

Day 15, 19 at pre-dose, then at 0.5, 1, 2, 3, 4, 6, 8, 12, 16 and 24 hours post-dose

Hydrochlorothiazide: Day 2, 3, 13, 18 at pre-dose

Day 4 and 19: at pre-dose, then at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16 and 24 hours post-dose

Pharmacokinetic calculations

The PK parameters AUC_{τ} , C_{\min}^{SS} , C_{\max}^{SS} and t_{\max}^{SS} for aliskiren and hydrochlorothiazide were calculated, using non-compartmental methods.

Statistical Analysis – For both aliskiren and hydrochlorothiazide, log-transformed PK parameters AUC_{τ} 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.

RESULTS:

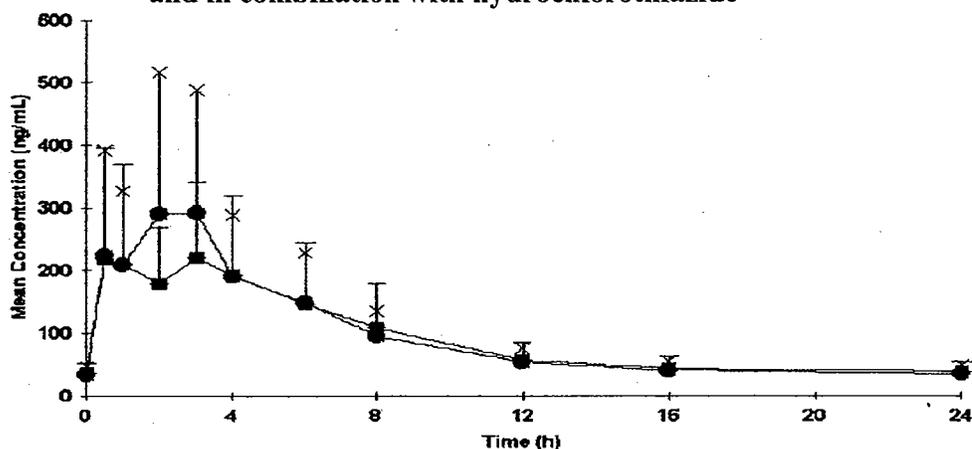
Twenty-two subjects were enrolled and all subjects (13 females and 9 males; 11 Caucasians, 2 Black and 9 other) completed the study. There were no drop-outs due to adverse events or withdrawals of consent.

Pharmacokinetics

Aliskiren

Aliskiren AUC_{τ} and C_{\max}^{SS} were decreased by 7% and 22%, respectively, when co-administered with hydrochlorothiazide. However, those differences were not statistically significant since high Aliskiren inter-subject variability was observed (40% and 51% for AUC_{τ} and C_{\max}^{SS} , respectively).

Figure 1 Mean Aliskiren concentrations when treated with Aliskiren alone and in combination with hydrochlorothiazide



• Represents the mean value of mono-therapy (Day 15), X represents standard deviation of mono-therapy, ■ represents mean value of combination therapy (Day 19), — represents standard deviation of combination therapy.

Source: Appendix 4-Table 1 and Table 2

Statistical results for Aliskiren

Parameter	Ratio of geometric means (A+B:B)	90% CI for ratio
AUC _t (ng.h/mL)	0.93	(0.83, 1.05)
C _{max} ^{ss} (ng/mL)	0.78	(0.64, 0.95)

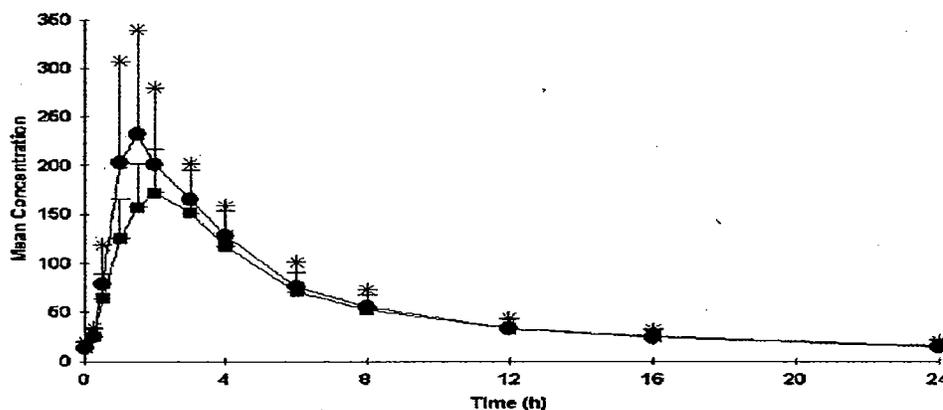
Treatment A = Hydrochlorothiazide 25mg

Treatment B = Aliskiren 300mg

Hydrochlorothiazide

Hydrochlorothiazide AUC_t and C_{max}^{ss} were decreased by 10% and 26% when co-administered with aliskiren. The ratio between monotherapy and combination therapy was not within the 90% CI. However, the differences are of no clinical significance.

Figure 2 Mean hydrochlorothiazide concentrations (ng/mL) during hydrochlorothiazide treatment alone (Day 4) and combination therapy with Aliskiren (Day 19)



● Represents the mean value of hydrochlorothiazide alone (Day 4) mono-therapy, x represents standard deviation of hydrochlorothiazide alone, ■ represents mean value of combination therapy, — represents standard deviation of combination therapy.

Source: Appendix 4-Table 3 and Table 4

Statistical Results for HCTZ

Parameter	Ratio of geometric means (A+B:A)	90% CI for ratio
AUC _t (ng.h/mL)	0.90	(0.87, 0.93)
C _{max} ^{ss} (ng/mL)	0.74	(0.69, 0.79)

Treatment A = Hydrochlorothiazide 25mg

Treatment B = Aliskiren 300mg

SAFETY:

There were no serious adverse events during the study. A total of 73 adverse events were reported by 18 subjects, of which 66 (90%) were rated as mild, 7 (10%) rated as moderate, and none as severe. The majority of adverse events (57/73, 78%) were related to study drug. Dizziness was the most commonly reported adverse event. Ten (10) subjects reported a total of 11 incidences of dizziness. All were considered mild in severity, and 10 were considered study drug related. Other commonly reported adverse events were headache, abdominal pain, nausea, and fatigue. The aliskiren/hydrochlorothiazide combination therapy had the highest incidences of adverse events reported (37/73, 51%). However, there were no drop-outs due to adverse events.

CONCLUSIONS:

- No pharmacokinetic difference was observed in the steady-state pharmacokinetic exposure of Aliskiren when dosed alone or in combination with hydrochlorothiazide in healthy volunteers.
 - A pharmacokinetic decrease in C_{max}^{ss} was observed when Aliskiren was dosed in combination with hydrochlorothiazide in healthy volunteers. Clinical significance of this decrease is doubtful since exposure remains identical.
 - No difference was observed in the steady-state pharmacokinetic exposure of hydrochlorothiazide when dosed alone or in combination with Aliskiren in healthy volunteers.
 - A pharmacokinetic decrease in C_{max}^{ss} was observed when hydrochlorothiazide was dosed with Aliskiren in healthy volunteers. Clinical significance of this decrease is doubtful since exposure remains identical.
 - Both aliskiren and hydrochlorothiazide were safe and well tolerated when administered alone or in combination.
-

REVIEWER'S COMMENT:

1. The study report did not contain a bioanalytical report for Aliskiren. Because of high inter-subjects variability, reliability of study results will be dependent on the validated assay results. Demonstration of consistency, linearity and accuracy of assay methodology will be pivotal in assessing this study.
2. It remains unclear whether HCTZ was measured by LC/MS/MS method or by LC/UV method since the assay methodology is reported differently in the synopsis with different values for LLOQ (2 ng/mL) than in the study report (1 ng/mL).
3. The sponsor should be required to submit the missing data.

STUDY SPP100A 2334 – AN OPEN-LABEL, MULTIPLE-DOSE STUDY TO EVALUATE THE PHARMACOKINETICS, SAFETY AND TOLERABILITY OF SPP100 (ALISKIREN) WHEN GIVEN ALONE AND IN COMBINATION WITH KETOCONAZOLE TO HEALTHY VOLUNTEERS

STUDY INVESTIGATOR AND SITE:

REPORT # SPP100A 2334

EDR VOLUME 6

STUDY DATES: September 09, 2005 – September 20, 2005

OBJECTIVES:

Primary

To characterize the pharmacokinetics of Aliskiren following once a day dosing alone and in combination with ketoconazole in healthy volunteers.

Secondary

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

FORMULATION:

Aliskiren 300 mg tablets (Batch: X299IA KN: 6000937.006, Exp. Date: not provided), by Novartis

Ketoconazole 200 mg tablets (TEVA, Lot # 23141, Exp. Date: 3/2007) purchased by the investigator.

STUDY DESIGN:

This was a single-center, open-label, multiple-dose, sequential, drug-drug interaction study under fasted conditions. Subjects were administered 300 mg aliskiren for 7 days. Then, subjects were administered 300 mg aliskiren plus ketoconazole (200mg Q 12h) for 4 days. Subjects were admitted to the study center at least 17 hours prior to the first dose of study drug and remained domiciled until the end of study evaluation.

ANALYTICAL METHODS:

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

Ketoconazole plasma concentrations: plasma ketoconazole was determined by a validated HPLC/UV method with a LLOQ established at 10.0 ng/mL.

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

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

Aliskiren - Days 5, 6, 9, and 10: at pre-dose

Days 7, 11: at pre-dose, then at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16 and 24 hours post-dose

Ketoconazole - Day 7 to 11: pre-dose (AM dose)

Pharmacokinetic calculations

Aliskiren AUC_{τ} , C_{\min}^{SS} , C_{\max}^{SS} , and t_{\max}^{SS} were calculated, using non-compartmental methods.

Statistical Analysis – Log-transformed aliskiren AUC_{τ} 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.

RESULTS:

Twenty-one subjects were enrolled and 20 subjects (10 males and 10 females; 13 Caucasians, 2 Blacks and 5 other) completed the study. Subject 5105 was discontinued due to protocol violation.

Pharmacokinetics

Aliskiren AUC_{τ} and C_{\max}^{SS} were increased by 76% and 81%, respectively, with co-administration of ketoconazole and a decrease in CL/F of 57%.

Figure 1 Mean (+SD) plasma aliskiren concentrations with monotherapy (Day7) and then combination therapy with ketoconazole (Day 11)

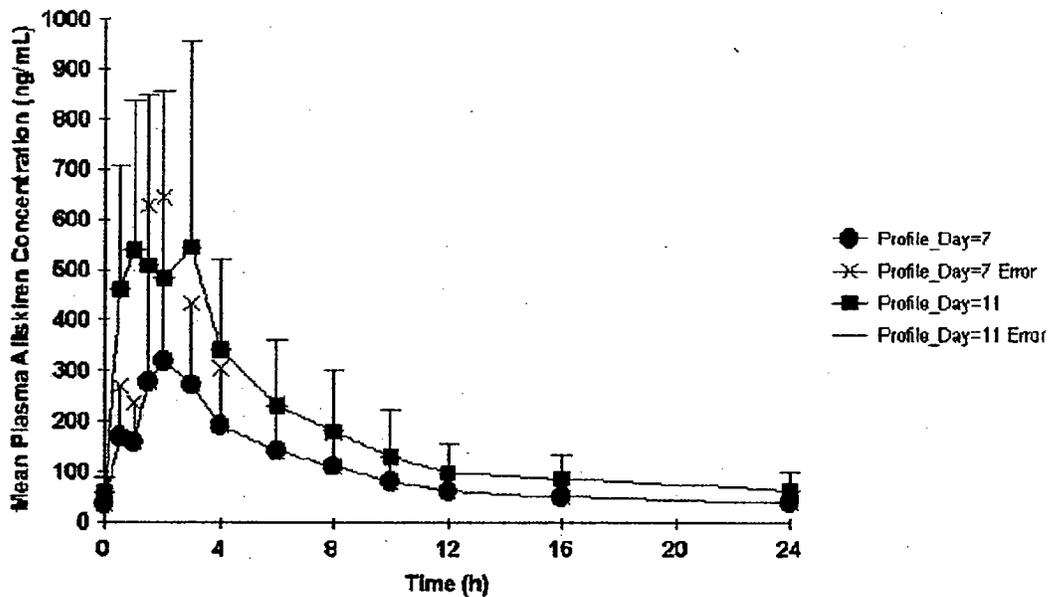


Table 1 Summary analysis results of aliskiren statistics

Parameter	Ratio of geometric means (A+B:A)	90% CI for ratio
AUC _t (ng.h/mL)	1.76	(1.64, 1.89)
C _{max} ^{ss} (ng/mL)	1.81	(1.57, 2.09)

Treatment A = Aliskiren 300mg, Treatment B = Ketoconazole 200mg

SAFETY:

There were no serious adverse events during this study. A total of 8 subjects experienced adverse events (total number of adverse effects were 10). Most of these were mild to moderate in severity. The most frequently occurring adverse events were gastrointestinal (nausea) and nervous system disorders (headache). All of these adverse events were considered to be drug related. There were no drop-outs due to adverse events.

CONCLUSIONS:

Ketoconazole is known to inhibit CYP3A and transporter p-glycoprotein. The results of in vitro studies indicate that aliskiren is metabolized by CYP3A4 but the contribution of this enzyme on aliskiren metabolism is minimal. Thus, the increased systemic exposure and peak plasma concentration of aliskiren when co-administered with ketoconazole is considered to be most likely the result of the inhibition of p-glycoprotein. Combination use of aliskiren and ketoconazole seemed safe and well tolerated.

REVIEWER'S COMMENT:

1. 
2. Ketoconazole was not optimally dosed since 200 mg was administered twice daily instead of the recommended 400 mg once daily for this type of study. As a result,, true assessment of ketoconazole's impact on the pharmacokinetics of Aliskiren is still unclear.
3. Aliskiren's expiration/manufacturing date was not provided.
4. Ketoconazole's pharmacokinetics in the presence of aliskiren were not assessed in this study.

STUDY (SPP100 CRD10) SPP100A 0018 – A PHASE I, OPEN-LABEL, RANDOMIZED, BALANCED, TWO-PERIOD CROSSOVER STUDY TO INVESTIGATE THE EFFECT OF CIMETIDINE ON THE PHARMACOKINETICS OF A SINGLE ORAL DOSE OF ALISKIREN IN HEALTHY MALE SUBJECTS

STUDY INVESTIGATOR AND SITE:

REPORT # (SPP CRD10) SPP100A 0018

VOLUMES in EDR, Section 8

STUDY DATES: July 20, 2001 – August 23, 2001

OBJECTIVES:

Primary

To assess the effect of cimetidine on the pharmacokinetics of a single dose of aliskiren in healthy male subjects.

Secondary

To assess the safety and tolerability of single doses of aliskiren in healthy male subjects.

