 (71.0%)	663.8 $\pm$ 467.8 (70.5%)	75.1 $\pm$ 82.3 (109.6%)
FMI Tablet	1.0 (0.25; 6.2)	119.6 $\pm$ 91.1 (76.1%)	654.6 $\pm$ 351.4 (53.7%)	719.8 $\pm$ 389.4 (54.1%)	71.7 $\pm$ 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)

The 90% confidence intervals for the geometric mean ratios of the AUCs for the two aliskiren formulations were within the bioequivalence range of 0.8–1.25. The median  $t_{max}$  was 1.5 h for the FMI tablet and 1 h for the overencapsulated tablet, with a similar range for both formulations. The point estimate for the  $C_{max}$  geometric ratio was within the range of 0.8–1.25, and the 90% CI was 0.70–0.90.

A total of 58 subjects were enrolled, with 48 subjects completing all four treatment periods of the study. All available PK data was included in the analysis.

Subjects #5114 and #5129 only completed Treatment Period 1. They were replaced by Subjects #6114 and #6129 respectively. Subjects #5130 and #5132 only completed Treatment Period 1, but they were not replaced. PK parameters were not derived for Subjects #5114, #5129, #5130 or #5132, so they were not included in the statistical analysis of the PK parameters.

Subjects #5108, #5117 and #5137 only completed Treatment Periods 1 and 2, and Subjects #5102, #5119 and #5124 only completed Treatment Periods 1, 2 and 3, but none of these subjects were replaced. PK parameters were derived for these subjects, so they were included in the statistical analysis of the PK parameters.

#### **SAFETY:**

All subjects who received at least one treatment were included in the safety and tolerability evaluation.

There was one event reported during the study, which, by definition, met the criteria of a serious adverse event as per Novartis internal reporting procedures: Subject #5119 had a positive serum pregnancy test upon check-in for Period 4. The subject was immediately discontinued from the study and the event was appropriately reported to Novartis Clinical Safety and Epidemiology on the Clinical Trial Pregnancy form. Approximately six weeks later, the subject reported that she had electively terminated the pregnancy. Novartis standard procedure defines termination of a pregnancy, whether elective, spontaneous or therapeutic, as a "medically significant" event that requires medical or surgical intervention. Hence, the termination of the pregnancy was reported as a serious adverse event. The subject returned to the study site post-procedure, at which time her follow up serum hCG results were negative. She had no complications and the event was considered fully resolved. The relationship to study drug was deemed "not suspected" by the Investigator.

Overall, a total of 25 subjects experienced 48 total adverse events. By treatment, 17 subjects had adverse events while taking the FMI tablet, and 15 while taking the overencapsulated tablet. By inspection, there were no differences observed in the incidence of adverse events among the treatments. The most frequently occurring adverse events were nervous system disorders (eight cases of headache reported by seven subjects and three of dizziness, reported by three subjects). Forty-one of the 48 total adverse events observed during the study were mild in severity, five were moderate, and two were severe. Twelve of the 48 events were suspected to be related to study medication.

One subject experienced diarrhea mild in nature (#5110) and not suspect of study drug.

In addition to Subject #5119, discussed above, one additional subject was prematurely discontinued from the study due to an adverse event: Subject #5124 was dropped from the study on Day 32 due to neck pain, which was not suspected to be related to study drug.

All but a few of the subjects had one or more abnormalities in serum chemistry, hematology, and/or urinalysis during the study; with the exception of the three subjects described below, none of the abnormalities were considered by the Investigator to be clinically significant. Many of the abnormalities were isolated instances or were only of relatively minor deviation from normal.

Subject #5102 was dropped from study at baseline Period 4 due to low hemoglobin and hematocrit values. Subject #5114 was dropped at baseline Period 2 due to the presence of RBCs in urine, and #5129 was discontinued from the study also at baseline Period 2 for elevated liver enzymes.

Most of the subjects had one or more incidents of vital signs abnormalities during the study, about half of which involved orthostatic changes in pulse (increase of > 20 bpm upon standing). There was no pattern suggesting that the frequency of these instances was more prominent during any of the treatment periods. Upon inspection, mean vital signs did not show any remarkable changes during treatment.

Twenty-three subjects had clinically insignificant ECG abnormalities during the study, with similar incidence between the two treatment sequences.

#### **CONCLUSIONS:**

According to the sponsor:

- Aliskiren FMI tablets and overencapsulated tablets are bioequivalent with respect to overall drug exposure (AUCs).
- The rate of absorption ( $t_{max}$ ) is similar for the FMI tablets and the overencapsulated tablets.
- The maximum concentration during the absorptive phase is similar for the FMI tablets and the overencapsulated tablets, as indicated by the point estimate for the  $C_{max}$  geometric ratio being within the range of 0.8–1.25 (90% CI = 0.70–0.90).
- Aliskiren is safe and well tolerated when given as 150-mg single doses of either the FMI tablet or the overencapsulated tablet.

#### **REVIEWER'S COMMENT:**

1. In this study, the sponsor extended the fasting period post drug administration from 4 to 5 hours in order to eliminate any possibility of food interfering with the pharmacokinetic results.
2. This over-encapsulated formulation was used in studies 2203 and 2204.
3. Demographics table has 10 subjects excluded from study; but in narrative they replaced 2 making it 8 subjects excluded from study – table needs updating and not sure if table is accurate with final subjects in study.
4. Sponsor states that there's high intra-subject variability; but does not provide the final calculations they obtained.

**STUDY SPP100A2209** – AN OPEN LABEL, NON-RANDOMIZED, PARALLEL-GROUP STUDY TO CHARACTERIZE AND COMPARE THE SAFETY, TOLERABILITY AND PHARMACOKINETICS OF MULTIPLE DOSES OF ALISKIREN ALONE OR IN COMBINATION WITH IRBESARTAN IN SUBJECTS WITH MILD TO SEVERE RENAL IMPAIRMENT WITH THAT IN MATCHED HEALTHY CONTROL SUBJECTS.

**STUDY INVESTIGATOR AND SITE:**

**REPORT # SPP100A2209**

**EDR VOLUME 6**

**STUDY DATES:** April 15, 2004 – December 21, 2005

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**OBJECTIVES:**

**Primary**

1. To compare safety and tolerability of multiple doses of aliskiren alone or in combination with Irbesartan in subjects with mild to moderate renal impairment to matched healthy control subjects.
2. To compare the safety and tolerability of multiple doses of aliskiren in severe renal impairment to matched healthy control subjects.

**Secondary**

1. To compare pharmacokinetics of multiple doses of aliskiren alone or in combination with Irbesartan in subjects with mild to moderate renal impairment with that in matched healthy control subjects.
2. To compare pharmacokinetics of multiple doses of aliskiren in severe renal impairment with that in matched healthy control subjects.

**FORMULATION:**

SPP100                      300mg tablets (KN# 6000973.001, Batch#X1540603) by  
Novartis

Irbesartan                    300mg tablet (Aprovel®, EU/1/97/046/007 Batch# 201213) by  
Novartis

**STUDY DESIGN:**

This was a single-center, open label, non-randomized, parallel group, and multiple dose study consisting of two groups. Group 1 included male subjects with mild (n=6), moderate (n=5) and severe (n=6) renal impairment defined as CrCL 50-80 mL/min, 30-49 mL/min and < 30 mL/min respectively (17 subjects in total). Group 2 included 17 healthy subjects matched for age and weight with normal renal function (CrCL > 80 mL/min). Subjects were administered 300 mg aliskiren for 7 days and co-administered 300 mg aliskiren plus 300 mg Irbesartan for additional 7 days. Patients with severe renal impairment and their corresponding healthy subjects did not participate in the co-administration portion of the study with Irbesartan. Mild and moderate renal impairment patients with their corresponding matched-healthy subjects did participate in the co-administration portion of the study with Irbesartan.

### **ANALYTICAL METHODS:**

**Aliskiren plasma and urine concentrations:** samples were analyzed by a HPLC/MS/MS method and was validated appropriately. The assay was linear over the measured concentration range of 0.5 to 100 ng/mL with  $r^2 > 0.9963$  with an LLOQ of 1 ng/mL.

### **PK SAMPLE COLLECTION/CALCULATIONS, PD ASSESSMENTS/CALCULATIONS AND STATISTICAL ANALYSIS:**

**Blood samples** were collected for aliskiren:

Day 1, 7 and 14: at pre-dose, 0.5, 1, 2, 4, 6, 8 and 12 hours post-dose

Day 5, 6, 12, 13 and pre-dose.

**Urine samples** were collected:

Days 1, 7 and 14 at pre-dose and 0-6, 6-12 and 12-24 h post-dose.

### **Pharmacokinetic calculations**

The following pharmacokinetic parameters were determined using non-compartmental method(s):  $AUC_{0-24h, Day 1}$ ,  $AUC_{\tau}$ ,  $C_{min,ss}$ ,  $C_{avg,ss}$ ,  $C_{max, Day 1}$ ,  $C_{max, ss}$ ,  $t_{max, Day 1}$ ,  $CL/F$ ,  $CL_r$ , and the accumulation factor (R).

Statistical Analysis – Log transformed aliskiren pharmacokinetic parameters AUC,  $C_{max}$ , and  $C_{min}$  were analyzed. The linear model used for the analysis included a random factor for matched Pair (matched pair of subjects) and fixed factors Status (mild, moderate, and severe), Day (Day 1 as single dose aliskiren, Day 7 as multiple dose aliskiren, and Day 14 as multiple dose aliskiren with Irbesartan), and Group (renal impaired and healthy control), together with interactions of Day x Group and Status x Day x Group. The factor Pair was nested in Status.

### **SAFETY:**

Monitoring and recording of all adverse events was performed throughout the study, at pre-dose and at end-of-study. Other safety assessments included monitoring of hematology, blood chemistry and urine parameters, periodic monitoring of vital signs during treatment periods and performance of physical examinations and ECGs.

### **RESULTS:**

Thirty-three males (all Caucasian) were enrolled and completed the study.

### **Pharmacokinetics**

Multiple dosing of aliskiren in healthy and renally impaired subjects resulted in increases in AUC.

### **Renal impairment on Aliskiren Pharmacokinetics**

Aliskiren AUC was increased in the renally impaired population when compared to age and weight-matched healthy subjects on day 1 of treatment and after multiple dosing. Increases in AUC did not seem to correlate with severity of renal impairment.