FORMULATION:

SPP100 150 mg capsules (Aliskiren, Batch no.S100-HCG-023, Exp. 09 July 2002) by Speedel

Cimetidine 800 mg tablets (Batch no. 025360, Exp. 31 July 2004) purchased by the investigator from the local pharmacy

STUDY DESIGN:

This was a single-center, open-label, randomized, balanced, 2-period, cross-over, single dose study in a fasted state. Each subject (12) received two single oral doses of aliskiren (150 mg), once alone and then once with cimetidine (800 mg daily) administered for 5 days and then aliskiren administered once on the third day. There was a minimum of 14 days between each aliskiren dose. Six subjects received aliskiren alone and other 6 subjects were co-administered cimetidine and aliskiren, in each period. There was a minimum of 14 days between each dose of aliskiren. Aliskiren were administered in fasted state.

ANALYTICAL METHODS:

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

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

Blood samples were collected for aliskiren at the following time points:

Pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 30, 36, 48 and 72 hours post-dose

Pharmacokinetic calculations

Pharmacokinetic parameters listed below were determined using non-compartmental method(s):

Table 1 Pharmacokinetic parameters calculated

Parameter	Definition
AUC(0-t _l)	Area under the plasma drug concentration-time curve from time zero up to the last quantifiable concentration
AUC(0-∞)	Area under the plasma drug concentration-time curve from zero time to infinity
AUC _{ex}	Percentage of AUC that is due to extrapolation from t _l to infinity
C _{max}	Maximum observed plasma concentration
t _{max}	Time of maximum observed plasma concentration
t _{lag}	Time before the start of absorption
λ _z	Terminal elimination rate constant
t _{1/2}	Terminal elimination half-life
t _z	Time of last quantifiable plasma concentration
MRT	Mean residence time
CL/F	Apparent total plasma clearance
V _d /F	Apparent volume of distribution during the elimination phase

Statistical Analysis –Log-transformed aliskiren pharmacokinetic parameters AUC_{0-∞}, C_{max}, t_{max} and t_{1/2} were analyzed by analysis of variance or by nonparametric methods. Geometric least squares means or medians, ratios or median differences, and 90% confidence intervals were calculated for the comparison between aliskiren given in combination with cimetidine and aliskiren given alone. Subjects were random effects and treatment, sequence and period were fixed effects.

RESULTS:

Twelve male (Caucasian) were enrolled and all completed the study. There were no study drop-outs due to adverse events or withdrawals of consent.

Pharmacokinetics

Effect of cimetidine on aliskiren PK

The pharmacokinetics of aliskiren was tending to increase by co-administration of cimetidine. However, the changes were less than 20% and the differences were neither statistically significant nor considered clinically relevant according to the sponsor.

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Geometric Mean Plasma Concentrations of Aliskiren (Semi-logarithmic Scale)

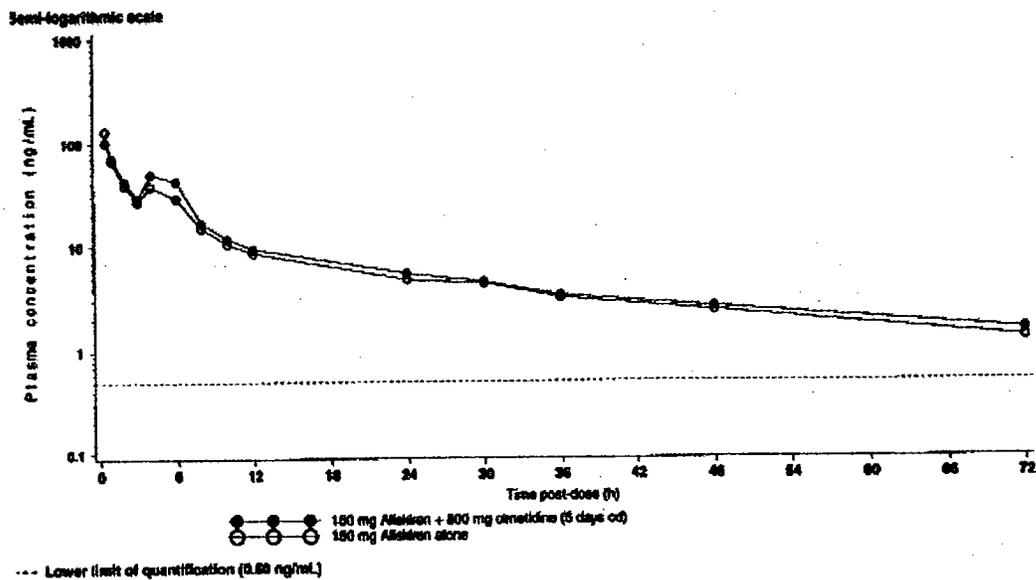


Table 2 Aliskiren pharmacokinetic parameters with monotherapy (150 mg) and co-administration with cimetidine (800 mg for 5 days)

Parameter	150 mg Aliskiren & 800 mg cimetidine (A) (N=12)	150 mg Aliskiren alone (B) (N=12)	Ratio of least squares means (90% CI) (A/B)
AUC(0-t ₂) (ng.h/mL)	695 (44.0)	608 (27.4)	1.14 (0.90 – 1.46)
AUC(0-∞) (ng.h/mL)	778 (43.0)	663 (25.8)	1.17 (0.94 – 1.47)
C _{max} (ng/mL)	176 (66.0)	148 (56.9)	1.19 (0.77 – 1.84)
t _{max} † (h)	0.50 (0.50 – 4.00)	0.517 (0.50 – 4.02)	0.37 (-0.02 – 1.73)
t _{lag} † (h)	0 (0 – 0)	0 (0 – 0)	NC
t _{1/2} (h)	31.0 (47.7)	26.9 (24.0)	1.15 (0.96 – 1.38)
MRT (h)	24.7 (41.2)	21.6 (28.7)	NC
CL/F (mL/min)	3212 (43.0)	3772 (25.8)	NC
V _d /F (L)	8612 (66.4)	8779 (40.9)	NC

Source: Section 9.2 (Tables 1 and 2)

Geometric mean (CV%) data are presented

† Median (min-max); Median difference (90% CI) (A-B)

N = Number of subjects studied

NC = Not calculated

SAFETY:

Among 9 observed adverse effects, 3 (Dizziness; mild and moderate, Headache; mild) were considered to be drug related. There were no severe adverse events.

CONCLUSIONS:

Cimetidine is a known inhibitor of P-450 enzymes. Although the contribution is small, in vitro data suggests that aliskiren is metabolized by CYP3A. Thus, inhibition of P-450 may change aliskiren's pharmacokinetics. Aliskiren AUC increased with co-administration of cimetidine. Since aliskiren PK profiles have relatively high inter-subject variation, these changes by cimetidine were not considered clinically relevant by the sponsor.

REVIEWER'S COMMENT:

1. Dose of Aliskiren (150mg) used in this study is not the maximum dose (300mg/day). As a result, the changes in aliskiren pharmacokinetics with cimetidine co-administration may be more pronounced than observed in this study since Aliskiren is not dose proportional

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STUDY (SPP100CRD11) SPP100A0019 – A PHASE I, SINGLE -BLIND, RANDOMIZED, BALANCED, TWO -PERIOD CROSSOVER STUDY TO INVESTIGATE THE PHARMACODYNAMIC AND PHARMACOKINETIC INTERACTION BETWEEN MULTIPLE ORAL DOSES OF ALISKIREN AND A SINGLE ORAL DOSE OF WARFARIN IN HEALTHY MALE AND FEMALE SUBJECTS

STUDY INVESTIGATOR AND SITE:

REPORT # (SPP100CRD11) SPP100A0019

EDR VOLUME 8

STUDY DATES: August 15, 2001 – November 14, 2001

OBJECTIVES:

Primary

- To assess the effect of Aliskiren on the pharmacodynamics of warfarin in healthy male and female subjects.
- To assess the effect of Aliskiren on the pharmacokinetics of warfarin in healthy male and female subjects.

Secondary

To assess the safety and tolerability of Aliskiren in healthy male and female subjects.

FORMULATION:

SPP100	150 mg capsules (Batch# S100-HCG-022, Exp. 12-2001) Speedel
Warfarin	5 mg tablets — Batch# E0E200A, Exp. 4-2003) by Dupont Pharma
Placebo	To aliskiren capsules (Batch# SPP8001-HCG-010 Exp. 10-2002) Speedel

STUDY DESIGN:

This was a single-center, single-blind, randomized, balanced, 2-period cross-over multiple-dose study. Each subject was either administered 150 mg of aliskiren or placebo for 11 days. On study 8 day subjects were administered 5 mg of warfarin. Aliskiren was administered in the fasted state.

ANALYTICAL METHODS:

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

Warfarin plasma (R- and S-)concentrations: samples were analyzed by an acceptable and validated LC/MS/MS method with a LLOQ established at 1.0 ng/mL for both.

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

Aliskiren - Days 6 to 11 pre-dose

Warfarin - Day 8: Pre -dose, then at 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120 and 144 h post-dose

Pharmacokinetic calculations

Pharmacokinetic parameters listed below were determined using non-compartmental methods:

Table 1 Pharmacokinetic parameters of (R)- and (S)- Warfarin

Parameter	Definition
AUC(0-t _z)	Area under the plasma concentration-time curve from time zero up to the last quantifiable concentration
AUC(0-∞)	Area under the plasma concentration-time curve from time zero to infinity
AUC _{ex}	Percentage of AUC that is due to extrapolation from t _z to infinity
C _{max}	Maximum observed plasma concentration
t _{max}	Time of maximum observed plasma concentration
λ _z	Terminal elimination rate constant
t _{1/2}	Terminal elimination half-life
t _z	Time of occurrence of the last plasma drug concentration above the lower limit of quantification

Statistical Analysis –Log-transformed warfarin pharmacokinetic parameters AUC_{0-∞}, C_{max}, t_{max} and t_{1/2} were analyzed by nonparametric methods. Least squares means or medians, ratios or median differences, and 90% confidence intervals were calculated for the comparison between warfarin given in combination with aliskiren and warfarin given alone.

Pharmacodynamic calculations

Pharmacodynamic parameters listed below were determined using non-compartmental methods:

Table 2 Pharmacodynamic parameters of (R)- and (S)- Warfarin

Parameter	Definition
AUC(0-144 h), PT	Area under the PT versus time curves from time zero up to 144 h post-dose
R _{max, PT}	Maximum observed PT value
T _{max, PT}	Time of maximum observed PT value
AUC(0-144 h), INR	Area under the INR versus time curves from time zero up to 144 h post-dose
R _{max, INR}	Maximum observed INR value
T _{max, INR}	Time of maximum observed INR value

Statistical Analysis –Log-transformed warfarin pharmacodynamic parameters AUC_{0-144,PT}, R_{max,PT}, t_{max, PT}, AUC_{0-144,INR}, R_{max,INR}, and t_{max, INR} were analyzed by nonparametric methods. Least squares means or medians, ratios or median differences, and 90% confidence intervals were calculated for the comparison between warfarin given in combination with aliskiren and warfarin given alone.

SAFETY:

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

RESULTS:

Sixteen subjects were enrolled and 15 subjects (12 male and 3 female, 14 Caucasian, 2 Black) completed the study. There were no drop-outs due to adverse events. Subject 11 withdrew their consent after the 2nd dose of aliskiren.

Pharmacokinetics

Trough Plasma concentrations of aliskiren:

Parameter	Day 6 Pre-dose	Day 7 Pre-dose	Day 8 Pre-dose	Day 9 Pre-dose	Day 10 Pre-dose	Day 11 Pre-dose
Geometric mean (CV%)	7.43 (43.76)	7.59 (40.85)	8.56 (51.51)	9.23 (56.92)	9.46 (54.04)	10.41 (51.87)
Arithmetic mean (SD)	8.01 (3.042)	8.15 (3.154)	9.60 (5.119)	10.62 (6.537)	10.60 (5.164)	11.59 (5.479)
Median	7.98	7.90	8.91	8.67	9.81	9.65
Min	/	/	/	/	/	/
Max	/	/	/	/	/	/
N	15	15	15	15	15	15

Source: Section 10.3 (Table 7)

N = Number of subjects studied

Effect of aliskiren on Warfarin PK

C_{max} of both (R)- and (S)- warfarin were statistically significantly increased with t_{max} of both forms decreasing with co-administration of aliskiren. However, AUC and elimination half life values were not affected by co-administration of aliskiren. As a result, the decrease in C_{max} was not considered to be of any clinical relevance according to the sponsor.

Table 3 Summary of Pharmacokinetic Parameters for (R)- Warfarin and Associated Statistical Analysis

Parameter	150 mg Aliskiren and 25 mg warfarin (A) (N=15)	Placebo and 25 mg warfarin (B) (N=15)	Ratio of least squares means 90% CI (A/B)
AUC(0-t _z) (ng.h/mL)	56246 (27.3)	56003 (24.5)	1.00 (0.95 - 1.06)
AUC(0-∞) (ng.h/mL)	62138 (29.1)	61680 (26.0)	1.00 (0.94 - 1.07)
C _{max} (ng/mL)	1353 (29.4)	1528 (23.3)	0.89 (0.82 - 0.96)
t _{max} † (h)	1.00 (0.500 - 4.00)	0.500 (0.500 - 8.00)	0.24 (-0.25 - 0.50)
t _z (h)	41.5 (15.7)	41.7 (12.8)	0.99 (0.92 - 1.07)

Source: Section 10.3 (Tables 1 and 2)

Geometric mean (CV%) data presented

t_z = 144 h post-dose

† Median (min-max); Median difference (90% CI) (A-B)

N = Number of subjects studied

Table 4 Summary of Pharmacokinetic Parameters for (S)- Warfarin and Associated Statistical Analysis

Parameter	150 mg Aliskiren plus 25 mg warfarin (A) (N=15)	Placebo plus 25 mg warfarin (B) (N=15)	Ratio of least squares means 90% CI (A/B)
AUC(0- t_e) (ng.h/mL)	38441 (25.5)	36673 (21.9)	1.04 (0.96 - 1.13)
AUC(0- ∞) (ng.h/mL)	40359 (27.8)	38081 (23.1)	1.06 (0.96 - 1.16)
C_{max} (ng/mL)	1397 (27.6)	1586 (23.6)	0.88 (0.80 - 0.97)
t_{max}^\dagger (h)	1.00 (0.500 - 4.00)	0.500 (0.500 - 1.00)	0.25 (0.00 - 1.00)
$t_{1/2}$ (h)	30.9 (23.1)	29.5 (16.6)	1.05 (0.96 - 1.14)

Source: Section 10.3 (Tables 4 and 5)

Geometric mean (CV%) data presented

t_e = 144 h post-dose

† Median (min-max); Median difference (90% CI) (A-B)

N = Number of subjects studied

Pharmacodynamics

There were no observed changes in the pharmacodynamic parameters with aliskiren co-administration.

Mean changes from baseline (Day 8, pre-dose) in PT are summarised in the following figure:

Figure A: Mean Changes From Baseline in PT

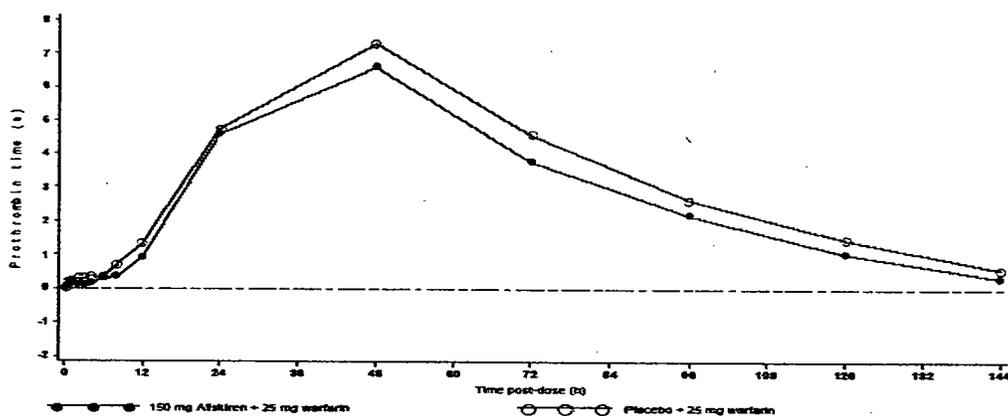


Table 5 Summary of Pharmacodynamic Parameters for PT

Parameter	150 mg Aliskiren and 25 mg warfarin (A) (N=15)	Placebo and 25 mg warfarin (B) (N=15)	Ratio of least squares means 90% CI (A/B)
AUC(0-144 h) (s.h)	2195 (12.1)	2270 (13.5)	0.97 (0.93 - 1.00)
R_{max} (s)	19.5 (20.4)	19.8 (22.0)	0.99 (0.95 - 1.02)
t_{max}^\dagger (h)	47.9 (23.9 - 48.1)	47.9 (23.9 - 48.0)	0.00 (0.00 - 0.00)

Source: Section 10.2 (Tables 1 and 2)

Geometric mean (CV%) data are presented

† Median (min-max); Median difference (90% CI) (A-B)

N = Number of subjects studied

Mean changes from baseline (Day 8, pre-dose) in INR are summarised in the following figure:

Figure B: Mean Changes from Baseline in INR

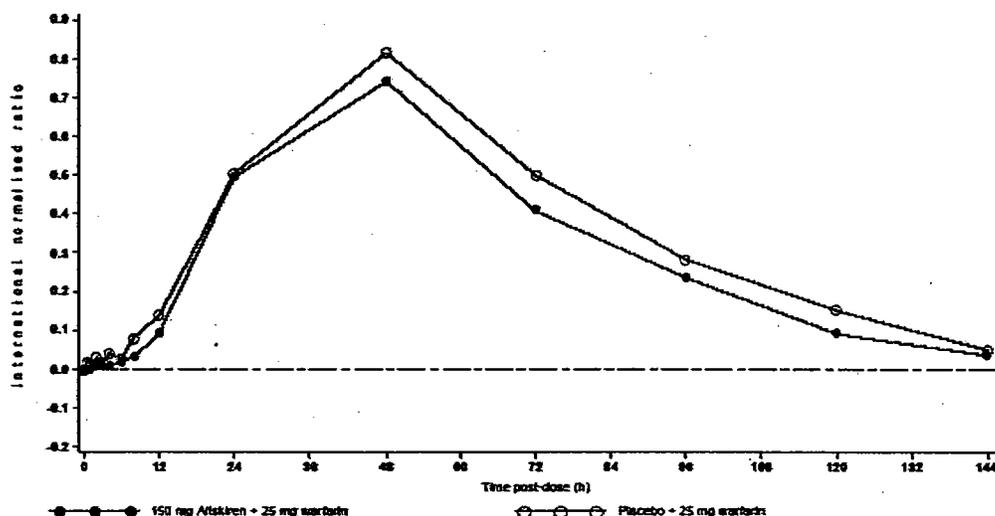


Table 6 Summary of Pharmacodynamic Parameters of INR

Parameter	150 mg Aliskiren and 25 mg warfarin (A) (N=15)	Placebo and 25 mg warfarin (B) (N=15)	Ratio of least squares means 90% CI (A/B)
AUC(0-144 h) (INR·h)	185 (15.4)	192 (18.0)	0.96 (0.93 – 1.00)
R _{max} (s)	1.75 (26.7)	1.79 (28.4)	0.98 (0.94 – 1.02)
t _{max} † (h)	47.9 (23.9 - 48.1)	47.9 (23.9 - 48.0)	0.00 (0.00 – 0.00)

Source: Section 10.2 (Tables 1 and 2)

Geometric mean (CV%) data are presented

† Median (min-max); Median difference (90% CI) (A-B)

N= Number of subjects studied

SAFETY:

Among the 49 observed adverse events, 28 were considered to be treatment related. Two of the most observed adverse events were dizziness and headache. There were no serious adverse events.

CONCLUSIONS:

There were slight changes in both forms of warfarin (C_{max} and t_{max}) by co-administration of aliskiren. However, exposure and elimination half life were not affected by aliskiren co-administration. In addition, pharmacodynamic parameters of warfarin (PT and INR) were not affected by aliskiren co-administration. Thus, there was no clinically significant drug-drug interaction between aliskiren and warfarin.

REVIEWER'S COMMENTS:

1. The reviewer concurs.

STUDY SPP100CRD12/SPP100A0020 – ALISKIREN - A PHASE I, OPEN-LABEL, RANDOMIZED, BALANCED, THREE-PERIOD CROSSOVER STUDY TO INVESTIGATE THE PHARMACOKINETIC INTERACTION BETWEEN SINGLE ORAL DOSES OF ALISKIREN AND CELECOXIB IN HEALTHY MALE SUBJECTS

STUDY INVESTIGATOR AND SITE:

REPORT # (SPP100CRD12) SPP100A0020

VOLUMES in EDR, Section 8

STUDY DATES: August 24, 2001 – October 13, 2001

OBJECTIVES:

Primary - To assess the possible pharmacokinetic interaction of celecoxib and Aliskiren following single oral doses in healthy male subjects.

Secondary - To assess the safety and tolerability of single oral doses of Aliskiren in healthy male subjects.

FORMULATION:

SPP100 150 mg capsules (Aliskiren, Batch# S100-HCG-023, Exp. 09 July 2002) by Speedel

Celecoxib 200 mg tablets (Celebrex[®], Batch# 548960, Exp. 31 January 2003) by Searle purchased from commercial source by the investigator

STUDY DESIGN:

This was a single-center, open-label, randomized, balanced, 3-period, cross-over single-dose study in 15 fasted male subjects. Each subject was divided into 3 groups/periods and administered 150 mg of aliskiren alone, 200 mg celecoxib alone, and 150 mg of aliskiren with 200 mg celecoxib in each treatment period. They all received all three treatments. There was minimum 14 days between each dose.

ANALYTICAL METHODS:

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

Celecoxib plasma concentrations: samples were analyzed by a validated HPLC method with a LLOQ established at 20 ng/mL.

PK SAMPLE COLLECTION/CALCULATIONS AND STATISTICAL ANALYSIS:

Blood samples were collected for aliskiren and celecoxib at the following time points:

Aliskiren - Pre-dose, then at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 30, 36, 48 and 72 h post-dose.

Celecoxib - Pre-dose, then at 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 30, 36, 48 and 72 h post-dose

Pharmacokinetic calculations

Pharmacokinetic parameters were determined from plasma concentrations of Aliskiren and celecoxib using non-compartmental procedures.

Table 1 Pharmacokinetic parameters of Aliskiren and Celecoxib

Parameter	Definition
AUC(0-t _z)	Area under the plasma drug concentration-time curve from time zero up to the last quantifiable concentration
AUC(0-∞)	Area under the plasma drug concentration-time curve from zero time to infinity
AUC _{ex}	Percentage of AUC that is due to extrapolation from t _z to infinity
C _{max}	Maximum observed plasma concentration
t _{max}	Time of maximum observed plasma concentration
t _{lag}	Time before the start of absorption
λ _z	Terminal elimination rate constant
t _{1/2}	Terminal elimination half-life
t _z	Time of last quantifiable plasma concentration
MRT	Mean residence time
CL/F	Apparent total plasma clearance
V _z /F	Apparent volume of distribution during the elimination phase

Statistical Analysis –Log-transformed aliskiren pharmacokinetic parameters AUC_{0-∞}, C_{max}, t_{max} and t_{1/2} were analyzed by analysis of variance or nonparametric methods. Geometric least squares means or medians, ratios or median differences, and 90% confidence intervals were calculated for the comparison between aliskiren given in combination with celecoxib and Aliskiren given alone or celecoxib given alone.

RESULTS:

Fifteen male (14 Caucasian and 1 mixed Caucasian and Afro-Caribbean) were enrolled and completed the study. There were no drop-outs due to adverse events or withdrawals of consent.

Pharmacokinetics

Effect of celecoxib on aliskiren

The systemic exposure of aliskiren was increased about 10% by co-administration of celecoxib. C_{max} of 3 subjects was increased by 250-600% following co-administration of celecoxib. Increases in systemic exposure of aliskiren (90-200%) was observed in the same 3 subjects. Because of high inter-subject variability (for AUC_{0-∞} at 47 and 49%, and C_{max}, at 59 and 69%), the differences were neither statistically significant nor considered to be clinically relevant by the sponsor.

Table 2 Summary of Aliskiren Pharmacokinetic Parameters and Statistical Analysis

Parameter	150 mg Aliskiren and 200 mg celecoxib (A) (N=15)	150 mg Aliskiren alone (B) (N=15)	Ratio of least squares means 90% CI (A/B)
AUC(0-4 _h) (ng·h/mL)	564 (48.9)	514 (49.2)	1.10 (0.88 – 1.37)
AUC(0-∞) (ng·h/mL)	623 (47.1)	570 (49.1)	1.09 (0.88 – 1.35)
C _{max} (ng/mL)	147 (58.7)	108 (68.8)	1.36 (0.97 – 1.91)
t _{max} † (h)	0.517 (0.500 – 4.03)	0.500 (0.500 – 6.00)	0.00 (-1.75 – 0.25)
t _{1/2} † (h)	0 (0 – 0)	0 (0 – 0.500)	NC
t _{1/2} (h)	29.5 (21.2)	27.7 (18.3)	1.06 (0.96 – 1.19)
MRT (h)	22.8 (22.1)	24.3 (17.1)	NC
CL/F (mL/min)	4010 (47.1)	4385 (49.1)	NC
V _d /F (L)	10236 (56.0)	10512 (51.0)	NC

Source: Section 9.2 (Table 1 and 2)
 Geometric mean (CV%) data are presented
 † Median (min-max); Median difference (90% CI) (A-B)
 N = Number of subjects studied
 NC = Not calculated

Figure A: Geometric Mean Plasma Concentrations of Aliskiren (linear scale)

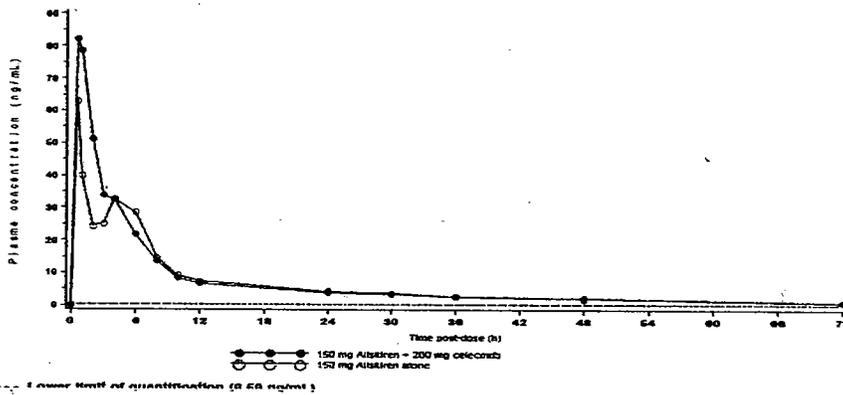
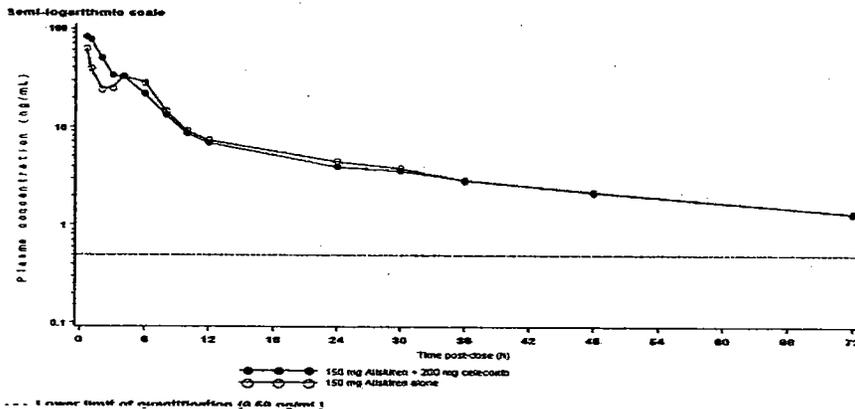


Figure B: Geometric Mean Plasma Concentrations of Aliskiren (semi-logarithmic scale)



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Effect of aliskiren on celecoxib

The PK profiles of celecoxib were decreased about 10% for AUC by co-administration of aliskiren. However, the difference was not statistically significant nor considered to be of clinical relevance.

Table 3 Summary of celecoxib Pharmacokinetic Parameters and Statistical Analysis

Parameter	150 mg Aliskiren plus 200 mg celecoxib (A) (N=15)	150 mg celecoxib alone (C) (N=15)	Ratio of least squares means 90% CI (A/C)
AUC(0-t ₂) (ng.h/mL)	6570 (32.8)	6757 (34.1)	0.97 (0.92 – 1.03)
AUC(0-∞) (ng.h/mL)	6924 (31.2)	7230 (32.1)	0.96 (0.90 – 1.02)
C _{max} (ng/mL)	886 (46.9)	918 (39.6)	0.97 (0.86 – 1.09)
t _{max} † (h)	3.00 (1.00 - 4.00)	3.00 (1.00 - 6.00)	0.00 (-0.98 – 0.50)
t _{lag} † (h)	0 (0 – 0.500)	0 (0 – 0.500)	NC
t _{1/2} (h)	6.90 (38.9)	7.33 (44.4)	0.94 (0.76 – 1.17)
MRT (h)	9.66 (36.1)	9.94 (38.6)	NC
CL/F (mL/min)	481 (31.2)	461 (32.1)	NC
V _d /F (L)	288 (60.3)	293 (58.1)	NC

Source: Section 9.2 (Tables 4 and 5)

Geometric mean (CV%) data are presented

† Median (min-max); Median difference (90% CI) (A-C)

N = Number of subjects studied

NC = Not calculated

SAFETY:

Among the 25 observed adverse effects, 8 were considered to be drug related. No severe adverse events were observed during the study.

CONCLUSIONS:

Celecoxib is known to interact with drugs metabolized by P-450 enzymes. Although the contribution seems to be small, in vitro data suggested that aliskiren is metabolized by CYP3A. Thus, celecoxib might interact and change aliskiren pharmacokinetically. Aliskiren AUC and C_{max} were slightly increased by co-administration of celecoxib. However, aliskiren PK profiles have relatively high inter-subject variability, so these changes by celecoxib were not considered clinically relevant. Celecoxib AUC was also increased by co-administration of aliskiren, however, celecoxib AUC intra-subject variability was also high and statistically no difference was observed.