**Table 1 Descriptive statistics of pharmacokinetic parameters on day 1 in healthy subjects that are matched to renal impairment patients by renal function category following administration of 300 mg aliskiren**

Subject Sub-Group	Subject ID	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (h)	AUC <sub>(0-24)</sub> (ng x h/mL)
Healthy-Mild	N	6	6	6
	Mean	212.2	2.3	741.0
	SD	145.1	1.5	275.5
	Median	193.5	2.0	703.4
Healthy-Moderate	N	5	5	5
	Mean	134.0	2.1	713.6
	SD	49.2	1.8	299.1
	Median	145.0	1.0	753.0
Healthy -Severe	N	5	5	5
	Mean	135.2	1.4	543.7
	SD	37.0	1.5	243.3
	Median	136.0	1.0	530.6

**Descriptive statistics of pharmacokinetic parameters on day 7 in healthy subjects matched to renal impairment patients following administration of 300 mg aliskiren**

	C <sub>max,ss</sub> (ng/mL)	T <sub>max,ss</sub> (h)	AUC <sub>t</sub> (ng x h/mL)	C <sub>min,ss</sub> (ng/mL)	CL/F (mL/h)	Fluctuation%	C <sub>avg,ss</sub> (ng/mL)
<b>Healthy -Mild</b>							
N	6	6	6	6	6	6	6
Mean	204	2.3	1109.4	17.2	320551	396.6	47.0
SD	93.9	1.8	477.3	7.2	174199	94.7	19.4
Median	190.5	2.5	1083.4	18.0	280996	388.8	45.2
<b>Healthy -Moderate</b>							
N	5	5	5	5	5	5	5
Mean	197.6	2.0	1165.8	20.0	261786	366.7	48.6
SD	46.9	1.8	166.9	5.8	41161	81.6	7.0
Median	207.0	1.0	1201.0	20.7	249572	360.0	50.1
<b>Healthy -Severe</b>							
N	5	5	5	5	5	5	5
Mean	342.6	1.5	1575.7	15.9	357204	398.0	65.7
SD	381.3	1.4	1261.5	7.8	281790	191.4	52.6
Median	175.0	1.0	1130.5	18.2	265368	330.3	47.1

**Table 2 Descriptive statistics of PK parameters on day 1 in renally impaired subjects following administration of 300 mg of aliskiren**

Subject Sub-Group	Subject ID	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (h)	AUC <sub>(0-24)</sub> (ng x h/mL)
Mild	N	6	6	6
	Mean	215.6	2.3	1162.2
	SD	129.5	1.5	571.5
	Median	177.5	2.0	961.6
Moderate	N	5	5	5
	Mean	467.2	2.6	2068.7
	SD	583.3	1.9	2141.0
	Median	213.0	4.0	1340.3
Severe	N	6	6	6
	Mean	188.7	2.9	982.4
	SD	88.7	1.7	405.4
	Median	191.0	4.0	937.9

**Descriptive statistics of PK parameters on day 7 in renally impaired subjects following administration of 300 mg of aliskiren**

	$C_{max,ss}$ (ng/mL)	$T_{max,ss}$ (h)	$AUC_T$ (ng x h/mL)	$C_{min,ss}$ (ng/mL)	CL/F (ml/h)	Fluctuation %	$C_{avg,ss}$ (ng/mL)
<b>Mild</b>							
N	6	6	6	6	6	6	6
Mean	545.7	1.58	2799.0	36.1	185814	488.1	116.7
SD	430.2	1.28	2459.8	33.5	129766	250.4	102.5
Median	368.0	1.00	1812.1	23.3	173479	399.1	75.6
<b>Moderate</b>							
N	5	5	5	5	5	5	5
Mean	350.4	1.92	2449.3	39.0	157753	289.7	102.2
SD	281.0	1.94	1742.4	13.3	66070	75.9	72.7
Median	274.0	0.50	1767.6	32.8	169529	302.1	73.7
<b>Severe</b>							
N	6	6	6	6	6	6	6
Mean	200.1	2.17	1689.9	34.1	262254	231.1	70.4
SD	137.9	1.47	1015.5	16.0	201419	57.9	42.3
Median	135.0	1.52	1399.3	33.0	219227	235.9	58.3

**Effect of Irbesartan on aliskiren PK**

The Pharmacokinetics of aliskiren at steady state were not affected by co-administration of Irbesartan in subjects with normal renal function or in subjects with mild to moderate renal impairment.

**Table 3 Individual and mean pharmacokinetic parameters of aliskiren on day 14 in healthy subjects following administration of 300 mg aliskiren and 300 mg of Irbesartan**

Subject ID	$C_{max,ss}$ (ng/mL)	$T_{max,ss}$ (h)	$AUC_T$ (ng x h/mL)	$C_{min,ss}$ (ng/mL)	CL/F (mL/h)	Fluctuation %	$C_{avg,ss}$ (ng/mL)
<b>Healthy -Mild</b>							
N	6.0	6.00	6.0	6.0	6.0	6.0	6.0
Mean	142.2	0.76	944.6	18.1	384742	266	39.4
SD	122.8	0.27	441.5	7.2	186734	149	18.4
Median	97.0	0.77	930.8	16.6	332850	209	38.8
<b>Healthy -Moderate</b>							
N	5.0	5.00	5.0	5.0	5.0	5.0	5.0
Mean	226.4	0.90	1053.3	17.1	362275	450	43.9
SD	164.2	0.65	679.2	10.5	161860	149	28.3
Median	220.0	0.50	827.1	12.2	362735	482	34.5

**Table 4 Individual and mean aliskiren pharmacokinetic parameters on day 14 in subjects with renal impairment following administration of 300 mg aliskiren and 300 mg of Irbesartan**

	$C_{max,ss}$ (ng/mL)	$T_{max,ss}$ (h)	$AUC_T$ (ng x h/mL)	$C_{min,ss}$ (ng/mL)	CL/F (mL/h)	Fluctuation%	$C_{avg,ss}$ (ng/mL)
<b>Mild</b>							
N	6	6	6	6	6	6	6
Mean	249.1	4.00	2010.8	37.7	181892	260	83.8
SD	122.7	1.79	1041.7	24.2	80726	100	43.4
Median	217.5	4.00	1657.8	32.8	183496	245	69.1
<b>Moderate</b>							
N	5	5	5	5	5	5	5
Mean	316.4	1.97	2409.3	43.9	163316	246	100.4
SD	297.3	1.86	1528.6	19.4	89428	114	63.7
Median	212.0	0.85	2093.1	49.5	143330	215	87.2



**STUDY SPP100A2211 – AN OPEN LABEL, MULTIPLE DOSE STUDY TO EVALUATE THE PHARMACOKINETIC DRUG-DRUG INTERACTION BETWEEN FUROSEMIDE (20 MG) AND ALISKIREN (300 MG) WHEN GIVEN ALONE OR IN COMBINATION TO HEALTHY VOLUNTEERS**

**STUDY INVESTIGATOR AND SITE:**

**REPORT # SPP100A2211**

**VOLUMES in EDR, Section 6**

**STUDY DATES: May 15 – November 5, 2004**

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**OBJECTIVES:**

**Primary**

To investigate the potential for a pharmacokinetic interaction between aliskiren and furosemide following once a day dosing in healthy volunteers.

**Secondary**

To assess the safety and tolerability of co-administration of aliskiren and furosemide in healthy volunteers

**FORMULATION:**

**SPP100** 300 mg tablets (Aliskiren, KN# 6000973.001, Batch no.X1540603, Exp. date: 06/2005) by Novartis

**Furosemide** 20 mg tablets (Batch no. 3036306, Exp. date: 03/2007) purchased by the investigator from the local pharmacy

**STUDY DESIGN:**

This was a single-center, open-label, multiple dose, cross-over study under fasted conditions. Subjects were administered furosemide 20 mg for 3days followed by 3days washout (Period 1) then aliskiren 300 mg for 7days and Aliskiren 300 mg plus furosemide 20 mg for 3days. Subjects were domiciled from the day prior to first administration of drug to day 17 and were not permitted to take xanthine containing food or beverages, alcohol, and cigarettes during that time. Breakfast was not provided during drug administration periods. Subjects were fasted for at least 10 hr before the administration of study drugs and continued to fast at least 4 hr after drug administration.

**ANALYTICAL METHODS:**

**Aliskiren plasma concentrations:** samples were analyzed by a validated HPLC/MS/MS method with an LLOQ of 0.5 ng/mL.

**Furosemide plasma concentrations:** was determined by a validated HPLC/MS/MS method with an established LLOQ of 5 ng/mL.

**PK SAMPLE COLLECTION/CALCULATIONS AND STATISTICAL ANALYSIS:**

**Blood samples** were collected for aliskiren and furosemide concentrations at the following time points during all treatments:

**Aliskiren:** Day 13 and 16: at pre-dose, then at 0.5, 1, 2, 4, 6, 8, 12, 16 and 24 hours post-dose

**Furosemide:** Day 3 and 16: at pre-dose, then at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 hours post-dose

**Pharmacokinetic calculations**

The PK parameters  $AUC_{\tau}$ ,  $C_{min}^{ss}$ ,  $C_{max}^{ss}$ ,  $t_{max}^{ss}$ , for both aliskiren and furosemide were calculated, using non-compartmental methods. Descriptive statistics of all calculated PK parameters were determined.

**Statistical Analysis** – For both aliskiren and furosemide, log-transformed PK parameters, AUC and  $C_{max}^{ss}$ , were analyzed by a linear mixed effect model, with treatment as a fixed factor and subject as a random factor. The resulting 90% confidence interval of the appropriate treatment mean ratios were used to examine the drug-drug interaction. Subjects that were withdrawn were not replaced.

**SAFETY:**

Monitoring and recording of all adverse events beginning after the first dose, pre-dose and end-of-study monitoring of hematology, blood chemistry and urine parameters, periodic monitoring of vital signs during treatment periods and performance of physical examinations and ECGs.

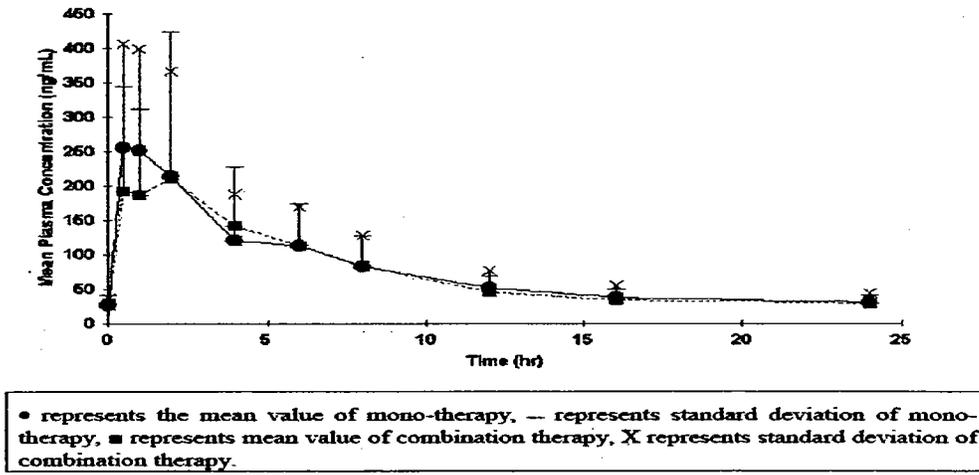
**RESULTS:**

Twenty-two subjects were enrolled and 21 subjects (17 males and 4 females; 4 Caucasians, 1 Black and 17 other race) completed the study. Subject 5109 withdrew informed consent after the first dose of furosemide.

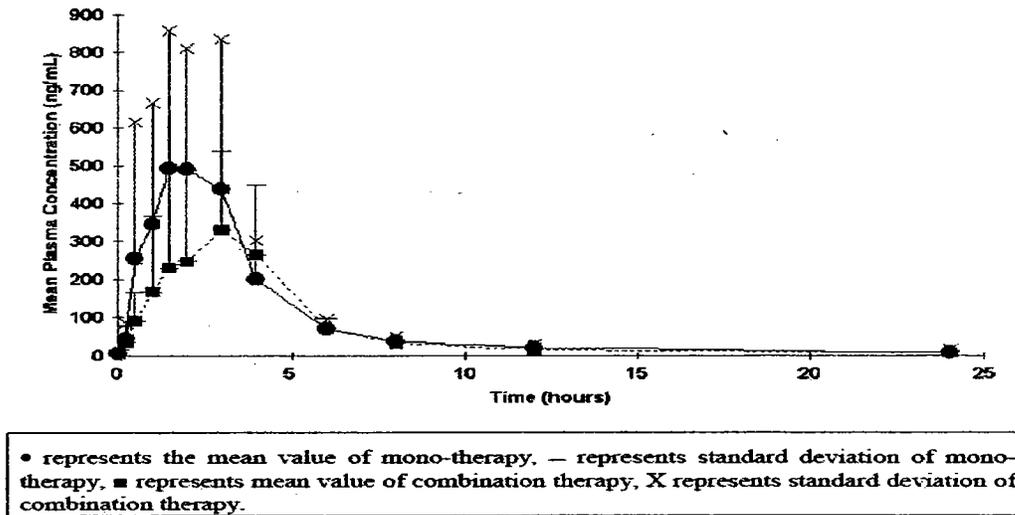
**Pharmacokinetics**

Furosemide decreased aliskiren  $C_{max}$  and AUC, however, the effect on AUC was less than 10% and practically negligible. On the other hand, aliskiren co-administration did reduce the AUC and  $C_{max}$  of furosemide by 28% and 49%, respectively.

**Figure 1** Mean (SD) plasma concentration-time profile of Aliskiren 300 mg monotherapy (Day13) and furosemide/aliskiren (20/300mg) combination therapy (Day 16)



**Figure 2** Mean plasma concentration-time profile of furosemide 20 mg alone (Day 3) and furosemide/aliskiren (20/300mg) combination therapy (Day 16)



**Table 1**  
**Statistical analysis results of the pharmacokinetic interaction**  
**between SPP100 and furosemide**

Analyte	Test treatment	Reference treatment	Parameter	Ratio of geometric means (test/ref)	90% CI for the ratio
Aliskiren	Aliskiren+furosemide	Aliskiren	AUC <sub>t</sub>	0.93	(0.84, 1.04)
			C <sub>max, ss</sub>	0.80	(0.65, 0.97)
Furosemide	Aliskiren+furosemide	Furosemide	AUC <sub>t</sub>	0.72	(0.64, 0.81)
			C <sub>max, ss</sub>	0.51	(0.39, 0.66)

**SAFETY:**

There were no adverse-event-related dropouts (ADO) in this study. Fourteen (14) of the 21 subjects that received drug reported AEs. The most commonly reported AEs were headache and dry mouth. The incidence of adverse events indicated that adverse events were observed more frequently during aliskiren treatment (9 subjects) and aliskiren - furosemide combination treatment (7 subjects) than the furosemide treatment (3 subjects). Seven subjects in the aliskiren monotherapy group reported nervous system disorders. The number of subjects who showed gastrointestinal disorders was similar in the aliskiren monotherapy (2), the aliskiren - furosemide combination treatment (2), and the furosemide treatment (1). The majority of adverse events were mild in severity. There was one severe adverse event. On Day 14 of the study, subject 5111 suffered a headache, which was determined by the investigator to be related to the study treatment. The subject was treated with one Tylenol (500 mg) on Day 14. On Day 16 of the study, the subject suffered a headache again but it was moderate in severity, no headaches were reported after Day 16. All of the adverse events were resolved by study completion.

**CONCLUSIONS:**

Furosemide decreased aliskiren C<sub>max</sub> and AUC, however, the effect on AUC was less than 10% and practically negligible. Aliskiren reduces the C<sub>max</sub> and AUC of furosemide by 28% and 49%, respectively. The sponsor has proposed labeling precautions about co-administration with furosemide that seem appropriate.

**REVIEWER'S COMMENT:**

1. The dose of furosemide used in the study was the minimal clinical dose of 20 mg.
2. On page 35, the title of Fig. 7-2 should be "Mean plasma concentration-time profile of aliskiren alone (Day 13) and furosemide/aliskiren combination therapy (Day 16)"

**STUDY SPP100A2214** – AN OPEN LABEL, MULTIPLE DOSE STUDY TO EVALUATE THE PHARMACOKINETIC DRUG-DRUG INTERACTION BETWEEN LANOXIN (DIGOXIN) AND ALISKIREN WHEN GIVEN ALONE OR IN COMBINATION TO HEALTHY VOLUNTEERS.

**STUDY INVESTIGATOR AND SITE:**

**REPORT # SPP100A2214**

**VOLUMES** in EDR, Section 6

**STUDY DATES:** November 15 – January 13, 2005

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**OBJECTIVES:**

**Primary**

- To characterize the pharmacokinetics of Aliskiren following once a day dosing alone or in combination with digoxin in healthy volunteers.
- To investigate the pharmacokinetics of digoxin alone or in combination with Aliskiren in healthy volunteers

**Secondary**

To assess safety and tolerability of co-administration of Aliskiren and digoxin in healthy volunteers.

**FORMULATION:**

SPP100                      300 mg tablets (Batch No. X199FA, Exp. Date not provided) by Novartis

Digoxin                      0.25 mg tablets (Batch No. 14304, Exp. Date: 08/2006) were purchased by the investigator from the local pharmacy

**STUDY DESIGN:**

This was a single-center, open, multiple-dose, two-period, cross-over drug-drug interaction study under fasted conditions in 22 healthy male and female volunteers between the ages of 18 to 45 years. Subjects were administered 300 mg aliskiren for 7 days followed by 10 days washout then digoxin 0.25 mg for 9 days followed by aliskiren plus digoxin for 7 days. Subjects were confined to the study center for at least 24 hours before administration of study drug until 24 hours after the last dose for days 1 – 7 and 17 - 33. During the domiciled period, subjects were not permitted to take xanthine containing food or beverages, alcohol, and cigarettes. Breakfast was not provided except during the washout periods. Subjects were fasted at least 10 hr before the administration of study drug and continued to fast at least 4 hr after administration.

**ANALYTICAL METHODS:**

**Aliskiren plasma concentrations:** samples were analyzed by a validated HPLC/MS/MS method with a LLOQ of 0.5 ng/mL.

**Digoxin plasma concentrations:** plasma digoxin were determined by a validated HPLC/MS/MS method with a LLOQ of 0.2ng/mL.

**PK SAMPLE COLLECTION/CALCULATIONS, PD ASSESSMENTS/CALCULATIONS AND STATISTICAL ANALYSIS:**

**Blood samples** were collected for aliskiren and digoxin concentrations at the following time points during all treatments:

Aliskiren: Day 5, 6, 31, 32 pre-dose, and Day 7, 33: at pre-dose, 0.5, 1, 2, 4, 6, 8, 12, 16 and 24 hours post-dose

Digoxin: Day 20-25, 28-32 pre-dose, and Day 26 and 33: at pre-dose, 0.5, 1, 2, 4, 6, 8, 12, 16 and 24 hours post-dose

**Pharmacokinetic calculations**

The PK parameters  $AUC_{\tau}$ ,  $C_{min}^{ss}$ ,  $C_{max}^{ss}$ ,  $t_{max}^{ss}$ , for both aliskiren and digoxin were calculated, using non-compartmental methods. Descriptive statistics of all calculated PK parameters were determined.

**Statistical Analysis** – For both Aliskiren and digoxin, log-transformed PK parameters AUC and  $C_{max}$  were analyzed by a linear mixed effect model, with treatment as a fixed factor and subject as a random factor. The resulting 90% confidence interval of the appropriate treatment means ratios were used to examine the drug-drug interactions. Subjects that were withdrawn were not replaced.

**SAFETY:**

Monitoring and recording of all adverse events beginning after the first dose, pre-dose and end-of-study monitoring of hematology, blood chemistry and urine parameters, periodic monitoring of vital signs during treatment periods and performance of physical examinations and ECGs.

**RESULTS:**

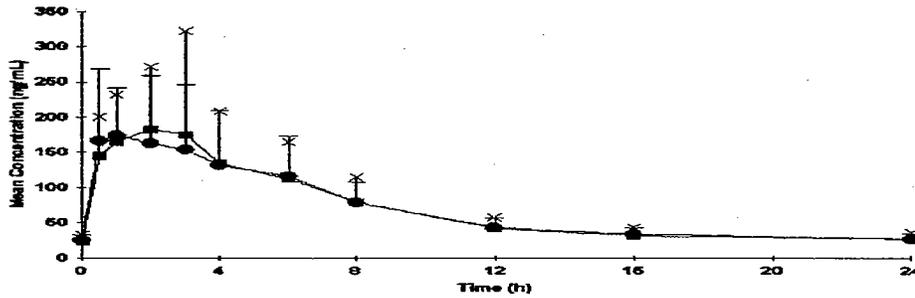
Twenty-two subjects were enrolled and 19 subjects (16 males and 6 females; 11 Black, 6 Caucasians, and 5 other race) completed the study. Subject 5103 withdrew informed consent, 5111 dropped out by protocol violation and 5121 discontinued due to abnormal test value (QTc prolongation).

**Pharmacokinetics**

Aliskiren PK profiles were not affected by co-administration of digoxin and digoxin PK profiles were not affected vice versa.

## Aliskiren

Figure 1 Mean Aliskiren concentrations in healthy volunteers when treated with Aliskiren and combination therapy (with digoxin)



• represents the mean value of mono-therapy, — represents standard deviation of mono-therapy, ■ represents mean value of combination therapy, X represents standard deviation of combination therapy.

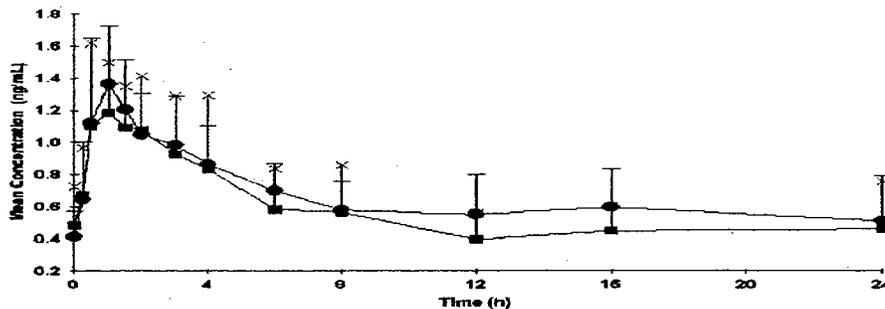
Table 1  
Summary analysis results of Aliskiren PK parameters

Parameter	Ratio of geometric means	
	(A+B:A)	90% CI for ratio
AUC <sub>T</sub> (ng.h/mL)	1.02	(0.93, 1.13)
C <sub>max</sub> <sup>ss</sup> (ng/mL)	0.98	(0.80, 1.19)

Treatment A = Aliskiren 300mg, Treatment B = Digoxin 0.25mg

## Digoxin

Figure 2 Mean digoxin concentrations in healthy volunteers during digoxin treatment alone and combination therapy (with Aliskiren)



• represents the mean value of mono-therapy, — represents standard deviation of mono-therapy, ■ represents mean value of combination therapy, X represents standard deviation of combination therapy.

The difference in digoxin AUC between the monotherapy and co-administration with aliskiren was about 15%, not of clinical significance.

**Table 2**  
**Summary analysis results of digoxin PK parameters**

Parameter	Ratio of geometric means (A+B:B)	90% CI for ratio
AUC <sub>τ</sub> (ng.h/mL)	0.85	(0.75, 0.97)
C <sub>max</sub> <sup>ss</sup> (ng/mL)	0.91	(0.84, 0.99)

Treatment A = Aliskiren 300mg, Treatment B = Digoxin 0.25mg

**SAFETY:**

There were no deaths or serious adverse events reported. One subject was discontinued due to adverse effect (QTc prolongation at day 26 and 27 during combination therapy). A total of 60 adverse events were reported by 17 subjects, of which 46 (77%) were rated as mild, 14 (23%) rated as moderate, and none were rated severe. The majority of adverse events (36/60, 60%) were indicated as not related to the study drug. Headache was the most commonly reported adverse event. Other commonly reported events were diarrhea, sore throat, and dizziness. The digoxin monotherapy had the highest incidences of AEs (42%).