REVIEWER'S COMMENT:

1. The highest recommended dose of celecoxib is 400 mg and for Aliskiren 300 mg daily. Instead, the sponsor gave lower doses of celecoxib (200 mg) and Aliskiren (150 mg). However, in study 2235 the maximum dose of both medications was given and no drug interaction was observed.

2. No differences in safety data nor demographic data was observed in the three subjects mentioned earlier (subjects with high C_{max} and AUCs) when compared with other subjects in the study.

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STUDY SPP100A 2235 AN OPEN-LABEL, MULTIPLE-DOSE STUDY TO EVALUATE THE PHARMACOKINETICS, SAFETY AND TOLERABILITY OF SPP100 (ALISKIREN) AND CELECOXIB (CELEBREX®) ADMINISTERED ALONE AND IN COMBINATION IN HEALTHY SUBJECTS

STUDY INVESTIGATOR AND SITE:

REPORT # SPP100A 2235

EDR VOLUME June 13, 2006 submission

STUDY DATES: June 7, 2005 – July 7, 2005

Objectives:

Primary objectives

- To characterize the pharmacokinetics of aliskiren following once daily dosing alone or in combination with celecoxib in healthy subjects.
- To investigate the pharmacokinetics of celecoxib following twice daily dosing alone and in combination with aliskiren in healthy subjects.

Secondary objective

- To assess the safety and tolerability of aliskiren and celecoxib co-administration in healthy subjects

FORMULATION:

SPP100 150 mg tablets (Aliskiren, Batch# X316 1004, Re-test April 2006) by Speedel

Celecoxib 200 mg tablets (Celebrex®, Batch# 168740DH, Re-test April 2007) by Searle purchased by the investigator

Design: This study employed an open-label, two-period, sequential, multiple-dose design. A total of 22 healthy volunteers were enrolled into the study. The subjects were admitted to the study center at least 24 hours prior to the initial dosing of Aliskiren for baseline evaluation. If subjects met all eligibility criteria at baseline, they were randomized into the study and confined to the site on days 1-6 (period 1) and days 10-23 (period 2). In period 1, subjects received 200 mg celecoxib b.i.d. over 4.5 days (Day 1 to morning of Day 5). Period 1 was followed by a 5-day washout period. In period 2, subjects received 300 mg aliskiren q.d. on Days 11 to 17 followed by 300 mg aliskiren q.d. co-administered with 200 mg celecoxib b.i.d. from Day 18 to the morning of Day 22. Blood samples for aliskiren plasma concentrations were obtained on days 17 and 22 for up to 16 h post-dose. Blood samples for celecoxib plasma concentrations occurred on days 5 and 22 for up to 12 h post-dose. All study medications were taken in fasted conditions. The study was completed with the end of study evaluations on Day 23, after the last blood sample was collected.

ANALYTICAL METHODS:

The assays were acceptable.

Within-study assay validation was performed by analysis of QC samples together with the study samples. The lower limit of quantitation (LLOQ) of aliskiren was 0.5 ng/mL. The lower limit of quantification (LLOQ) of celecoxib was 10.0 ng/mL.

PK SAMPLE COLLECTION/CALCULATIONS AND STATISTICAL ANALYSIS:

Blood samples were collected for aliskiren and celecoxib at the following time points:

Aliskiren:

- Days 15 and 16: pre-dose
- Day 17: pre-dose, 1, 2, 3, 4, 6, 8, 10, 12 and 16* h post-dose
- Day 18: 24 h post-dose (of Day 17; assessment is prior to dosing on Day 18)
- Days 20 and 21: pre-dose
- Day 22: pre-dose, 1, 2, 3, 4, 6, 8, 10, 12 and 16* h post-dose
- Day 23: 24 h post-dose (of Day 22)

*Depending on the time of dosing, the 16 h post-dose time point could have been on the next day

Celecoxib:

- Days 3 and 4: pre-morning dose
- Day 5: pre-dose, 1, 2, 3, 4, 6, 8, 10 and 12 h post-dose
- Days 20 and 21: pre-morning dose
- Day 22: pre-dose, 1, 2, 3, 4, 6, 8, 10 and 12 h post-dose

Pharmacokinetic evaluations: The PK parameters AUC_{0-t} ($AUC_{0-\tau}$), C_{min}^{ss} , C_{max}^{ss} , t_{max}^{ss} were evaluated for aliskiren and celecoxib. The main criteria for assessing the drug interaction of celecoxib on Aliskiren were comparisons of celecoxib AUC_{0-t} , and C_{max}^{ss} . The main criteria for assessing the drug interaction of aliskiren on celecoxib were comparisons of aliskiren AUC_{0-t} , and C_{max}^{ss} .

Statistical methods: For both aliskiren and celecoxib, log-transformed PK parameters AUC_{0-t} 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 test for drug-drug interactions.

RESULTS:

Number of subjects: 18 subjects were required to complete the study, 22 subjects entered and completed.

Pharmacokinetics**Effect of Celecoxib on Aliskiren**

Table 1 summarizes the PK parameters which were used to assess differences between aliskiren alone (Day 17) and aliskiren in combination with celecoxib (Day 22).

Table 1 Aliskiren PK parameters on Day 17 and Day 22

	Day 17		Day 22	
	C_{max}^{ss} (ng/mL)	AUC_{0-t} (ng•h/mL)	C_{max}^{ss} (ng/mL)	AUC_{0-t} (ng•h/mL)
N	22	22	22	22
Mean	241.6	1480	235.5	1266
SD	167.7	888	183.3	727
Min				
Median	180.5	1159	183.0	1101
Max				
CV%	69.4	60	77.8	57

Effect of Aliskiren on Celecoxib

Table 2 summarizes the PK parameters which were used to assess differences between celecoxib alone (Day 5) and celecoxib in combination with aliskiren (Day 22).

Table 2 Celecoxib PK parameters on Day 5 and Day 22

	Day 5		Day 22	
	C_{max}^{ss} (ng/mL)	AUC_{0-t} (ng•h/mL)	C_{max}^{ss} (ng/mL)	AUC_{0-t} (ng•h/mL)
N	22	22	22	22
Mean	902	6324	921	5972
SD	326	2559	299	2146
Min				
Median	943	5702	859	5383
Max				
CV%	36.1	40.5	32.5	35.9

Statistics:

The summary of the analysis results of AUC_{0-t} and C_{max}^{ss} for aliskiren is presented in Table 3. Aliskiren AUC_{0-t} values were 12% lower (ratio of geometric mean) and C_{max}^{ss} values were similar when aliskiren was co-administered with celecoxib compared to aliskiren administered alone.

Table 3 Statistical analysis results of Aliskiren PK parameters

Parameter	Ratio of geometric means	
	(A+B:B)	90% CI for ratio
AUC_{0-t} (ng.h/mL)	0.88	(0.77, 1.00)
C_{max}^{ss} (ng/mL)	1.00	(0.78, 1.27)

Treatment A = Celecoxib 200mg, Treatment B = Aliskiren 300mg

The summary of the analysis results of AUC_{0-t} and C_{max}^{ss} for celecoxib is presented in Table 4. Celecoxib AUC_{0-t} and C_{max}^{ss} values were similar (ratio of geometric mean) when aliskiren was co-administered with celecoxib compared to celecoxib administered alone.

Table 4 Statistical analysis results of Celecoxib PK parameters

Parameter	Ratio of geometric means	
	(A+B:A)	90% CI for ratio
AUC_{0-t} (ng.h/mL)	0.95	(0.88, 1.03)
C_{max}^{ss} (ng/mL)	1.02	(0.88, 1.18)

Treatment A = Celecoxib 200mg, Treatment B = Aliskiren 300mg

SAFETY:

There were no serious adverse events reported in the study. All 22 enrolled subject completed the study per protocol.

A total of 33 adverse events were reported by 11 subjects, of which 21 (64%) were rated as mild and 12 (36%) rated as moderate. No severe adverse events were reported. Nineteen (19) adverse events were suspected to be related to the study drug and 14 had no suspected causality.

The most common adverse events were (i.e. 3 or more events): headache/head pressure (9), dizziness/orthostatic dizziness (7), loose stool and abdominal pain (3 each). All reported adverse events resolved spontaneously with one subject taking concomitant medication (Subject 5102 took once 1000 mg ASS (acetylsalicylic acid) for common cold).

There were no clinically significant changes in ECG or laboratory parameters.

Deviations from normal blood pressure and pulse rate were not considered clinically significant. In 7 cases a decrease in systolic blood pressure greater than 20 mmHg occurred. In one of the 7 cases, the fall in blood pressure was accompanied by symptoms and reported as an adverse event (subject 5109; orthostatic hypotension).

Conclusions:

- Under steady-state conditions co-administration of aliskiren did not alter celecoxib pharmacokinetics.
- Under steady-state conditions co-administration of celecoxib did not alter aliskiren pharmacokinetics.
- Aliskiren 300 mg was safe and well tolerated when administered alone or in combination with Celecoxib 200 mg b.i.d. to healthy subjects.

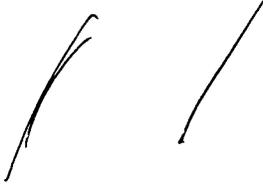
REVIEWER'S COMMENT:

1. Upon reviewing individual trough concentrations for Aliskiren, it is difficult to determine if subjects reached steady-state in period 1 before the administration of celecoxib in period 2. However, the variability was high ranging from 51.7% (day 18) to 63.6% (day 15)
2. The same phenomenon occurred regarding the attainment of steady-state with celecoxib monotherapy during period 1.

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Study (SPP100 CRD13) SPP100A 0021 – ALISKIREN - A PHASE I, OPEN-LABEL, RANDOMIZED, BALANCED, THREE-PERIOD CROSSOVER STUDY TO INVESTIGATE THE PHARMACOKINETIC INTERACTION BETWEEN SINGLE ORAL DOSES OF ALISKIREN AND ATENOLOL IN HEALTHY MALE SUBJECTS

STUDY INVESTIGATOR AND SITE:



REPORT # (SPP100CRD13) SPP100A 0021

EDR VOLUME 8

STUDY DATES: August 08, 2001 – September 19, 2001

OBJECTIVES:

Primary - To assess the possible pharmacokinetic interaction of atenolol and Aliskiren following single oral doses in healthy male subjects.

Secondary - To further assess the safety and tolerability of single oral doses of Aliskiren in healthy male subjects.

FORMULATION:

SPP100 150 mg capsules (Aliskiren, Batch# S100-HCG-023, Exp. 09 July 2002) by _____

Atenolol 100 mg tablets (Batch# 9072IAF, Exp. 30 November 2003) purchased from a commercial source by the investigator

STUDY DESIGN:

This was a single-center, open label, randomized, balanced, 3-period, cross-over, single-dose study in 15 male healthy volunteers. Each subject was administered 150 mg of aliskiren alone, 100 mg atenolol alone or 150 mg of aliskiren with 100 mg of atenolol. Subjects were divided into 3 groups and all received all three treatments. There was a minimum of 14 days between each treatment. Aliskiren was administered in the fasted state.

ANALYTICAL METHODS:

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

Atenolol plasma concentrations: samples were analyzed by an acceptable validated HPLC method with a LLOQ of 10 ng/mL.

PK SAMPLE COLLECTION/CALCULATIONS AND STATISTICAL ANALYSIS:

Blood samples were collected for aliskiren and atenolol during the following time points:

Aliskiren - Pre-dose, then at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 30, 36, 48 and 72 h post-dose

Atenolol - Pre-dose, then at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48 and 72 h post-dose

Pharmacokinetic calculations

Pharmacokinetic parameters were determined for Aliskiren and atenolol using non-compartmental procedures.

Table 1 Pharmacokinetic parameters of Aliskiren and atenolol

Parameter	Definition
AUC(0-t _z)	Area under the plasma drug concentration-time curve from time zero up to the last quantifiable concentration
AUC(0-∞)	Area under the plasma drug concentration-time curve from zero time to infinity
%AUC _{ex}	Percentage of AUC that is due to extrapolation from t _z to infinity
C _{max}	Maximum observed plasma concentration
t _{max}	Time of maximum observed plasma concentration
t _{lag}	Time before the start of absorption
λ _z	Terminal elimination rate constant
t _{1/2}	Terminal elimination half-life
t _z	Time of last quantifiable plasma concentration
MRT	Mean residence time
CL/F	Apparent total plasma clearance
V _d /F	Apparent volume of distribution during the elimination phase

Statistical Analysis –Log-transformed aliskiren pharmacokinetic parameters AUC_{0-∞}, C_{max}, t_{max} and t_{1/2} were analyzed by analysis of variance or nonparametric methods. Geometric least squares means or medians, ratios or median differences, and 90% confidence intervals were calculated for the comparison between aliskiren given in combination with atenolol and Aliskiren given alone or atenolol given alone.

RESULTS:

Fifteen male (all Caucasian) were enrolled and all completed the study. There were no drop-outs from the study due to adverse events or withdrawals of consent.

Pharmacokinetics

Effect of atenolol on aliskiren PK

The systemic exposure and C_{max} of aliskiren were not affected by co-administration of atenolol. The differences were less than 10%. High inter-subject variability for aliskiren was observed.