**CONCLUSIONS:**

This study is acceptable. There are no changes in PK profile of both drug in combination or individual administration. It should be noted that one subject was discontinued from study due to QTc prolongation during combination administration at day 26 and 27.

**REVIEWER'S COMMENT:**

1. The reviewer concurs.
2. No expiration date or manufacturing date was provided for aliskiren.

**APPEARS THIS WAY  
ON ORIGINAL**

**STUDY SPP100A2216** – AN OPEN LABEL, MULTIPLE DOSE STUDY TO EVALUATE THE PHARMACOKINETIC DRUG-DRUG INTERACTION BETWEEN VALSARTAN AND ALISKIREN WHEN GIVEN ALONE OR IN COMBINATION IN HEALTHY VOLUNTEERS.

**STUDY INVESTIGATOR AND SITE:**

**REPORT # SPP100A2216**

**EDR VOLUME 6**

**STUDY DATES:** February 03 – February 26, 2005

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**OBJECTIVES:**

**Primary**

To investigate the pharmacokinetic interaction between aliskiren and valsartan following once a day dosing alone or in combination in healthy volunteers

**Secondary**

- To investigate the pharmacodynamic interaction between aliskiren and valsartan following once a day dosing alone or in combination in healthy volunteers
- To investigate the safety and tolerability of co-administration of aliskiren and valsartan in healthy volunteers

**FORMULATION:**

SPP100      300 mg tablets (Batch No. X095 0304) by Novartis

Valsartan      320 mg tablets (Diovan, Batch No. F0112W1, Exp. Date: 09/2006)  
purchased by the investigator from the local pharmacy

**STUDY DESIGN:**

This was a single-center, open, two-period, multiple doses, cross-over drug-drug interaction study under fasted conditions in 22 healthy volunteers. Subjects were administered 320 mg valsartan for 4 days followed by 3 days of washout then aliskiren 300 mg for 7 days followed by aliskiren plus valsartan for 4 days. Subjects were confined to the study center for at least 24 hours before administration of study drug until the end of study. Subjects were not permitted to take xanthine containing food or beverages, alcohol, and cigarettes while domiciled. Breakfast was not provided during the treatment periods. Subjects were fasted at least 10 hr before the administration of study drug and continued to fast at least 4 hr after administration. blood samples to determine plasma active rennin (total rennin concentration), plasma rennin activity (PRA), aldosterone, angiotensin I (Ang I), and angiotensin II (Ang II) were obtained on study days 4, 14, and 18.

**ANALYTICAL METHODS:**

**Aliskiren plasma concentrations:** samples were analyzed by a validated HPLC/MS/MS method with a LLOQ established at 0.5 ng/mL.

**Valsartan plasma concentrations:** plasma valsartan were determined by a validated HPLC/MS/MS method with a LLOQ established at 20 ng/mL.

**PK SAMPLE COLLECTION/CALCULATIONS, PD ASSESSMENTS/CALCULATIONS AND STATISTICAL ANALYSIS:**

**Blood samples** were collected for aliskiren and valsartan concentrations at the following time points during all treatments:

**Aliskiren:** Day 12, 13, 16, 17: pre-dose, and Day 14, 18: at pre-dose, 0.5, 1, 2, 4, 6, 8, 12, 16 and 24 hours post-dose

**Valsartan:** Day 2, 3, 16, 17: pre-dose, and Day 4 and 18: at pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 12, 16 and 24 hours post-dose

**Pharmacokinetic calculations**

The PK parameters  $AUC_{\tau}$ ,  $C_{min}^{ss}$ ,  $C_{max}^{ss}$ ,  $t_{max}^{ss}$ , for both aliskiren and valsartan were calculated, using non-compartmental methods. Descriptive statistics of all calculated PK parameters were determined.

**Exploratory pharmacodynamic assessments**

- AR, PRA, and aldosterone (7 mL blood per time point): On days 4, 14, and 18: predose, 1, 2, 4, 6, 12, 24 hours postdose

- Plasma Ang I and Ang II: (5 mL blood per time point): On days 4, 14, and 18: predose, 6, 12, 24 hours postdose

- PD parameters: The primary pharmacodynamic variable to be used for assessment will be the  $C_{max}$  and  $AUC_{0-24}$  of PAR. Descriptive statistics will be provided for the secondary pharmacodynamic variables.

- PD evaluations: descriptive PD analysis

**Statistical Analysis** – For all aliskiren and valsartan, log-transformed PK parameters  $AUC$  and  $C_{max}$  were analyzed by a linear mixed effect model, with treatment as a fixed factor and subject as a random factor. The resulting 90% confidence interval of the appropriate treatment mean ratios was used to test for any drug-drug interaction.

**SAFETY:**

Safety and tolerability assessments included the monitoring and recording of all adverse events and of concomitant medications/significant non-drug therapies, routine laboratory tests, ECG recordings, vital signs, and physical examinations during screening and after the completion of the study.

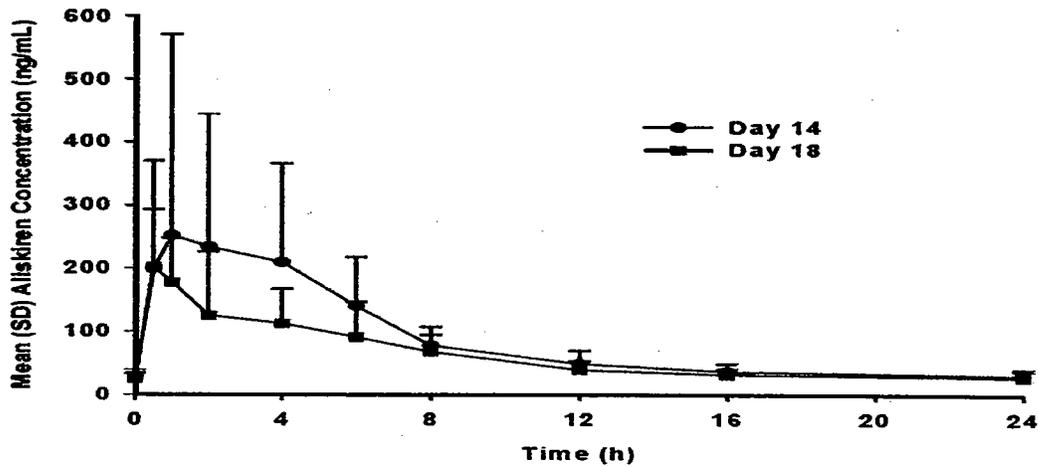
**RESULTS:**

Nineteen subjects were enrolled and 18 subjects (13 males and 5 females; 6 Caucasians, 2 Black, and 10 other race) completed the study. Subject 5116 withdrew consent and did not complete the study.

**Pharmacokinetics**

Aliskiren AUC and  $C_{max}$  were reduced by 26% and 28%, respectively, when co-administered with valsartan.

**Figure 1** Mean aliskiren concentrations at steady state on Day 14 given alone and on Day 18 given in combination with valsartan to healthy subjects



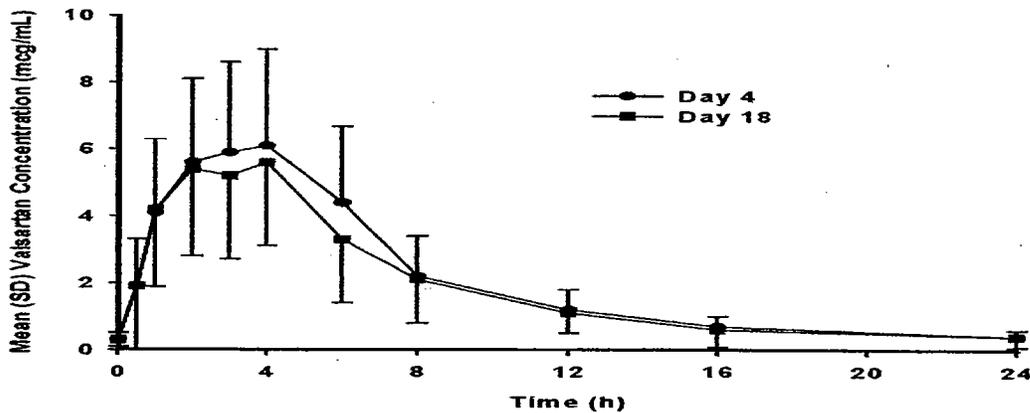
**Table 1** Summary analysis results of aliskiren PK parameters

Parameter	Ratio of geometric means (A+B:B)	90% CI for ratio
AUC <sub>(0-t)</sub> (ng.h/mL)	0.74	(0.63, 0.85)
$C_{max}^{ss}$ (ng/mL)	0.72	(0.52, 0.99)

Treatment A = Valsartan 320mg, Treatment B = Aliskiren 300mg

Valsartan PK was not affected by aliskiren co-administration to the extent of being clinically significant.

**Figure 2** Mean valsartan concentrations at steady state on Day 4 given alone and on Day 18 given in combination with aliskiren to healthy subjects



**Table 2 Summary analysis results of valsartan PK parameters**

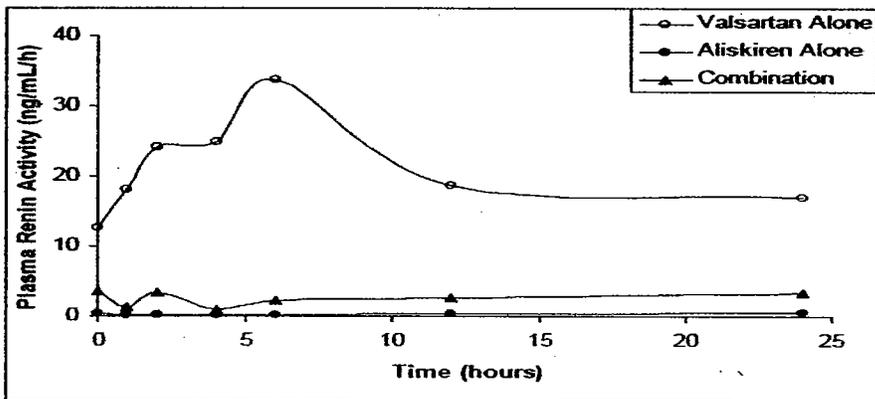
Parameter	Ratio of geometric means	
	(A+B:A)	90% CI for ratio
AUC <sub>(0-4)</sub> (µg.h/mL)	0.86	(0.75, 0.98)
C <sub>max</sub> <sup>ss</sup> (µg/mL)	0.88	(0.74, 1.04)

Treatment A = Valsartan 320mg, Treatment B = Aliskiren 300mg

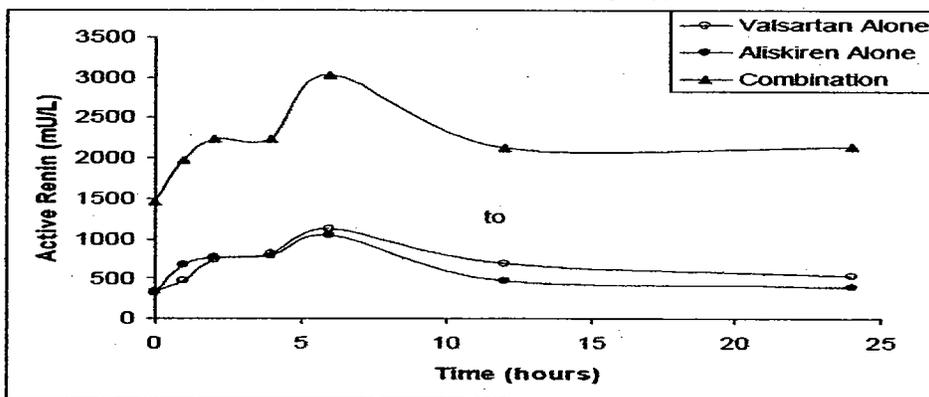
**Pharmacodynamics:**

Aliskiren's PK profile was affected by valsartan (Figure 1) however, the pharmacodynamics of aliskiren as determined by PRA (Figure 3), did not change with co-administration of valsartan. Active rennin in plasma was synergistically increased (Figure 4) when valsartan was co-administered with aliskiren.