Figure A: Geometric Mean Plasma Concentrations of Aliskiren (Linear Scale)

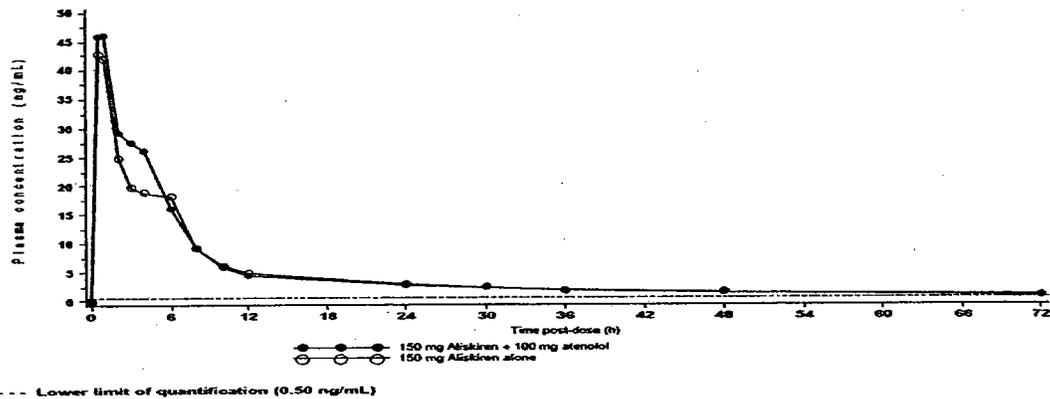


Figure B: Geometric Mean Plasma Concentrations of Aliskiren (Semi-logarithmic Scale)

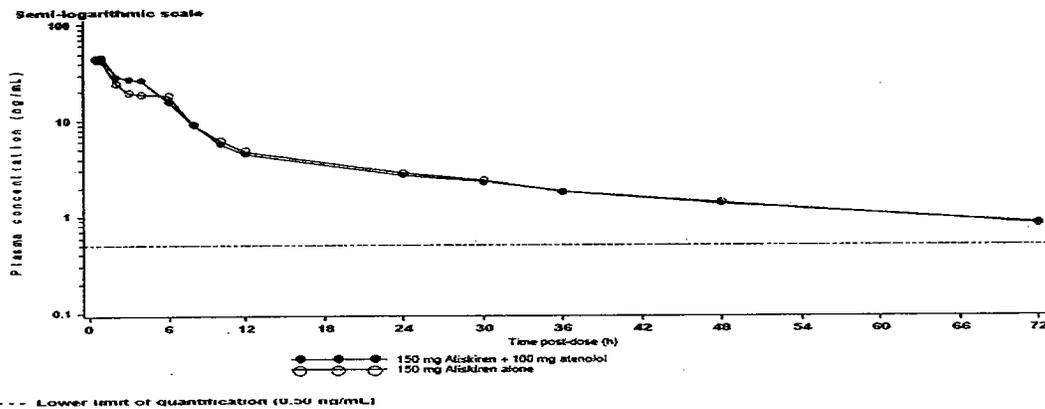


Table 2 Summary of Aliskiren Pharmacokinetic Parameters and Statistical Analysis

Parameter	150 mg Aliskiren & 100 mg atenolol (A) (N=15)	150 mg Aliskiren alone (B) (N=15)	Ratio of least squares means (90% CI) (A/B)
AUC(0-t _z) (ng·h/mL)	359 (48.3)	346 (58.8)	1.04 (0.84 – 1.28)
AUC(0-∞) (ng·h/mL)	399 (48.0)	388 (59.4)	1.03 (0.84 – 1.26)
C _{max} (ng/mL)	82.8 (86.4)	80.8 (69.9)	1.02 (0.69 – 1.53)
t _{max} † (h)	0.50 (0.50 – 4.00)	0.50 (0.50 – 6.02)	0.00 (-1.01 – 0.25)
t _{lag} † (h)	0 (0 – 0)	0 (0 – 0)	NC
t _{1/2} (h)	30.2 (20.4)	29.5 (24.2)	1.02 (0.92 – 1.15)
MRT (h)	23.6 (18.3)	24.1 (29.9)	NC
CL/F (mL/min)	6268 (48.0)	6436 (59.4)	NC
V _d /F (L)	16380 (46.8)	16408 (52.3)	NC

Source: Section 9.2 (Tables 1 and 2)
 Geometric mean (CV%) data are presented
 † Median (min-max); Median difference (90% CI) (A-B)
 N = Number of subjects studied
 NC = Not calculated

Effect of aliskiren on atenolol PK

PK profiles of atenolol were not affected by co-administration of aliskiren.

Table 3 Summary of the Pharmacokinetic Parameters of Atenolol and Associated Statistical Analysis

Parameter	150 mg Aliskiren & 100 mg atenolol (A) (N=15)	100 mg atenolol alone (C) (N=15)	Ratio of least squares means (90% CI) (A/C)
AUC(0-t ₂) (ng.h/mL)	6037 (26.7)	6142 (34.3)	0.98 (0.91 – 1.06)
AUC(0-∞) (ng.h/mL)	6212 (26.6)	6385 (32.5)	0.97 (0.91 – 1.04)
C _{max} (ng/mL)	649 (29.1)	695 (29.6)	0.93 (0.84 – 1.04)
t _{max} † (h)	4.00 (2.00 – 6.02)	3.00 (2.00 – 6.00)	0.00 (0.00 – 0.50)
t _{lag} † (h)	0 (0 – 0)	0 (0 – 0)	NC
t _{1/2} (h)	7.69 (24.2)	8.01 (37.5)	0.96 (0.83 – 1.11)
MRT (h)	10.5 (15.6)	10.5 (22.3)	NC
CL/F (mL/min)	268 (26.6)	261 (32.5)	NC
V _z /F (L)	179 (34.0)	181 (39.2)	NC

Source: Section 9.2 (Tables 4 and 5)

Geometric mean (CV%) data are presented

† Median (min-max); Median difference (90% CI) (A-C)

N = Number of subjects studied

NC = Not calculated

SAFETY:

Among the 9 observed adverse events with aliskiren or aliskiren plus atenolol, 5 events (3 Fatigue and 2 Dizziness) were considered to be drug related. There were no severe adverse events reported during the study.

CONCLUSIONS:

Both drugs did not interfere with each other and no specific safety concern was observed while co-administration of aliskiren and atenolol. Although diastolic pressure did decrease by the administration of atenolol, aliskiren or the combination, no additive or synergistic lowering effect of aliskiren with atenolol was observed.

REVIEWER'S COMMENT:

The maximum dose of aliskiren or atenolol was not used; but it seems unlikely from the results in this study that any additional information would be obtained if maximum doses were used in another study.

Study CSPP100A 2230 – AN OPEN-LABEL, MULTIPLE-DOSE STUDY TO EVALUATE THE PHARMACOKINETICS, SAFETY, AND TOLERABILITY OF SPP100 (ALISKIREN) AND ATENOLOL (TENORMIN®) ADMINISTERED ALONE AND IN COMBINATION IN HEALTHY SUBJECTS

REPORT # CSPP100A 2230

EDR VOLUME June 13, 2006 submission

Study CRD13 SPP0021 was reviewed by the clinical pharmacology reviewer even though this study was promised by the sponsor in case this study report did not come-in on time to allow a thorough review. The results of this study were the same as the earlier study. The differences between this study and the earlier one is that aliskiren was administered at a 300 mg dose, the final formulation was used, the study included females as well as males, and it was a multiple dose versus single dose study. Below is a brief synopsis.

Investigator(s): _____

Study period: first subject dosed 02-Aug-05 last subject completed 19-Aug-05

Objectives:

Primary objectives: To characterize the pharmacokinetics of Aliskiren following once a day dosing alone or in combination with Atenolol in healthy subjects.

To investigate the pharmacokinetics of Atenolol alone and in combination with Aliskiren in healthy subjects.

Secondary objective: To assess the safety and tolerability of Aliskiren and Atenolol co-administration in healthy subjects.

Investigational drug:

Drug	Strength	Batch No.	Re-test date
SPP100 (Aliskiren) tablets	300 mg	X199FA	12-2005

Comparator drug:

Drug	Strength	Batch No.	Expiry date
Atenolol — tablets	100 mg	FL 14P1	10-2009

Design: This was an open-label, two-period, multiple-dose study in healthy volunteers. A total of 18 male and female subjects were required to complete the study.

The study consisted of a 21-day screening period, two treatment periods with baselines, a 3-day washout period between the two treatment periods and a study completion evaluation on Day 17 (i.e. 24h after the last drug intake).

In period 1 (study days -1 to 4), subjects received 100 mg Atenolol daily on Days 1 to 3. Blood samples for Atenolol plasma concentrations were collected until 24 h post-dose on Day 4.

In period 2 (study days 6 to 17), subjects received 300 mg Aliskiren daily on Days 7 to 13, followed by 300 mg Aliskiren and 100 mg Atenolol daily on Days 14 to 16. Blood samples for Aliskiren plasma concentrations were collected until 24 h post-dose on Day 14. Blood samples for Aliskiren and Atenolol plasma concentrations were collected until 24 h post-dose on Day 17. A treatment overview is shown in Table 1.

Table 1 Treatment overview

	Period 1	Wash-out		Period 2	
Day -1	Day 1-3	Day 4-6	Day 6	Day 7-13	Day 14-16
Baseline	Atenolol 100 mg daily (Treatment A)	No drug administration	Baseline	Aliskiren 300 mg daily (Treatment B)	Aliskiren 300 mg and Atenolol 100 mg daily (Treatment C)

All morning treatments were given after an overnight fast of at least 10 hours. Breakfast was served 2 hours post-dose and a lunch at 5 hours post-dose. On the days of PK profiling (Days 3, 13 and 16), the subjects stayed fasted until 4 hours post-dose. After the 4-hour post-dose PK blood sampling, the subjects received a lunch (similar in content for all subjects in both study periods).

The subjects were domiciled at the study site from approximately 24 hours prior to the first drug administration (Day -1; Baseline Day of Period 1) until after having performed the morning assessments on Day 4. They returned to the study center approximately 24 h prior to drug administration in Period 2 (Day 6, Baseline of Period 2), and remained domiciled until the morning of Day 17.

The study completion evaluations were performed on Day 17 (i.e. 24 h after the last drug intake), prior to discharge from the study center.

Bioanalytical method Automated solid phase extraction of plasma samples followed by concentration of the extracts and analysis of the reconstituted samples by HPLC-MS/MS using Turbo Ion Spray (TIS).

Lower Limit of quantification (LLOQ) 0.500 ng/mL using 0.200 mL of plasma (expressed in base)

The assay was validated and acceptable upon assessment.

Pharmacokinetic evaluations:

Blood collection:

Estimated total blood volume taken per subject: 355 mL

Aliskiren: Blood samples of 5 mL were collected for Aliskiren determination at:

- pre-dose on Days 11, 12, 14 and 15
- pre-dose and at 1, 2, 3, 4, 6, 8, 10, 12, 16h* post-dose on Days 13 and 16
- 24h post-dose on Day 17.

Atenolol: Blood samples of 5 mL were collected for Atenolol determination at:

- pre-dose and at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16h* post-dose on Days 3 and 16
- 24h post-dose on Day 4 and Day 17.

Pharmacokinetic analysis:

All completed subjects were included in the pharmacokinetic data analysis. The following pharmacokinetic parameters were determined: AUC_t , C_{min}^{ss} , C_{max}^{ss} , t_{max}^{ss}

Statistical analysis:

For both Aliskiren and Atenolol, the log-transformed PK parameters AUC_t 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 geometric mean ratios was used to test for drug-drug interactions. A lack of interaction was concluded if all 90% CI of the ratio of the geometric means for C_{max} and AUC were contained within the pre-specified interval (0.80 to 1.25).

Results:**Safety and tolerability:**

There were no serious adverse events reported in the study. Seventy-one (71) adverse events were reported by 15 subjects during the study. There were 2 withdrawals from the study: Subjects 5117 and 5121 withdrew their consent on Day 12 due to personal reasons.

All reported adverse events were transient and resolved spontaneously with one subject taking concomitant medication (Subject 5112 took amoxicillin for otitis externa).

Sixty-six of the adverse events were mild in severity and five were moderate. Sixty events were suspected to be related to the study drug, and 11 had no suspected causality.

Pharmacokinetics:

Atenolol pharmacokinetic parameters are presented in Table 2.

Table 2 Descriptive statistics for Atenolol pharmacokinetic parameters when given alone (Day 3) and in combination therapy with Aliskiren (Day 16)

	Day 3			Day 16				
	C _{max} ^{ss} ng/mL	t _{max} ^{ss} H	AUC _t ng.h/mL	C _{min} ^{ss} ng/mL	C _{max} ^{ss} ng/mL	t _{max} ^{ss} H	AUC _t ng.h/mL	C _{min} ^{ss} ng/mL
N	22	22	22	22	20	20	20	20
Mean	589.5	3.2	5353	38.1	585.3	2.7	5061	37.4
SD	202.2	0.9	1611	20.6	197.6	0.9	1479	25.8
Min								
Median	616.5	3.0	5518	38.2	571.5	3.0	5240	41.9
Max								
CV%	34.3	28.5	30.1	54.1	33.8	32.0	29.2	69.0

Table 3 Descriptive statistics for Aliskiren pharmacokinetic parameters when given alone (Day 13) and in combination therapy with Atenolol (Day 16)

	Day 13				Day 16			
	C _{max} ^{ss} ng/mL	t _{max} ^{ss} h	AUC _t ng.h/mL	C _{min} ^{ss} ng/mL	C _{max} ^{ss} ng/mL	t _{max} ^{ss} h	AUC _t ng.h/mL	C _{min} ^{ss} ng/mL
N	20	20	20	20	20	20	20	20
Mean	303.8	2.9	1481	21.4	337.2	2.1	1496	20.9
SD	239.1	1.5	697	10.8	270.4	1.0	757	9.8
Min								
Median	207.0	3.0	1277	21.4	241.0	2.0	1504	20.1
Max								
CV%	78.7	52.5	47.1	50.3	80.2	51.0	50.6	46.9
Geometric Mean	240.0	2.4	1334	19.4	246.1	1.8	1289	18.7

Statistics:

The summary of the analysis results of AUC_t and C_{max}^{ss} for Aliskiren is presented in Table 4. Co-administration atenolol does not appear to have an effect on Aliskiren exposure as the 90% confidence interval for ratio of means was in the range of 0.80-1.25 for AUC_t . Although the 90% confidence interval was wider for aliskiren C_{max}^{ss} , the ratio of the geometric mean was close to 1.

Table 4 Summary analysis results of Aliskiren PK parameters

Parameter	Ratio of geometric means	
	(A+B:B)	90% CI for ratio
AUC_t (ng.h/mL)	0.97	(0.82, 1.14)
C_{max}^{ss} (ng/mL)	1.03	(0.75, 1.40)

Treatment A = Atenolol 100mg, Treatment B = Aliskiren 300mg

The summary of the analysis results of AUC_t and C_{max}^{ss} for Atenolol is presented in Table 5. It could be concluded that Aliskiren has no effect on pharmacokinetics of Atenolol since the 90% confidence interval for the ratio of means is entirely contained in the range of (0.80, 1.25) for both parameters AUC_t and C_{max}^{ss} .

Table 5 Summary analysis results of Atenolol PK parameters

Parameter	Ratio of geometric means	
	(A+B:A)	90% CI for ratio
AUC_t (ng.h/mL)	0.91	(0.85, 0.98)
C_{max}^{ss} (ng/mL)	0.96	(0.87, 1.05)

Treatment A = Atenolol 100mg, Treatment B = Aliskiren 300 mg

**APPEARS THIS WAY
ON ORIGINAL**

Study (SPP100CRD14) SPP100A 0022 – ALISKIREN - A PHASE I, OPEN-LABEL, RANDOMIZED, BALANCED, THREE-PERIOD CROSSOVER STUDY TO INVESTIGATE THE PHARMACOKINETIC INTERACTION BETWEEN SINGLE ORAL DOSES OF ALISKIREN AND LOVASTATIN IN HEALTHY MALE SUBJECTS

STUDY INVESTIGATOR AND SITE:



REPORT # (SPP100CRD14) SPP100A 0022

EDR VOLUME 8

STUDY DATES: July 25, 2001 – September 21, 2001

OBJECTIVES:

Primary

1. To assess the effect of lovastatin on the pharmacokinetics of a single oral dose of Aliskiren in healthy male subjects.
2. To assess the effect of aliskiren on the pharmacokinetics of single oral doses of lovastatin in healthy male subjects.

Secondary - To assess the safety and tolerability of single oral doses of Aliskiren in healthy male subjects.

FORMULATION:

SPP100	150 mg capsules (Aliskiren, Batch no.S100-HCG-023, Exp. 09 July 2002) by —
Lovastatin	40 mg tablets (Batch# 0119180, Exp. October 2003) purchased from commercial source by the investigator

STUDY DESIGN:

This was a single-center, open label, randomized, balanced, 3-period cross-over, single-dose study. Each subject was administered 150 mg of aliskiren alone, 40 mg lovastatin alone or 150 mg of aliskiren with 40 mg lovastatin. Subjects were divided into 3 groups and administered all three treatments in a random fashion. There was a minimum of 14 days between each treatment. Aliskiren was administered in the fasted state.