**Figure 3 Mean PRA versus time following administration of valsartan alone (Day 4), aliskiren alone (Day14), and the combination (Day 18)**



**Figure 4 Mean plasma AR versus time following administration of valsartan alone (Day 4), aliskiren alone (Day14), and the combination (Day 18)**

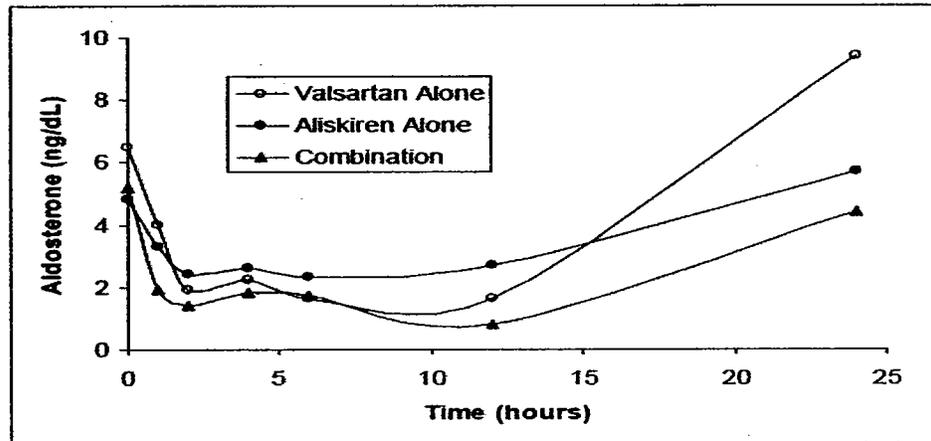


Aldosterone levels decreased following administration of either valsartan or aliskiren alone reaching minimum values of 1.6-2 ng/dL (normal range 2-14 ng/dL) for up to 12 hours post-dose; the reduction in aldosterone levels tended to be slightly greater following combination treatment.

The samples for Ang I and Ang II were not collected and processed appropriately and the data were therefore not analyzed.

Although the study was conducted in normotensive healthy volunteers, blood pressure (supine, systolic and diastolic) tended to be lower during combination treatment. The reductions in the systolic blood pressure with the combination was statistically significant than either monotherapy ( $p < 0.05$ ).

**Figure 5** Mean aldosterone versus time following administration of valsartan alone (Day 4), aliskiren alone (Day14), and the combination (Day 18)



**Table 3** Mean (SD) supine systolic and diastolic blood pressure at steady-state following administration of aliskiren, valsartan and the combination

Blood Pressure	Valsartan Alone	Aliskiren Alone	Combination
Systolic	115 (15)	116 (11)	104 (16)*
Diastolic	63 (11)	62 (7)	58 (10)

\* $p < 0.05$  compares to either monotherapy

#### **SAFETY:**

There were no deaths or serious adverse events (SAEs) in this study. Subject 5116 was discontinued from the study after Day 14 by withdrawing consent. The reason was due to AEs (headache, diarrhea) that first occurred during period 1 (valsartan treatment). Seventeen subjects reported a total of 66 AEs, occurring from the evening before dosing on Day 1 to the completion of the study. Of the 66 AEs, 2 (3%) occurred the evening prior to dosing, 28 (42.4%) occurred during valsartan treatment, 23 (34.9%) during aliskiren treatment, and 13 (19.7%) during the combination treatment. Forty-five (68.2%) AEs were rated as mild and 21 (31.8%) as moderate. Of the 66 reported AEs, 48 (72.2%) were suspected to be related to drug. Of the AEs suspected to be drug related, 16 occurred during treatment with valsartan alone, 19 with aliskiren alone, and 13 with combination treatment. Diarrhea was the most frequently reported AE (7 occurrences, 10.6%). Six subjects reported diarrhea and each occurrence was study drug related. Headache and loss of appetite were the next most frequently reported AEs (6 occurrences each, 9.1%). Six subjects reported loss of appetite and each occurrence was determined to be related to study drug. Four subjects reported headaches; 2 of the 6 occurrences were determined to be study drug related. Two subjects experienced nausea and emesis during treatment with aliskiren and the combination. Headache occurred

more frequently during treatment with valsartan and loss of appetite occurred more frequently with combination drug treatment, while other AEs appeared to be equally distributed across treatments.

It should be noted that 14 subjects had at least one clinically non-significant abnormal ECG reading during the study. There were 5 instances where the QT interval increased to above 460 msec, and in 1 case over 490 msec. All of these prolongations occurred while the subjects were receiving aliskiren only. No actions were taken because of these readings.

**CONCLUSIONS:**

Although aliskiren AUC and  $C_{max}$  were decreased by co-administration of valsartan, plasma rennin activity levels remained similar as with aliskiren monotherapy and aldosterone level was suppressed when aliskiren was administered with valsartan. In addition, relatively large inter-subject variability with aliskiren PK profiles was observed. Thus, decreased PK profiles of aliskiren by valsartan were not considered to be clinically significant.

**REVIEWER'S COMMENT:**

Valsartan clearly affects the pharmacokinetics of Aliskiren; but the changes ( $C_{max}$  and AUC are reduced by 28% and 26%, respectively) are of no clinical significance since aliskiren has a shallow dose-response curve. However, when active rennin in plasma is measured, the combination clearly results in higher active rennin levels and plasma rennin activity with the combination is not any different than with aliskiren alone. Aliskiren seems to reduce the PRA levels dramatically when both drugs are co-administered in comparison to valsartan monotherapy. Active rennin levels are the same for both monotherapies and increases when both drugs are co-administered.

**APPEARS THIS WAY  
ON ORIGINAL**

**STUDY SPP100A 2218 – AN OPEN LABEL, MULTIPLE DOSE STUDY TO EVALUATE THE PHARMACOKINETIC DRUG-DRUG INTERACTION BETWEEN AMLODIPINE AND ALISKIREN WHEN GIVEN ALONE OR IN COMBINATION TO HEALTHY VOLUNTEERS**

**STUDY INVESTIGATOR AND SITE:**

**REPORT # SPP100A 2218**

**EDR VOLUME 6**

**STUDY DATES: February 24, 2005 – May 11, 2005**

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**OBJECTIVES:**

**Primary**

- To characterize the pharmacokinetics of aliskiren following once a day dosing alone or in combination with amlodipine to healthy volunteers.
- To investigate the pharmacokinetics of amlodipine alone or in combination with aliskiren in healthy volunteers.

**Secondary**

To investigate the tolerability of co-administration of aliskiren and amlodipine in healthy volunteers.

**FORMULATION:**

SPP100

300 mg tablets (Aliskiren, Batch no.X199FA) by Novartis

Amlodipine

10 mg tablets (Norvasc<sup>®</sup>, Batch no. 4QL274A, Exp. 10/2008) purchased by the investigator from the local pharmacy

**STUDY DESIGN:**

This was a single-center, open label, two-period, randomized, multiple-dose study. In period 1, subjects were administered 10 mg amlodipine for 14 days followed by 7 days of washout. In period 2, subjects were administered 300 mg aliskiren for 14 days followed by co-administered 300 mg aliskiren plus 10 mg amlodipine for 14 days. The subjects were admitted to the study center at least 12 hours prior to the initial dosing of amlodipine for baseline evaluation, and discharged the following morning after dosing. All subjects remained domiciled on PK sampling days 14, 35, and 49, until the last blood sample was drawn.

**ANALYTICAL METHODS:**

**Aliskiren plasma concentration** samples were analyzed by a validated and acceptable HPLC/MS/MS method with a LLOQ of 0.5 ng/mL.

**Amlodipine plasma concentration** samples were analyzed by a validated and acceptable HPLC/MS/MS method with a LLOQ of 0.5 ng/mL.

### **PK SAMPLE COLLECTION/CALCULATIONS, AND STATISTICAL ANALYSIS:**

**Blood samples** were collected for aliskiren and amlodipine at the following time points for all treatments:

#### **Aliskiren**

Days 33, 34, 47, 48 at predose

Days 35 and 49 pre-dose, then at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours post dose.

#### **Amlodipine**

Days 12, 13, 47, 48 at predose

Days 14 and 49 pre-dose, then at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours post dose.

#### **Pharmacokinetic calculations**

The following pharmacokinetic parameters were determined using non-compartmental method(s):  $AUC_{\tau}$ ,  $C_{\min}^{ss}$ ,  $C_{\max}^{ss}$ ,  $t_{\max}^{ss}$  and CL/F.

**Statistical Analysis** – For both aliskiren and amlodipine, log-transformed PK parameters  $AUC_{\tau}$  and  $C_{\max}^{ss}$  were analyzed by a linear mixed effect model, with treatment as a fixed factor and subject as a random factor. The resulting 90% confidence intervals of the appropriate treatment mean ratios was used to examine the drug-drug interactions.

#### **SAFETY:**

Monitoring and recording of all adverse events commencing after the first dose, pre-dose time periods and end-of-study monitoring of hematology, blood chemistry and urine parameters, periodic monitoring of vital signs during treatment periods and performance of physical examinations and ECGs.

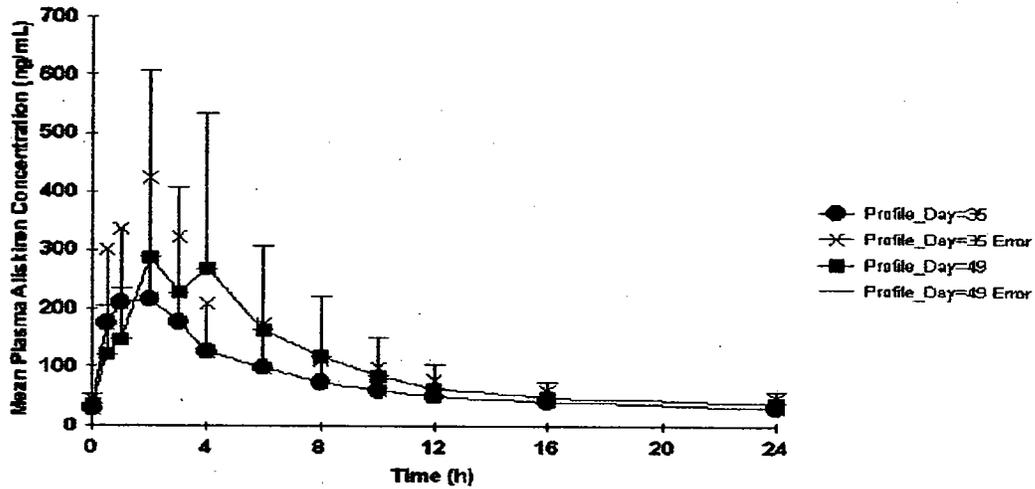
#### **RESULTS:**

Twenty five subjects were enrolled and 18 subjects (10 female and 8 male, 1 Black and 17 other race) completed the study. Four subjects (5108, 5111, 5117 and 5121) were discontinued due to protocol violations. Subjects 5112 and 5120 withdrew consent and subject 5118 was lost to follow-up. There was one adverse effect related to study withdrawal; subject 5121 had a positive pregnancy test on day 48 and was withdrawn from study.

#### **Pharmacokinetics**

**Aliskiren** - Exposure and plasma peak concentration of aliskiren were increased by 29% and 18%, respectively, by co-administration of amlodipine.

**Figure 1** Mean plasma aliskiren concentrations in healthy volunteers when treated with aliskiren alone (Day 35) and then with combination therapy (Day 49)



**Table 1** Mean and Descriptive Statistics for Aliskiren Pharmacokinetic Parameters in Healthy Subjects on Day 35 and Day 49

Day 35	Aliskiren Alone				
Descriptive Statistics	$C_{max}^{ss}$ (ng/mL)	$t_{max}^{ss}$ (h)	$C_{min}^{ss}$ (ng/mL)	$AUC_t$ (h x ng/mL)	CL/F (mL/h)
N	19	19	19	19	19
Mean	336	1.5	27.2	1809	206260
SD	179	1.0	14.2	827	104538
Day 49	Aliskiren Combination Therapy with Amlodipine				
Descriptive Statistics	$C_{max}^{ss}$ (ng/mL)	$t_{max}^{ss}$ (h)	$C_{min}^{ss}$ (ng/mL)	$AUC_t$ (h x ng/mL)	CL/F (mL/h)
N	18	18	18	18	18
Mean	448	3.4	33.6	2470	159934
SD	318	1.9	17.8	1425	85366

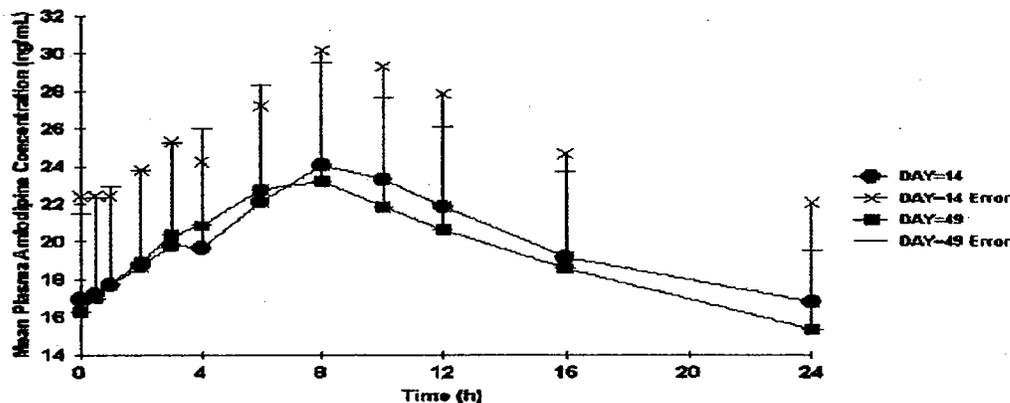
**Table 2** Summary analysis results of Aliskiren PK parameters

Parameter	Ratio of geometric means	
	(A+B:B)	90% CI for ratio
$AUC_t$	1.29	(1.07, 1.55)
$C_{max}^{ss}$	1.18	(0.83, 1.69)

Treatment A = Amlodipine 10mg/day, Treatment B = Aliskiren 300mg/day

**Amlodipine** - There were no observed effects on amlodipine PK when co-administered with aliskiren.

**Figure 2** Mean plasma amlodipine concentrations in healthy volunteers during monotherapy and combination therapy



**Table 3** Summary analysis results of Amlodipine PK parameters

Parameter	Ratio of geometric means	
	(A+B:A)	90% CI for ratio
AUC <sub>t</sub>	0.98	(0.92, 1.05)
C <sub>max</sub> <sup>ss</sup>	0.98	(0.93, 1.05)

Treatment A = Amlodipine 10mg/day, Treatment B = Aliskiren 300mg/day

**SAFETY:**

There was no serious adverse effects reported during the study. Among 29 reported adverse effects, 27 were mild and 2 were moderate. The most frequently observed adverse effect by aliskiren monotherapy or combination therapy was headache.

**CONCLUSIONS:**

Aliskiren systemic exposure and peak plasma concentration were increased by 29% and 18%, respectively, by co-administration of amlodipine. However, inter-subject variability was high and it was not possible to obtain statistical significance. Amlodipine PK parameters were not affected by co-administration of aliskiren. The combination of amlodipine and aliskiren was considered to be well tolerated and safe.

**REVIEWER'S COMMENT:**

1. / / / /
2. However, no dosage adjustment is required.
2. No expiration date was provided for Aliskiren.

**STUDY SPP100A 2220 – AN OPEN LABEL, MULTIPLE DOSE STUDY TO EVALUATE THE PHARMACOKINETIC DRUG-DRUG INTERACTION BETWEEN METFORMIN AND ALISKIREN WHEN GIVEN ALONE OR IN COMBINATION TO HEALTHY VOLUNTEERS**

**STUDY INVESTIGATOR AND SITE:**

**REPORT # SPP100A 2220**

**EDR VOLUME 6**

**STUDY DATES: December 03, 2004 – December 22, 2004**

**OBJECTIVES:**

**Primary**

To investigate the pharmacokinetic interaction between aliskiren and metformin following once a day dosing alone and in combination in healthy volunteers

**Secondary**

To investigate the safety and tolerability of co-administration of aliskiren and metformin in healthy volunteers

**FORMULATION:**

**SPP100** 150 mg tablets (Aliskiren, 6000937.001 / X154 0603, Exp. Date not provided) by Novartis

**Metformin** 1000 mg tablets (Glucophage<sup>®</sup>, NDC 60505-0192-0 / GN 7278, Exp. Date not provided) purchased by the investigator from the local pharmacy

**STUDY DESIGN:**

This was a single-center, open-label, multiple dose, 2-period, cross-over drug-drug interaction study under fasted conditions. Subjects were administered 1000 mg metformin for 4 days followed by 4 days washout then aliskiren 300 mg for 11 days followed by 300 mg aliskiren plus 1000 mg metformin for 4 days. Subjects were confined to the study center for at least 24 hours before drug administration until the end of study. During the domiciled period, subjects were not permitted to take xanthine containing foods or beverages, alcohol, or cigarettes. Subjects were fasted at least 10 hr before the administration of study drug and continued to fast for at least 4 hr after drug administration.

**ANALYTICAL METHODS:**

**Aliskiren plasma concentrations:** samples were analyzed by a validated HPLC/MS/MS method with a LLOQ established at 0.5 ng/mL.

**Metformin plasma concentrations:** plasma metformin were determined by a validated GC/MS/MS method with a LLOQ of established at 15 ng/mL.

### **PK SAMPLE COLLECTION/CALCULATIONS, AND STATISTICAL ANALYSIS:**

**Blood samples** were collected for aliskiren and metformin concentrations at the following time points during all treatments:

**Aliskiren** - Day 13, 14, 17, 18 at pre-dose

Day 15, 19: at pre-dose, then at 0.5, 1, 2, 4, 6, 8, 12, 16 and 24 hours post-dose

**Metformin** - Day 2, 3, 17, 18 at pre-dose

Day 4 and 19: at pre-dose, then 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16 and 24 hours post-dose

### **Pharmacokinetic calculations**

$AUC_{\tau}$ ,  $C_{\min}^{SS}$ ,  $C_{\max}^{SS}$ ,  $t_{\max}^{SS}$ , for both aliskiren and metformin were calculated, using non-compartmental methods.

**Statistical Analysis** –log-transformed AUC and Cmax were analyzed by a linear mixed effect model, with treatment as a fixed factor and subject as a random factor. The resulting 90% confidence interval of the appropriate treatment mean ratios was used to test for any drug-drug interaction.

### **SAFETY:**

Safety and tolerability assessments included the monitoring and recording of all adverse events and concomitant medications/significant non-drug therapies, routine laboratory tests, ECG recordings, vital signs, and physical examinations during screening and after the completion of the study.

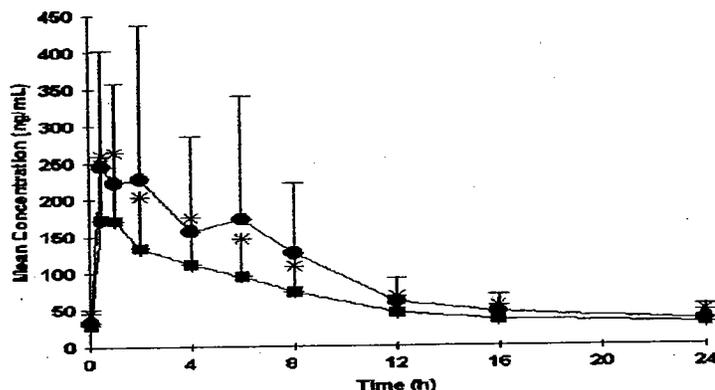
### **RESULTS:**

Twenty two subjects were enrolled and 19 subjects (10 males and 9 females; 3 Caucasians, 16 Black) completed the study. Subject 5103 and 5122 withdrew consent for reasons not related to any adverse events; which resulted in them not completing the study.

### **Pharmacokinetics**

**Aliskiren**  $AUC_{\tau}$  and  $C_{\max}^{SS}$  were reduced by 27% and 29%, respectively, by co-administration of metformin. However, those differences were not statistically significant since high aliskiren inter-subject variability was observed (20% and 40% for  $AUC_{\tau}$  and  $C_{\max}^{SS}$ , respectively).

**Figure 1** Mean aliskiren concentrations in healthy volunteers during aliskiren monotherapy (day 15) and in combination with metformin (day 19)



• Represents the mean value of monotherapy (day 15), — represents standard deviation of monotherapy, ■ represents mean value of combination therapy (day 19), \* represents standard deviation of combination therapy.