ANALYTICAL METHODS:

Aliskiren plasma concentrations: samples were analyzed by an acceptable validated LC/MS/MS method with a LLOQ of 1.0 ng/mL.

Lovastatin and lovastatin hydroxyacid plasma concentrations: samples were analyzed by an acceptable validated LC/MS/MS method with a LLOQ of 0.2 ng/mL for lovastatin and 1.0 ng/mL for lovastatin hydroxyacid.

PK SAMPLE COLLECTION/CALCULATIONS AND STATISTICAL ANALYSIS:

Blood samples were collected for aliskiren and lovastatin during the following time points:

Aliskiren - Pre-dose, then at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 30, 36, 48 and 72 h post-dose

Lovastatin - Pre-dose, then at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 48 and 72 h post-dose

Pharmacokinetic calculations

Pharmacokinetic parameters were determined from plasma concentrations of Aliskiren, lovastatin and lovastatin hydroxyacid using non-compartmental procedures.

Table 1 Pharmacokinetic parameters to be calculated for Aliskiren and lovastatin

Parameter	Definition
AUC(0-t _z)	Area under the plasma drug concentration-time curve from time zero up to the last quantifiable concentration
AUC(0-x h)	Area under the plasma drug concentration-time curve from time zero up to a fixed timepoint (x = 12, 16 and 24 h) (for lovastatin lactone and lovastatin hydroxy acid only)
AUC(0-16 h)	Area under the plasma drug concentration-time curve from time zero up to 16 h post-dose
AUC(0-24 h)	Area under the plasma drug concentration-time curve from time zero up to 24 h post-dose
AUC(0-∞)	Area under the plasma drug concentration-time curve from zero time to infinity
%AUC _{ex}	Percentage of AUC that is due to extrapolation from t _z to infinity
C _{max}	Maximum observed plasma concentration
t _{max}	Time of maximum observed plasma concentration
t _{lag}	Time before the start of absorption
λ _z	Terminal elimination rate constant
t _{1/2}	Terminal elimination half-life
t _z	Time of last quantifiable plasma concentration
MRT	Mean residence time
CL/F	Apparent total plasma clearance (not for lovastatin metabolite)
V _d /F	Apparent volume of distribution during the elimination phase (not for lovastatin metabolite)

Statistical Analysis –Log-transformed aliskiren pharmacokinetic parameters AUC_{0-t_z}, AUC_{0-∞} (aliskiren only), AUC₀₋₂₄ (lovastatin and lovastatin hydroxyacid only), C_{max}, t_{max} and t_{1/2} (aliskiren only) were analyzed by a mixed-effect model. Geometric least squares means or medians, ratios or median differences, and 90% confidence intervals were calculated for the comparison between aliskiren given in combination with lovastatin, aliskiren given alone, or lovastatin given alone.

RESULTS:

Fifteen male (all Caucasian) volunteers were enrolled and all completed the study. There were no drop-outs due to adverse events or withdrawals of consent.

Pharmacokinetics

Effect of lovastatin on aliskiren PK

Intra-subject variability of C_{max} between aliskiren mono therapy and combination therapy were differing from 82% reduction to 900% increase. Relatively high inter-subject variations for aliskiren PK parameters were observed in both mono therapy and combination therapy, systemic exposure and C_{max} of aliskiren were not statistically different.

Table 2 Summary of aliskiren Pharmacokinetic Parameters and Statistical Analysis

Parameter	150 mg Aliskiren & 40 mg lovastatin (A) (N=15)	150 mg Aliskiren alone (B) (N=15)	Ratio of least squares means (90% CI) (A/B)
AUC(0-t _z) (ng.lv/mL)	488 (58.6)	478 (39.5)	1.02 (0.86 – 1.21)
AUC(0-∞) (ng.lv/mL)	541 (58.9)	530 (39.2)	1.02 (0.87 – 1.21)
C _{max} (ng/mL)	126 (88.2)	120 (76.8)	1.05 (0.68 – 1.63)
t _{max} † (h)	0.583 (0.500 – 4.00)	0.500 (0.500 – 4.00)	0.04 (-0.50 – 0.50)
t _{lag} † (h)	0 (0 - 0)	0 (0 - 0)	NC
t _{1/2} (h)	27.6 (26.0)	28.7 (16.9)	0.96 (0.87 – 1.06)
MRT (h)	23.2 (26.3)	23.6 (20.5)	NC
CL/F (mL/min)	4618 (58.9)	4719 (39.2)	NC
V _Z /F (L)	11040 (53.9)	11724 (40.5)	NC

Source: Section 9.2 (Tables 1 and 2)

Geometric mean (CV%) data are presented

† Median (min-max) & median difference (90% CI) (A-B)

N = Number of subjects studied

NC = Not calculated

Effect of aliskiren on lovastatin PK

PK profiles of lovastatin were not affected by co-administration of aliskiren. Less than a 10% increase/decrease in PK parameters (AUC_{0-tz}, AUC₀₋₂₄ and C_{max}) by co-administration with aliskiren. These differences were not statistically significantly different between combination treatment and monotherapy. Although, lovastatin t_{max} was increased by 13% with combination treatment, the difference was not statistically significant due to high inter-subject variability.

Effect of aliskiren on lovastatin hydroxy acid PK

Lovastatin was metabolized to its active form lovastatin hydroxy acid and was detected in plasma at greater concentrations than the parent compound. Changes of less than 10% in the PK parameters (AUC_{0-tz}, AUC₀₋₂₄ and C_{max}) of either form was observed with aliskiren being co-administered. The differences were not statistically different between combination treatment and monotherapy.

Note: There were additional peaks of lovastatin and lovastatin hydroxy acid levels during the disposition phase in several subjects, the calculations of AUC_{0-∞} and t_{1/2} were difficult to calculate in those subjects.

Table 3 Summary of Pharmacokinetic Parameters for Lovastatin and Statistical Analysis

Parameter of lovastatin lactone	150 mg Aliskiren & 40 mg lovastatin (A) (N=15)	40 mg lovastatin alone (C) (N=15)	Ratio of least squares means (90% CI) (A/C)
AUC(0-4) (ng.h/mL)	34.2 (53.6)	31.6 (78.0)	1.08 (0.84 – 1.39)
AUC(0-24 h) (ng.h/mL)	28.2 (47.2)	27.8 (56.7)	1.02 (0.82 – 1.25)
AUC(0-∞) (ng.h/mL)	50.5 (38.8) ^a	51.7 (71.4) ^b	NC
C _{max} (ng/mL)	2.57 (53.9)	2.82 (57.2)	0.91 (0.73 – 1.13)
t _{max} † (h)	4.00 (1.50 – 6.00)	3.00 (1.00 – 12.0)	-0.13 (-2.00 – 1.50)
t _{lag} † (h)	0 (0 – 0.500)	0 (0 – 0)	NC
t _{1/2} (h)	16.5 (64.3) ^a	13.5 (42.3) ^b	NC
MRT (h)	24.6 (59.2) ^a	20.4 (50.3) ^b	NC
CL/F (mL/min)	13204 (38.8) ^a	12889 (71.4) ^b	NC
V _d /F (L)	18809 (84.2) ^a	15083 (62.3) ^b	NC

Source: Section 9.2 (Tables 4 and 5)

Geometric mean (CV%) data are presented

† Median (min-max) & median difference (90% CI) (A-C)

N = Number of subjects studied

NC = Not calculated

^a N= 8; ^b N = 10

Table 4 Summary of Pharmacokinetic Parameters for Lovastatin hydroxyacid and Statistical Analysis

Parameter of lovastatin hydroxy acid	150 mg Aliskiren & 40 mg lovastatin (A) (N=15)	40 mg lovastatin alone (C) (N=15)	Ratio of least squares means (90% CI) (A/C)
AUC(0-4) (ng.h/mL)	112 (82.9)	113 (80.3)	0.99 (0.90 – 1.08)
AUC(0-24 h) (ng.h/mL)	96.4 (56.3)	96.3 (55.7)	1.00 (0.92 – 1.08)
AUC(0-∞) (ng.h/mL)	214 (52.6) ^a	252 (20.5) ^b	NC
C _{max} (ng/mL)	11.2 (56.7)	11.7 (73.8)	0.96 (0.85 – 1.08)
t _{max} † (h)	4.00 (2.50 – 8.02)	4.00 (2.50 – 12.0)	0.00 (-0.75 – 1.25)
t _{lag} † (h)	0.500 (0 – 2.00)	0 (0 – 1.00)	NC
t _{1/2} (h)	15.0 (71.4) ^a	11.1 (116) ^b	NC
MRT (h)	22.3 (60.0) ^a	17.7 (94.9) ^b	NC

Source: Section 9.2 (Tables 7 and 8)

Geometric mean (CV%) data are presented

† Median (min-max) & median difference (90% CI) (A-C)

N = Number of subjects studied

NC = Not calculated

^a N= 7; ^b N = 4

SAFETY:

Among the 9 observed adverse events with aliskiren or aliskiren with lovastatin treatments, 3 events (dry mouth, dizziness and hot flushes) were not considered to be drug related. There was one drug related adverse event (flatulence). None were severe in nature.

CONCLUSIONS:

According to the of the in-vitro study results, aliskiren was metabolized by CYP3A4. However, contribution of CYP3A4 to the elimination of aliskiren was found to be low. Lovastatin is also known to be metabolized by CYP3A4 and the reason why this study was conducted. There was no considerable interaction found except for one outlier (see Reviewer's comment) that had a 900% increase in aliskiren C_{max} with co-administration of lovastatin at a dose of 40 mg.

REVIEWER'S COMMENT:

1. It remains unclear whether immediate-release or extended-release lovastatin was administered to volunteers in this study.

**APPEARS THIS WAY
ON ORIGINAL**

Study CSPP100A 2234 – AN OPEN-LABEL, MULTIPLE-DOSE STUDY TO EVALUATE THE PHARMACOKINETICS, SAFETY AND TOLERABILITY OF SPP100 (ALISKIREN) AND ATORVASTATIN (LIPITOR®) ADMINISTERED ALONE AND IN COMBINATION IN HEALTHY SUBJECTS

STUDY INVESTIGATOR AND SITE:

REPORT # 2234

EDR SECTION 8

STUDY DATES: June 28, 2005 – July 17, 2005

Objectives:

Primary objective:

- To characterize the pharmacokinetics of aliskiren alone and in combination with atorvastatin in healthy volunteers.
- To characterize the pharmacokinetics of atorvastatin alone and in combination with aliskiren in healthy volunteers.

Secondary objective

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

FORMULATION:

Aliskiren 300 mg tablet (Batch# X299IA, KN# 6000937.006, Exp. Date not provided) by Novartis

Atorvastatin 80 mg tablet (Batch# 04685V, Exp. Date not provided) purchased from commercial source by the investigator

Design: This was an open-label, two-period, multiple-dose study in healthy volunteers, carried out according to the following design:

Baseline 1	Period 1	Washout	Baseline 2	Period 2		End of study
Day -1	Days 1-4	Days 5-8	Day 8	Days 9-15	Days 16-19	Day 20
	Atorvastatin 80 mg q.d.			Aliskiren 300mg q.d.	Aliskiren 300 mg q.d. + Atorvastatin 80 mg q.d.	

Subjects who satisfied all inclusion criteria at screening (days -21 to -2) entered the study center on the evening of day -1 for baseline 1 safety assessments and to review inclusion/exclusion criteria to confirm patient eligibility. During Period 1, following an overnight fast of 10-12 hours, all subjects received atorvastatin 80 mg p.o. q.d. for 4 days. On days 1 to 3, blood samples were obtained pre-dose, and on day 4, to assess 24-hour atorvastatin pharmacokinetics.

On day 5, subjects were discharged from the study center for a 4-day washout and readmitted on the evening of day 8 for baseline 2, safety assessments and to review inclusion/exclusion criteria to confirm subject eligibility. During Period 2, following an overnight fast of 10-12 hours, all subjects received aliskiren 300 mg p.o. q.d. for 7 days. Thereafter, subjects received both aliskiren 300 mg p.o. q.d. and atorvastatin 80 mg p.o. q.d. for 4 days. On days 9 to 14 and days 16 to 18, blood samples were obtained pre-dose to measure trough drug concentrations. Blood samples were collected on day 15 to assess 24-hour aliskiren PK profiles and on day 19 to assess 24-hour PK profiles for both aliskiren and atorvastatin.

Criteria for inclusion: Male and female healthy non-smoking volunteers, between 18 and 45 years of age, in good health as determined by the screening and baseline evaluations, and who gave written informed consent. Females must have been either surgically sterile, using double-barrier local contraception, or post-menopausal.

ANALYTICAL METHODS:

Aliskiren was assayed in plasma by LC-MS/MS; LLOQ at 0.5 ng/mL

Atorvastatin, o-hydroxy-atorvastatin and p-hydroxy-atorvastatin in plasma by LC-MS/MS, LLOQ at 0.250 ng/mL

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

PK SAMPLE COLLECTION/CALCULATIONS AND STATISTICAL ANALYSIS:

Aliskiren:

Days 13, 14, 17 and 18: 1 h pre-dose

Days 15 and 19: 1 h pre-dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16 and 24 hours post-dose

Atorvastatin and metabolites:

Days 2, 3, 17 and 18: 1 h pre-dose

Days 4 and 19: 1 h pre-dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16 and 24 hours post-dose

Pharmacokinetic calculations

Pharmacokinetic parameters were determined from plasma concentrations of Aliskiren, atorvastatin and metabolites for:

AUC_{0-24} , C_{maxss} , T_{maxss}

Statistical methods: For aliskiren, atorvastatin and its metabolites, log-transformed PK parameters AUC_{0-24} and C_{maxss} 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 determine drug-drug interactions.

RESULTS:

Twenty-one (21) subjects were enrolled in this study and 20 completed it. Subject 5119 had elevated serum cotinine at the Period 2 baseline evaluation so was discontinued from the study at that point because of study ineligibility/protocol violation.

Pharmacokinetics

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ON ORIGINAL

Table 1 Descriptive statistics of plasma aliskiren PK parameters on Days 15 and 19 following administration of multiple doses of 300 mg aliskiren alone (Day 15) or in combination with atorvastatin (Day 19)

	Day 15			Day 19		
	C_{maxss} (ng/mL)	T_{maxss} (h)	AUC_{0-24} (ng x h/mL)	C_{maxss} (ng/mL)	T_{maxss} (h)	AUC_{0-24} (ng x h/mL)
N	20	20	20	20	20	20
Mean	448	2.43	2356	669	2.16	3349
SD	273	1.66	919	339	1.25	1013
Min						
Median	406	2.03	2355	632	2.00	3243
Max						
CV%	60.9	68.5	39.0	50.6	57.8	30.3

There was a 50% and 47% increase noted in the geometric means for C_{maxss} and AUC_{0-24} for aliskiren on Day 19 relative to Day 15. The T_{maxss} was essentially unchanged.