Source: Appendix 4, Table 1 and Appendix 4, Table 2

**Descriptive statistics for aliskiren PK parameters in healthy subjects on day 15 and day 19**

Day 15		Aliskiren Alone			
Descriptive Statistics	$C_{max}^{55}$ (ng/mL)	$t_{max}^{55}$ (h)	$C_{min}^{55}$ (ng/mL)	$AUC_{\tau}$ (h x ng/mL)	N
Mean	329.4	1.5	36.4	2278.2	19
SD	228.1	1.7	21.4	1403.5	
Median	256.0	0.6	32.0	1898.9	
Day 19		Aliskiren Combination with Metformin			
Descriptive Statistics	$C_{max}^{55}$ (ng/mL)	$t_{max}^{55}$ (h)	$C_{min}^{55}$ (ng/mL)	$AUC_{\tau}$ (h x ng/mL)	N
Mean	209.7	1.5	30.7	1546.8	19
SD	94.5	1.5	15.7	704.6	
Median	182.0	1.0	26.1	1301.6	

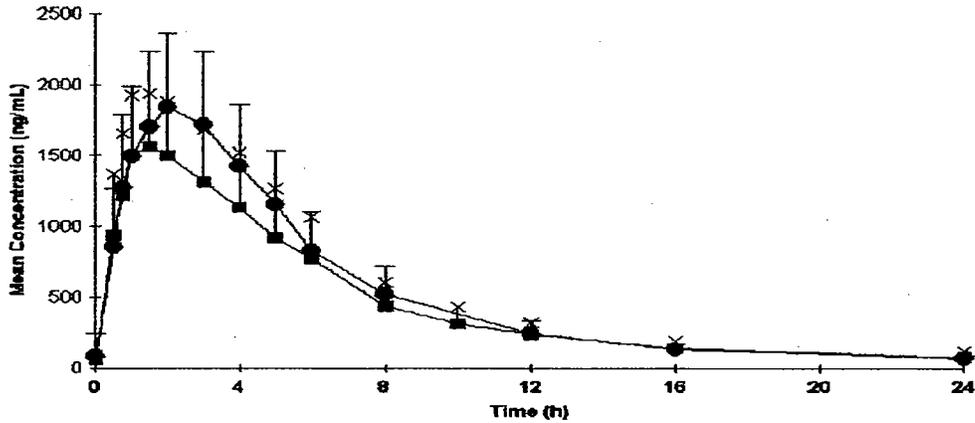
**Summary statistical analysis of aliskiren PK parameters**

Parameter	Ratio of geometric means	
	(A+B:B)	90% CI for ratio
$AUC_{\tau}$	0.73	(0.64, 0.84)
$C_{max}^{55}$	0.71	(0.56, 0.89)

Treatment A = metformin 1000mg, Treatment B = aliskiren 300mg o.d.

Metformin pharmacokinetics were lowered with aliskiren co-administration by 12% ( $AUC_{\tau}$ ) and 11% ( $C_{max}^{55}$ ). However, the 90% CI between monotherapy and combination therapy were within 80 – 125% and considered not statistically significant.

**Figure 2** Mean metformin concentrations in healthy volunteers during metformin treatment alone (day 4) and in combination with aliskiren (day 19)



• Represents the mean value of monotherapy (day 15), — represents standard deviation of monotherapy, ■ represents mean value of combination therapy (day 19), \* represents standard deviation of combination therapy

Source: Appendix 4, Table 3 and Appendix 4, Table 4

**Descriptive statistics for metformin PK parameters in healthy subjects on day 4 and day 19**

Day 4	Metformin Alone			
Descriptive Statistics	$C_{max}^{56}$ (ng/mL)	$t_{max}^{56}$ (h)	$C_{min}^{56}$ (ng/mL)	$AUC_t$ (h x ng/mL)
N	21	21	21	21
Mean	1953	2.25	65.5	12528
SD	532	0.64	26.5	3222
Median	1880	2.00	60.8	13227
Day 19	Metformin Combination with Aliskiren			
Descriptive Statistics	$C_{max}^{56}$ (ng/mL)	$t_{max}^{56}$ (h)	$C_{min}^{56}$ (ng/mL)	$AUC_t$ (h x ng/mL)
N	19	19	19	19
Mean	1715	1.62	76.4	10966
SD	378	0.81	37.6	2616
Median	1600	1.50	62.4	10643

**Summary statistical analysis of metformin PK parameters**

Parameter	Ratio of geometric means	
	(A+B:A)	90% CI for ratio
$AUC_t$	0.88	(0.80, 0.96)
$C_{max}^{56}$	0.89	(0.80, 0.99)

Treatment A = metformin 1000mg, Treatment B = aliskiren 300mg od

**SAFETY:**

A total of six subjects experienced adverse events while taking metformin alone, five while on aliskiren alone, and eight while receiving both drugs. The most frequently occurring adverse event was gastrointestinal (abdominal pain or discomfort, nausea, diarrhea, vomiting) in nature. Four of the 26 total adverse events observed during the study were moderate in severity, and the rest were mild. There were no serious adverse events during this study. Thirteen of the 26 events were suspected to be related to study medications.

Serum creatine kinase was elevated during treatment in Subjects 5105, 5114, 5115, 5121 and 5122, which was present at screening or baseline in all but Subject 5115. Subject 5105 was discontinued from the study because of persistently elevated serum creatine kinase values. The subject had an abnormally high serum creatine kinase at baseline (261 U/L; normal range = 0-200 U/L), but it elevated to 2052 U/L on day 4, when the last dose of metformin was administered. The subject's laboratory values continued to be monitored, and serum creatine kinase remained elevated at 2125 U/L on day 8 and 2940 U/L on day 9, when the subject was discontinued from the study. On day 20, the value had returned to below its baseline level but was still elevated (231 U/L) above the normal range.

**CONCLUSIONS:**

Aliskiren AUC and  $C_{max}$  were decreased by co-administration of metformin. Metformin AUC and  $C_{max}$  were lowered with aliskiren co-administration. However, they were within the 90% CI of 80 – 125% and of no clinical significance.

**REVIEWER'S COMMENT:**

1. Expiration dates for either medication was not provided.
2. Sponsor states that the pharmacokinetic effects of metformin on Aliskiren are of no clinical significance. However, metformin was administered at the low range of the maintenance dose at 1000 mg per day (range 1000 to 2550 mg per day). Metformin may have a more pronounced effect on the pharmacokinetics of aliskiren if taken at greater doses.

**APPEARS THIS WAY  
ON ORIGINAL**

**STUDY SPP100A 2221 – AN OPEN-LABEL, MULTIPLE-DOSE STUDY IN NORMAL HEALTHY VOLUNTEERS TO EVALUATE THE PHARMACOKINETICS, SAFETY AND TOLERABILITY OF SPP100 (ALISKIREN) AND RAMIPRIL (ALTACE®) ADMINISTERED ALONE AND IN COMBINATION**

**STUDY INVESTIGATOR AND SITE:**

**REPORT # SPP100A 2221**

**EDR VOLUME 6**

**STUDY DATES: November 28, 2004 – January 10, 2005**

**OBJECTIVES:**

**Primary**

- To characterize the pharmacokinetics of aliskiren following once a day dosing alone and in combination with ramipril in healthy volunteers
- To investigate the pharmacokinetics of ramipril alone and in combination with aliskiren in healthy volunteers

**Secondary**

To assess the safety and tolerability of aliskiren and ramipril co-administered in healthy volunteers

**FORMULATION:**

Product	KN / Batch Number
Aliskiren 150 mg tablet	3765070.008 / X198FA

by Novartis

Product	Lot Number / Batch Number
Ramipril 2.5 mg tablet	1063626 / NDC 61570-111-01
Ramipril 5.0 mg tablet	1067867 / NDC 61570-112-01
Ramipril 10 mg tablet	1078921 / NDC 61570-120-01

Ramipril (Altace®) purchased by investigator.

**STUDY DESIGN:**

This was a single-center, open-label, multiple-dose, 3-period drug-drug interaction study under fasted conditions. Forced titration was used to increase ramipril up to 10 mg as shown below. Period 1; subjects were administered ramipril 2.5 mg, 5 mg for one day and 10 mg for 4 days followed by a 4 day washout. Period 2; Subjects were then administered aliskiren 300 mg for 7 days. Period 3; subjects were administered 300 mg aliskiren plus ramipril through forced titration as in period 1. Subjects visited the study center on a daily basis during treatment periods 1 and 2, and stayed in the study center during treatment period 3 for drug administration and safety assessments.

**ANALYTICAL METHODS:**

**Aliskiren plasma concentrations:** samples were analyzed by a validated HPLC/MS/MS method with a LLOQ of 0.5 ng/mL.

**Ramipril and ramiprilat plasma concentrations:** were determined by a validated LC/MS/MS method with a LLOQ of 0.1 ng/mL for both ramipril and ramiprilat.

**PK SAMPLE COLLECTION/CALCULATIONS, PD ASSESSMENTS/CALCULATIONS AND STATISTICAL ANALYSIS:**

**Blood samples** were collected for aliskiren and ramipril concentrations at the following time points during all treatments:

**Aliskiren** - Day 15, 16, 21, 22: pre-dose

Day 17, 23: at pre-dose, then at 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16 and 24 hours post-dose

**Ramipril and ramiprilat** - Day 4, 5, 21, 22: pre-dose

Day 6 and 23: at pre-dose, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16 and 24 hours post-dose

**Pharmacokinetic calculations**

The PK parameters  $AUC_{\tau}$ ,  $C_{\min}^{ss}$ ,  $C_{\max}^{ss}$  and  $t_{\max}^{ss}$  for aliskiren, ramipril and ramiprilat were calculated, using non-compartmental methods.

**Statistical Analysis** – For aliskiren, ramipril and ramiprilat, log-transformed PK parameters  $AUC_{\tau}$  and  $C_{\max}^{ss}$  were analyzed by a linear mixed effect model, with treatment as a fixed factor and subject as a random factor. The resulting 90% confidence interval of the appropriate treatment mean ratios was used to test for any drug-drug interaction.

**SAFETY:**

Safety and tolerability assessments included the monitoring and recording of all adverse events and of concomitant medications/significant non-drug therapies, routine laboratory tests, ECG recordings, vital signs, and physical examinations during screening and after the completion of the study.

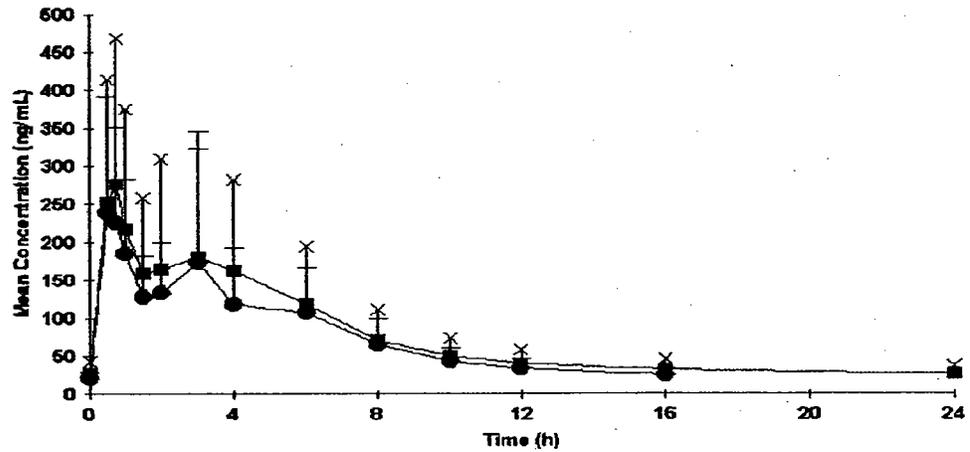
**RESULTS:**

Twenty one subjects were enrolled and 17 subjects (11 males and 7 females; 13 Caucasians, 5 Orientals and 1 other) completed the study. Subject 5104, 5111 and 5115 withdrew consent for reasons that were not related to adverse events. Subject 5113 was discontinued due to protocol violation.

**Pharmacokinetics**

**Aliskiren**  $AUC_{\tau}$  and  $C_{\max}^{ss}$  were increased by 12% and 31%, respectively, by co-administration with ramipril.  $T_{\max}$  was increased by 29% as well and  $C_{\min}^{ss}$  by 26%. However, those differences were not statistically significant since high inter-subject variability was observed for Aliskiren (46% and 41% for  $AUC_{\tau}$  and  $C_{\max}^{ss}$ , respectively) according to the sponsor.