Figure 1 Mean (+standard deviation) aliskiren concentrations in healthy volunteers when treated with aliskiren alone (Day 15) and in combination therapy with 80 mg atorvastatin (Day 19)

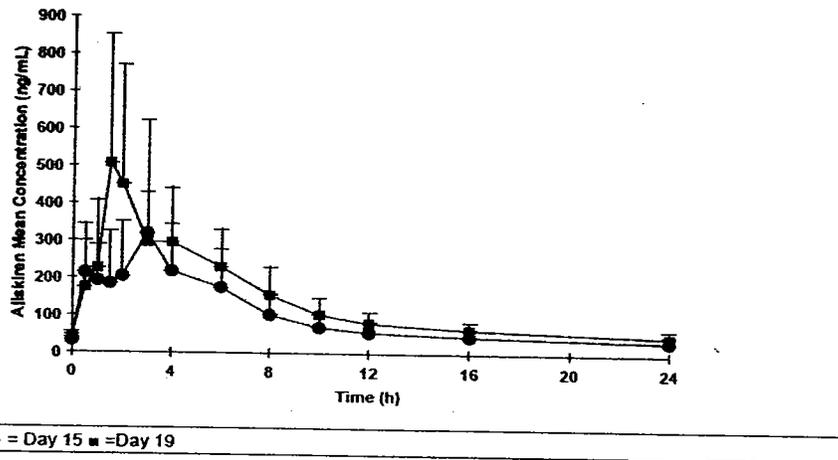
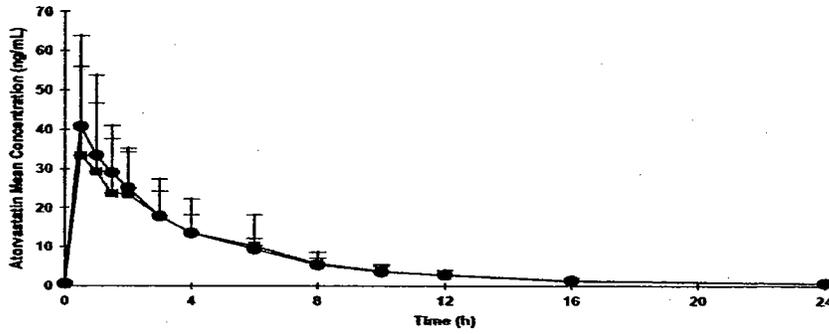


Table 2 Descriptive statistics of plasma atorvastatin PK parameters on Days 4 and 19 following administration of multiple doses of 80 mg atorvastatin once daily for 4 days

	Day 4			Day 19		
	C_{maxss} (ng/mL)	T_{maxss} (h)	AUC_{0-24} (ng x h/mL)	C_{maxss} (ng/mL)	T_{maxss} (h)	AUC_{0-24} (ng x h/mL)
N	21	21	21	20	20	20
Mean	46.4	0.8	166	39.3	1.1	157
SD	20.1	0.4	39	27.0	1.0	64
Min						
Median	43.3	0.5	162	32.1	0.6	140
Max						
CV%	43.4	55.5	23.7	68.7	88.9	40.7

No major differences were noted for atorvastatin between Day 4 and Day 19. There was an apparent decrease of about 23% in geometric mean for C_{maxss} on Day 19 relative to Day 4.

Figure 2 Mean (standard deviation) atorvastatin concentrations in healthy volunteers when treated with atorvastatin alone and in combination therapy (with aliskiren)

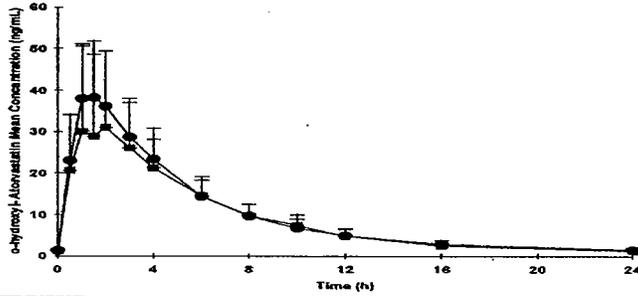


● = Day 4 ■ = Day 19

There was approximately a 22% decrease in geometric mean for C_{max} noted for o-hydroxy-atorvastatin on Day 19 relative to Day 14. No differences were noted between Day 4 and Day 19 for p-hydroxy-atorvastatin.

Figure 3

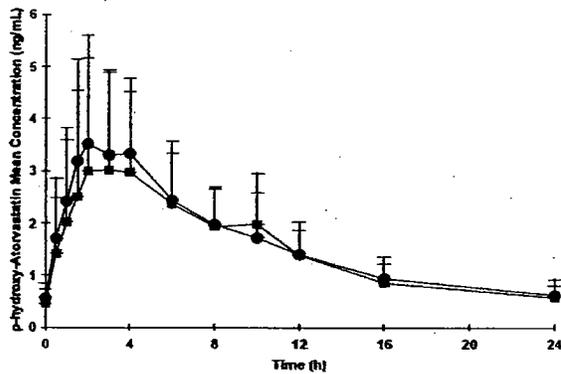
Mean (standard deviation) o-hydroxy-atorvastatin concentrations in healthy volunteers when treated with atorvastatin alone and in combination therapy (with aliskiren)



● = Day 4 ■ = Day 19

Figure 4

Mean (standard deviation) p-hydroxy-atorvastatin concentrations in healthy volunteers when treated with atorvastatin alone and in combination therapy (with aliskiren)



● = Day 4 ■ = Day 19

Statistics:

The summary of the analysis results of AUC_{0-24} and C_{maxss} for aliskiren is presented in Table 3. Aliskiren AUC_{0-24} values were 47% higher and C_{maxss} values were 50% higher when aliskiren was co-administered with atorvastatin compared to aliskiren administered alone.

Table 3 Statistical analysis results of Aliskiren PK parameters

Parameter	Ratio of geometric means	
	(A+B:B)	90% CI for ratio
AUC_{0-24} (ng.h/mL)	1.47	(1.29, 1.67)
C_{maxss} (ng/mL)	1.50	(1.22, 1.85)

Treatment A = Atorvastatin 80mg, Treatment B = Aliskiren 300mg

The summary of the analysis results of AUC_{0-24} and C_{maxss} for atorvastatin is presented in Table 4. Co-administration of aliskiren with atorvastatin had no effect on AUC_{0-24} of atorvastatin since the 90% confidence interval for the ratio of means was entirely contained in the range of (0.80, 1.25). Geometric mean of C_{maxss} of atorvastatin was 23% lower when co-administered with aliskiren.

Table 4 Statistical analysis results of Atorvastatin PK parameters

Parameter	Ratio of geometric means	
	(A+B:A)	90% CI for ratio
AUC_{0-24} (ng.h/mL)	0.91	(0.84, 1.00)
C_{maxss} (ng/mL)	0.77	(0.67, 0.88)

Treatment A = Atorvastatin 80mg, Treatment B = Aliskiren 300mg

The summary of the analysis results of AUC_{0-24} and C_{maxss} for o-hydroxy-atorvastatin is presented in Table 5. Co-administration of aliskiren with atorvastatin had no effect on AUC_{0-24} of o-hydroxy-atorvastatin since the 90% confidence interval for the ratio of means was entirely contained in the range of (0.80, 1.25). Geometric mean of C_{maxss} of o-hydroxy-atorvastatin was 22% lower when co-administered with aliskiren.

Table 5 Statistical analysis results of o-hydroxy-atorvastatin PK parameters

Parameter	Ratio of geometric means	
	(A+B:A)	90% CI for ratio
AUC_{0-24} (ng.h/mL)	0.89	(0.82, 0.98)
C_{maxss} (ng/mL)	0.78	(0.67, 0.91)

Treatment A = Atorvastatin 80mg, Treatment B = Aliskiren 300mg

The summary of the analysis results of AUC_{0-24} and C_{maxss} for p-hydroxy-atorvastatin is presented in Table 6. Co-administration of aliskiren with atorvastatin had no effect on AUC_{0-24} of p-hydroxy-atorvastatin since the 90% confidence interval for the ratio of means was entirely contained in the range of (0.80, 1.25). Although the confidence interval for C_{maxss} of p-hydroxy-atorvastatin was not entirely in the no interaction range, a decrease of 10% in geometric mean of p-hydroxy-atorvastatin was not considered clinically relevant.

The summary of the analysis results of AUC_{0-24} and C_{maxss} for p-hydroxy-atorvastatin is presented in Table 6. Co-administration of aliskiren with atorvastatin had no effect on AUC_{0-24} of p-hydroxy-atorvastatin since the 90% confidence interval for the ratio of means was entirely contained in the range of (0.80, 1.25). Although the confidence interval for C_{maxss} of p-hydroxy-atorvastatin was not entirely in the no interaction range, a decrease of 10% in geometric mean of p-hydroxy-atorvastatin was not considered clinically relevant.

Table 6 Statistical analysis results of p-hydroxy-atorvastatin PK parameters

Parameter	Ratio of geometric means	
	(A+B:A)	90% CI for ratio
AUC ₀₋₂₄ (ng.h/mL)	0.91	(0.82, 1.01)
C _{maxss} (ng/mL)	0.90	(0.75, 1.08)

Treatment A = Atorvastatin 80mg, Treatment B = Aliskiren 300mg

SAFETY:

Subject number 5120 experienced abdominal cramping with pain severe in nature on the first day of the aliskiren/atorvastatin therapy (day 16). However, he had been experiencing GI disorders and diarrhea on the first day of aliskiren monotherapy (day 9) that was considered mild in severity.

There were no serious adverse events during this study. Eleven (11) subjects experienced a total of 47 adverse events. Adverse events involving the nervous system appeared to be more frequent when aliskiren was given alone compared to atorvastatin alone or the combination of aliskiren and atorvastatin. Gastrointestinal side effects appeared to be more frequent when aliskiren was given alone or in combination with atorvastatin compared to atorvastatin alone. The most frequently occurring adverse events were nervous system disorders (headache, dizziness, lethargy, somnolence) and gastrointestinal disorders (diarrhea, loose stool, dry mouth, nausea, abdominal pain). Forty-six (46) of the 47 total adverse events observed during the study were mild in severity, and one was severe. Thirty-seven (37) of the 47 events were suspected to be related to study medication. None of the subjects was discontinued prematurely from the study because of an adverse event, and none received concomitant medication to treat any adverse event.

SPONSOR'S CONCLUSIONS:

- Co-administration of atorvastatin with aliskiren resulted in approximately a 50% increase in steady-state C_{max} and AUC of aliskiren.
- Co-administration of aliskiren with atorvastatin had no significant effect on the pharmacokinetics of atorvastatin or its two active hydroxy (ortho- and para-) metabolites.
- Aliskiren was safe and well-tolerated when given in multiple oral doses of 300 mg/day alone or in combination with multiple oral doses of 80 mg/day atorvastatin.

REVIEWER'S COMMENT:

1. Atorvastatin clearly increases the rate and extent of absorption of aliskiren. This change in both C_{max} (50%) and AUC (47%) is of clinical significance and worthy of mention in aliskiren's labeling.

**APPENDIX IV
QT STUDY REVIEW**

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**Interdisciplinary Review Team for QT Studies
Response to a Request for Consultation: NDA Review**

NDA	21985
Brand Name	Rasilez
Generic Name	Aliskiren
Sponsor	Novartis
Indication	Hypertension
Dosage Form	Oral tablet
Therapeutic Dose	150 mg, 300 mg
Duration of Therapeutic Use	Chronic Use
Application Submission Date	10 Feb 2006
Review Classification	Standard
Date Consult Due	26 Sept 2006
Clinical Division	Division of Cardiovascular and Renal Products

1.0 RECOMMENDATION

Please have the Sponsor submit ECGs via the ECG warehouse. Notify us when the ECGs are available for our review.

2.0 SUMMARY OF FINDINGS

- These findings are preliminary. Prior to making final conclusions, we would like to review the ECGs to verify the appropriateness of QT measurements.
- Based on our preliminary assessment, QTc results did not cross the threshold of regulatory concern; this was a negative study.
- Assay sensitivity was confirmed.

3.0 GOAL OF THE REVIEW

The purpose of this review was to analyze the thorough QT study submitted by the Sponsor.

4.0 BACKGROUND

4.1. Indication

Hypertension

4.2. Drug Class

Renin inhibitor

4.3. Regulatory Classification

4.4. Market approval status

This drug is not approved for use for any indication in the United States. To the best of our knowledge, aliskiren is not marketed elsewhere.

5.0 DRUG INFORMATION

5.1. Clinical Pharmacology

Table 1 summarizes the key features of the clinical pharmacology of aliskiren. The mean single dose and steady state time course of plasma concentrations following administration of 300 mg to healthy volunteers is presented in Figure 1.

Figure 1. Mean Concentration-Time profile for Aliskirin

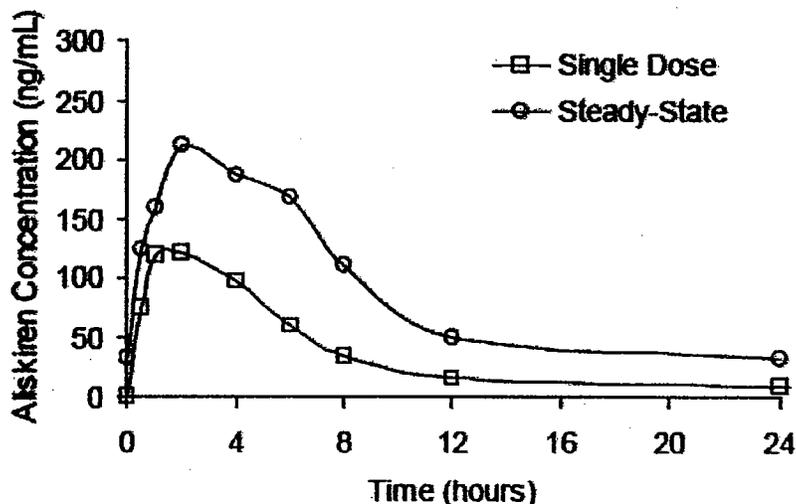


Table 1. Highlights of Clinical Pharmacology.