**Figure 1** Mean aliskiren concentrations in healthy volunteers when treated with aliskiren monotherapy and in combination with ramipril



• represents the mean value of mono-therapy, — represents standard deviation of mono-therapy, ■ represents mean value of combination therapy, X represents standard deviation of combination therapy.

Source: Appendix 4, Table 1 and Appendix 4, Table 2

**Mean and descriptive statistics for aliskiren PK parameters in healthy subjects on day 17 and day 23**

Day 17	Aliskiren Alone			
Descriptive Statistics	$C_{max}^{SS}$ (ng/mL)	$t_{max}^{SS}$ (h)	$C_{min}^{SS}$ (ng/mL)	$AUC_{\tau}$ (h x ng/mL)
N	17	17	17	17
Mean	296	1.27	20.14	1522
SD	167	1.49	7.55	613
Median	250	0.50	18.40	1275
Day 23	Aliskiren in Combination with Ramipril			
Descriptive Statistics	$C_{max}^{SS}$ (ng/mL)	$t_{max}^{SS}$ (h)	$C_{min}^{SS}$ (ng/mL)	$AUC_{\tau}$ (h x ng/mL)
N	17	17	17	17
Mean	382	1.64	25.47	1774
SD	187	1.55	10.80	864
Median	334	0.85	22.20	1715

**Summary analysis results of aliskiren PK parameters**

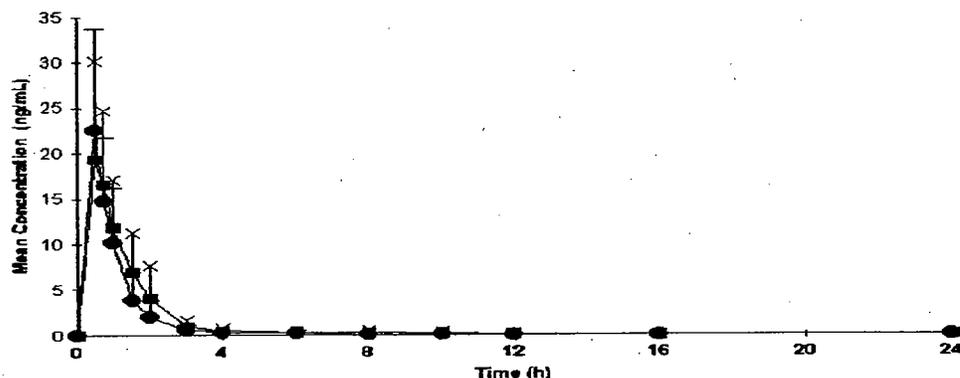
Parameter	Ratio of geometric means	
	(C+D:D)	90% CI for ratio
$AUC_{\tau}$ (ng.h/mL)	1.12	(0.98, 1.28)
$C_{max}^{SS}$ (ng/mL)	1.31	(1.06, 1.62)

Treatment C = Ramipril 10mg, Treatment D = Aliskiren 300mg

Ramipril  $AUC_{\tau}$  was increased by 22% and  $C_{max}^{SS}$  was decreased by 6% with aliskiren co-administration. Ramiprilat  $C_{max}^{SS}$  was decreased by 15% with aliskiren co-

administration. No change was observed in  $AUC_T$ . The ratio between monotherapy and combination therapy were within 90% CI and statistically not significant according to the sponsor.

**Figure 2** Mean ramipril concentrations in healthy volunteers during ramipril monotherapy (day 6) and in combination with aliskiren (day 23)



• represents the mean value of mono-therapy, — represents standard deviation of mono-therapy, ■ represents mean value of combination therapy, X represents standard deviation of combination therapy.

Source: Appendix 4, Table 3 and Appendix 4, Table 4

**Mean and descriptive statistics for ramipril PK parameters in healthy subjects on day 6 and day 23**

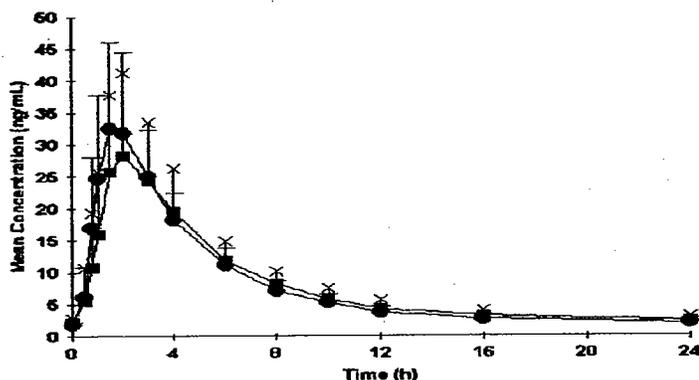
Day 6	Ramipril Alone			
Descriptive Statistics	$C_{max}^{SS}$ (ng/mL)	$t_{max}^{SS}$ (h)	$C_{min}^{SS}$ (ng/mL)	$AUC_T$ (h x ng/mL)
N	20	20	20	20
Mean	23.89	0.55	0.0	21.24
SD	9.87	0.13	0.0	9.74
Median	22.75	0.50	0.0	19.78
Day 23	Ramipril in Combination with Aliskiren			
Descriptive Statistics	$C_{max}^{SS}$ (ng/mL)	$t_{max}^{SS}$ (h)	$C_{min}^{SS}$ (ng/mL)	$AUC_T$ (h x ng/mL)
N	17	17	17	17
Mean	22.63	0.66	0.01	25.81
SD	9.72	0.28	0.03	9.62
Median	20.70	0.50	0.0	24.84

**Summary analysis results of ramipril PK parameters**

Parameter	Ratio of geometric means	
	(C+D:C)	90% CI for ratio
$AUC_T$ (ng.h/mL)	1.22	(1.11, 1.34)
$C_{max}^{SS}$ (ng/mL)	0.94	(0.79, 1.12)

Treatment C = Ramipril 10mg, Treatment D = Aliskiren 300mg

**Figure 3 Mean plasma ramiprilat concentrations in healthy volunteers during ramipril monotherapy and in combination with aliskiren**



• represents the mean value of mono-therapy, — represents standard deviation of mono-therapy, ■ represents mean value of combination therapy, X represents standard deviation of combination therapy.

Source: Appendix 4, Table 5 and Appendix 4, Table 6

**Mean and descriptive statistics for ramiprilat PK parameters in healthy subjects on day 6 and day 23**

Day 6	Ramiprilat (Ramipril alone)			
Descriptive Statistics	$C_{max}^{ss}$ (ng/mL)	$t_{max}^{ss}$ (h)	$C_{min}^{ss}$ (ng/mL)	$AUC_{\tau}$ (h x ng/mL)
N	20	20	20	20
Mean	34.1	1.8	1.77	191
SD	13.4	0.4	0.46	42
Median	31.6	2.0	1.78	190
Day 23	Ramiprilat (Ramipril in Combination with Aliskiren)			
Descriptive Statistics	$C_{max}^{ss}$ (ng/mL)	$t_{max}^{ss}$ (h)	$C_{min}^{ss}$ (ng/mL)	$AUC_{\tau}$ (h x ng/mL)
N	17	17	17	17
Mean	29.0	2.09	2.17	192
SD	12.7	0.48	0.59	50
Median	26.5	2.00	1.94	175

**Summary analysis results of ramiprilat PK parameters**

Parameter	Ratio of geometric means	
	(C+D:C)	90% CI for ratio
$AUC_{\tau}$ (ng.h/mL)	1.00	(0.95, 1.07)
$C_{max}^{ss}$ (ng/mL)	0.85	(0.76, 0.95)

Treatment C = Ramipril 10mg, Treatment D = Aliskiren 300mg

**SAFETY:**

There were no serious adverse events during this study. A total of 12 subjects experienced adverse events while taking ramipril alone, seven while receiving aliskiren alone, and nine while receiving both drugs. By inspection, there were no differences

observed in the incidence of adverse events among the treatments. The most frequently occurring adverse events were gastrointestinal, (abdominal pain, discomfort, vomiting, dry mouth) nervous system disorders (headache, dizziness), and respiratory/thoracic disorders (cough, dyspnea, throat pain, sinus congestion). Twenty-nine of the 47 (61.7%) total adverse events observed during the study were mild in severity, 17 were moderate (36.2%), and one was severe (2.1%). Nineteen of the 47 events (40.4%) were suspected to be related to study medications. There was a severe adverse effect reported (menstrual cramp). There were no drop-outs due to adverse events.

**CONCLUSIONS:**

Aliskiren PK parameters were slightly affected by co-administration of ramipril according to the sponsor. Aliskiren inter-subject variability was high leading to no statistical difference according to the sponsor. Aliskiren did not affect the pharmacokinetics of the metabolite or parental drug.

**REVIEWER'S COMMENT:**

1. Aliskiren  $AUC_{\tau}$  and  $C_{max}^{SS}$  were increased by 12% and 31%, respectively, by co-administration with ramipril.  $T_{max}$  was increased by 29% as well and  $C_{min}^{SS}$  by 26%. The 90% CI for  $C_{max}^{SS}$  was clearly not within 80 - 125%.
2. Changes observed in ramiprilat pharmacokinetics regarding a decrease in  $C_{max}$  of 15% with aliskiren co-administration is of no clinical significance.

APPEARS THIS WAY  
ON ORIGINAL

**STUDY SPP100A 2228 – AN OPEN LABEL, MULTIPLE DOSE STUDY TO EVALUATE THE PHARMACOKINETIC DRUG-DRUG INTERACTION BETWEEN HYDROCHLOROTHIAZIDE AND ALISKIREN WHEN GIVEN ALONE OR IN COMBINATION TO HEALTHY VOLUNTEERS**

**STUDY INVESTIGATOR AND SITE:**

**Report# 2228**

**Volumes in EDR Section 6**

**STUDY DATES: December 02, 2004 – December 20, 2004**

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**OBJECTIVES:**

**Primary**

To investigate the pharmacokinetic interaction between aliskiren and hydrochlorothiazide following once a day dosing alone or in combination to healthy volunteers.

**Secondary**

To assess tolerability of co-administration of aliskiren and hydrochlorothiazide in healthy volunteers.

**FORMULATION:**

**Aliskiren** 300 mg tables (Lot # X1540603, Exp. Date: 06/2005) by Novartis

**Hydrochlorothiazide** 25 mg tablets (Lot# 134806A, Exp, Date: 08/2007) purchased by investigator from local pharmacy

**STUDY DESIGN:**

This was a single-center, randomized, open-label, multiple-dose, two-period drug-drug interaction study under fasted conditions. Period 1: subjects were administered hydrochlorothiazide 25 mg for 4 days followed by a 4-day wash-out period. Period 2: subjects were administered aliskiren 300 mg for 7 days followed by 300 mg of aliskiren plus 25 mg hydrochlorothiazide for 4 days. Subjects were domiciled at least the day before the first study day to the end of the study.

**ANALYTICAL METHODS:**

**Aliskiren plasma concentrations:** Although the sponsor measured aliskiren plasma concentrations, aliskiren bioanalytical report was **not provided** in this data set.

**Hydrochlorothiazide plasma concentrations:** Hydrochlorothiazide was determined by a validated LC/MS/MS method with a LLOQ established at 2.0 ng/mL.

**PK SAMPLE COLLECTION/CALCULATIONS, PD ASSESSMENTS/CALCULATIONS AND STATISTICAL ANALYSIS:**

**Blood samples** were collected for aliskiren and hydrochlorothiazide concentrations at the following time points during all treatments:

**Aliskiren:** Day 13, 14, 17, 18 at pre-dose