Therapeutic dose	150 to 300 mg QD without regards to meals	
Maximum dose tested	Single Dose	600 mg single dose
	Multiple Dose	300 mg QD for 7 days
Exposures Achieved	600 mg SD	420 ng/ml (C _{max})
	300 mg MD	321 ng/ml (C _{max})
Maximum tolerated dose	NA	
Principal adverse events	Headache, nasopharyngitis, diarrhea	
Absorption	Absolute Bioavailability	F = 2.6±0.8%
	T _{max}	1-3 hours
Distribution	V _{ss}	135 L (i.v. dose); extensive distribution
	V _d /F	4.6±2.1 L/kg
	% bound	47-51% (moderate protein binding)
Elimination	Route	•Primarily unchanged in feces •Renal excretion <1% of dose •Minimally metabolized:
	Terminal t _{1/2}	40 h
	CL	9 L/h
	Accumulation:	2-fold
Range of linear PK	Dose proportional increases in AUC: 75 mg to 600 mg	

Intrinsic Factors	Age	Exposure increase by 57% (AUC) in elderly (>65 y/o)
	Sex	Exposure higher in females (may be related to body weight)
	Race	No impact of race
Extrinsic Factors	Drug interactions	<ul style="list-style-type: none"> •DDI with drugs that inhibit, induce, or metabolized by P450 are not expected •Ketoconazole: increase exposure by 76% (AUC) and 81% (Cmax). Concentration were 1.8-fold higher with 300 mg dose.
	Food Effects	<ul style="list-style-type: none"> •Meals decrease exposure 71-85% •Meals delay Tmax 1 h •Product label: to be taken with or without food
High Clinical Exposure scenario	<ul style="list-style-type: none"> •Mild to severe renal insufficiency increased exposure 0.8-2-fold (AUC) •Ketoconazole inhibitor via Pgp transporter 	

6.0. SPONSOR'S SUBMISSION

6.1. Overview

The sponsor conducted a randomized, double-blind, placebo and active-controlled, parallel group, multiple oral dose study to examine the effects of aliskiren on cardiac conduction (PR interval, QRS duration) and repolarization (QT interval) in healthy volunteers. Two hundred eighty three (283) subjects were randomized to receive either 300 mg aliskiren, 1200 mg aliskiren, placebo or 400 mg moxifloxacin as active control, once daily for 7 days.

The sponsor did not perform additional ECG monitoring in phase III.

6.2. QT/QTc Study Synopsis

6.2.1. Title: A randomized, double blind, multiple oral dose study to evaluate the effects of SPP100 on cardiac safety in healthy subject versus placebo with positive control (Avelox®) (First subject dosed: Sept. 29, 2004--last subject completed: May 2, 2005)

6.2.2. Protocol Number: SPP100A2208 (Part A)

6.2.3. Primary Objective: To determine the effect of multiple daily Aliskiren (SPP100) oral administration on cardiac conduction and repolarization (QT interval)

6.2.4. Design: This was a multi-center, double-blind (aliskiren versus placebo), parallel-group, placebo and active controlled, multiple-dose study in healthy volunteers. The design consisted of a 21-day screening period, a baseline period (Days -2 to -1), a single treatment period (Days 1 to 7) and a study completion evaluation 11 to 15 days following the last dose of study drug.

6.2.4.1. Justification for design provided:

No justification for the design was provided by the sponsor. However, a parallel study design is reasonable for this drug due to its long elimination half-life of 40 h.

6.2.5 Population: During enrollment, subjects were stratified by gender (male ~50%: female ~50%). Subjects within each stratum were randomized to be evenly allocated to the 4 treatments. A total of 315 subjects were enrolled into the 4 treatments.

6.2.6. Dosing/Treatment groups:**Table 3-1 Treatment groups**

Group	Treatment
A	SPP100 300 mg qd
B	SPP100 1200 mg qd
C	Avelox 400 mg qd
D	SPP100 Placebo qd

Note: According to Table 3-1 (study report), subjects received a single dose of Avelox.

6.2.6.1. Justification for dose provided

Based on the pivotal studies for Aliskiren, the highest dose recommended for treatment of hypertension will be 300 mg. According to the sponsor, "a generally accepted benchmark for safety pharmacology studies is to use approximately 5 times the highest efficacious clinical dose planned/used in pivotal studies." An increase of gastro-intestinal adverse events was seen starting from the dose of 850 mg over one week of treatment the high dose safety study with multiple dose administration. In light of this, the dose of 1200 mg (4 times the highest efficacious dose) was chosen based on previous studies indicating that GI tolerability may be limiting at doses above 1200 mg.

6.2.6.2. Instructions with regard to meals

Doses were administered under fasting conditions (fasted at least 10 h prior to administration of study drug and continue to fast for 4 h after dosing).

6.2.7. Study Schedule and Timing of Samples**Table 2. Highlights of Schedule of Interventions**

Study Day	-1	3, 5	7
Intervention	No treatment	Multiple doses	Steady state
12-Lead ECGs	Recorded in triplicate (Holter) pre-dose, and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 23 h post-dose	Recorded pre-dose and 3 h post dose	Recorded in triplicate (Holter) pre-dose, and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 14, 23 h post-dose
PK Samples for drug	None collected	Collected pre-dose and 3 h post-dose	Collected pre-dose, and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 23, 36, 48, and 72 h

			post-dose
Meal Instructions	Fasted conditions	Dosed under fasting conditions	Dosed under fasting conditions

Sponsor's justification for sampling schedule

The sponsor did not provided justification for sampling schedule.

6.2.8. QT Measurement: Holter monitoring (24 h) was performed and digital 12 lead ECG's were obtained before study drug administration and on the 7th day of drug administration (steady-state). The 12 lead ECG's were recorded at pre-dose, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 14 and 23 hours post-dose. The average of three ECG's (recorded within a 5 minute time interval) was used to determine cardiac intervals at each time point.

When provided, the lead II rhythm strip was used for assessment of conduction intervals to make interval duration measurements on 3 consecutive beats. If a rhythm strip was not provided, as many measurements as possible (often 1 and possibly 2) were performed from one of the available leads (II or V5). Digital ECG data were sent to eRT for processing and interpretation.

6.2.9. Controls: The Sponsor used both placebo and positive (moxifloxacin) controls.

6.2.10. Blinding: Aliskiren and placebo were blinded. There is no indication that moxifloxacin was blinded. The study was evaluator blinded.

6.2.11. Baseline: The Sponsor collected time-matched baseline QTc values on the day prior to initiating dosing (Day -1) of the study for each treatment.

6.3. Changes to the Study:

- Amendment 1 (Jan. 15, 2005): The protocol was amended to clarify text; change inclusion criterion from Metropolitan Life Table to Body Mass Index; add 12-lead ECG recordings at end of study and 8 hours post-drug administration; add plasma levels for Avelox; and add baseline vital signs.
- Amendment 2 (June 3, 2005): Revised the sample size based on the E14 guidance and the use of 10 msec (rather than 8 msec) as a 95% one-sided upper bound. An interim analysis was planned at the completion of 160 subjects (40/treatment arm) to determine additional subjects required to complete the study.

Reviewers' Assessment: These amendments did not affect the integrity of the study.

6.3. QT Study Results

6.3.1. ECG Review: No ECGs were found under this NDA in the ECG warehouse. Therefore, this review team is unable to verify the appropriateness of the QT measurements.

6.3.2. Analysis of Central Tendency: (from Sponsor)

The central tendency analysis of QTc interval data was performed in 2 ways: (1) time-matched analysis, and (2) time-averaged analysis. The time-matched analysis was the primary analysis. Our focus is for (1).

The sponsor proposed to use the average QTc value on Day -1 as the baseline. For each subject, the QTc value at each time point on Day 7 was subtracted from this averaged baseline value. The results are summarized in the following table (see next page).

Day 7 postdose time (h)	Estimated difference (90% CI of difference)			
	Cardiac interval (msec)	Aliskiren 300 mg vs placebo	Aliskiren 1200 mg vs placebo	Avelox® 400 mg vs placebo
0.0	QTcF	0.7 (-2.7, 4.0)	2.5 (-0.8, 5.8)	4.6 (1.3, 7.9)
	QTcI	-1.6 (-5.3, 2.1)	3.3 (-0.4, 6.9)	3.5 (-0.1, 7.1)
0.5	QTcF	1.2 (-2.1, 4.4)	4.2 (1.0, 7.4)	12.9 (9.7, 16.1)
	QTcI	0.6 (-2.7, 4.0)	4.0 (0.7, 7.3)	12.1 (8.8, 15.4)
1.0	QTcF	0.5 (-2.4, 3.4)	2.2 (-0.7, 5.0)	13.9 (11.0, 16.7)
	QTcI	-0.2 (-3.4, 2.9)	1.7 (-1.4, 4.7)	13.3 (10.2, 16.4)
1.5	QTcF	-1.0 (-4.0, 2.0)	-0.3 (-3.2, 2.6)	13.2 (10.2, 16.1)
	QTcI	-1.3 (-4.5, 2.0)	-0.9 (-4.1, 2.3)	12.9 (9.7, 16.1)
2.0	QTcF	-0.7 (-3.6, 2.2)	-0.4 (-3.3, 2.4)	12.9 (10.0, 15.8)
	QTcI	-1.2 (-4.4, 1.9)	-0.7 (-3.8, 2.4)	13.2 (10.1, 16.3)
3.0	QTcF	2.1 (-0.9, 5.1)	2.8 (-0.1, 5.7)	16.5 (13.5, 19.4)
	QTcI	1.9 (-1.2, 5.0)	2.5 (-0.6, 5.6)	16.5 (13.4, 19.6)
4.0	QTcF	1.7 (-1.2, 4.7)	3.2 (0.4, 6.1)	14.6 (11.7, 17.5)
	QTcI	1.3 (-1.9, 4.4)	2.4 (-0.7, 5.5)	14.7 (11.5, 17.8)
5.0	QTcF	1.5 (-1.7, 4.7)	0.2 (-2.9, 3.4)	6.6 (3.4, 9.7)
	QTcI	0.6 (-2.7, 3.8)	1.2 (-2.1, 4.4)	7.4 (4.2, 10.7)
6.0	QTcF	2.1 (-0.8, 4.9)	0.5 (-2.3, 3.3)	7.5 (4.7, 10.3)
	QTcI	0.5 (-2.8, 3.7)	0.8 (-2.4, 4.0)	6.9 (3.7, 10.1)
8.0	QTcF	3.3 (0.6, 6.0)	1.7 (-0.9, 4.4)	10.2 (7.5, 12.9)
	QTcI	2.5 (-0.3, 5.4)	1.7 (-1.0, 4.5)	10.7 (7.9, 13.5)
10.0	QTcF	0.0 (-2.8, 2.8)	0.8 (-2.0, 3.6)	8.3 (5.4, 11.1)
	QTcI	-0.9 (-4.0, 2.1)	0.6 (-2.3, 3.6)	8.6 (5.5, 11.6)
12.0	QTcF	1.4 (-1.4, 4.1)	1.6 (-1.1, 4.4)	6.0 (3.2, 8.8)
	QTcI	-0.1 (-3.1, 3.0)	2.6 (-0.4, 5.6)	5.7 (2.7, 8.7)
14.0	QTcF	1.3 (-2.0, 4.6)	0.1 (-3.2, 3.4)	3.5 (0.2, 6.8)
	QTcI	-0.8 (-4.3, 2.7)	-0.4 (-3.9, 3.0)	2.5 (-0.9, 6.0)
23.0	QTcF	2.0 (-1.1, 5.0)	5.2 (2.2, 8.1)	8.5 (5.4, 11.5)

Avelox® (moxifloxacin) group showed significant prolongation of QTc. All the 1-sided upper bounds of 95% confidence interval for the two dose Aliskiren groups are below 10 msec.

6.3.3. Exposure-Response Analysis

The sponsor evaluated the change in QTc at Tmax, for Aliskiren in response to drug exposure (Cmax and AUC). In addition, any effect if drug exposure on the maximum change in QTc was also examined.

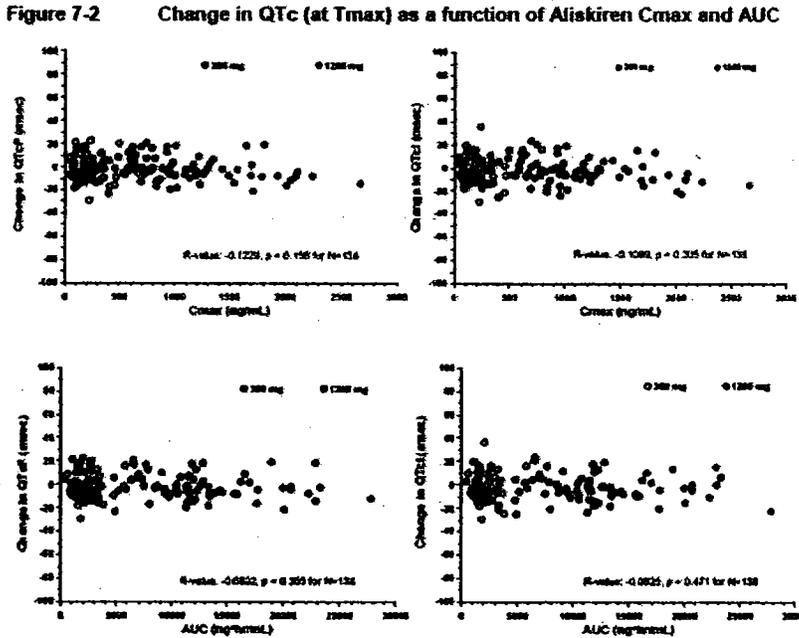
Pharmacokinetic parameters are presented in Table 3. The Cmax increased from 246 ng/mL in 300 mg treated group to 1115 ng/mL (4.5-fold) in 1200 mg treated group. Tmax values ranged from 0.5 h to 8 h.

Table 3. Mean (SD) Aliskiren Day 7 Pharmacokinetic Parameters

PK parameter	300 mg	1200 mg
Tmax ^a (h)	1.88 (0.58, 6.15)	1.6 (0.58, 8.12)
Cmax (ng/mL)	246.1 (194.1)	1115.2 (494.1)
AUC0-τ (ng·hr/mL)	2158.1 (1087.6)	12486.7 (4949.4)
N	66	72
a: median (min, max)		

The change in QTc interval at Tmax as a function of Aliskiren Cmax and AUC is plotted in the Figure 2. No correlation was observed between QTc interval and Cmax or AUC.

Figure 2. Change in QTc (at Tmax) as a Function of Aliskiren Cmax and AUC



Reviewer's Comments:

- The exposure following once daily administration of 1200 mg aliskerin for 7 days was 4.5- to 5.5-fold greater than the therapeutic dose. The increased exposure is greater than what was observed with inhibition with ketoconazole.
- Administration of aliskerin under fasting conditions is acceptable as meals decrease the bioavailability.
- The timing of ECG recordings and blood samples for pharmacokinetic assessments were adequate to fully characterize the time-course of aliskerin effects on the QT/QTc interval.
- Exposure-response analysis conducted by both the sponsor and reviewer indicate a lack of a relationship between aliskerin exposure and the change in the QTcF interval.

7.0. REVIEWERS' ASSESSMENT

For the time-matched analysis the sponsor proposed, they adjusted post dose QTc by the average of all the baseline values; therefore, the sponsor actually did not perform a time-matched baseline adjustment. We performed the following analysis. For each subject, we subtracted QTc at each time point on Day 7 by the QTc value at the same time point on Day -1 for all treatment groups, and then we averaged over all the subjects. The mean difference of the drug (two doses) and placebo as well as the 1-sided 95% upper confidence intervals are provided. The mean difference of moxifloxacin and placebo as well as 1-sided 95% lower bound are also calculated and provided in the following table. For the moxifloxacin comparison, we adjusted α using the Bonferroni method.

As can be seen from the following table, since there are at least one time point where the lower bound of the adjusted 1-sided 95% confidence interval for the baseline adjusted mean difference of moxifloxacin and placebo is above 5 msec, the assay sensitivity was established. Since all the 1-sided 95% upper bounds for the baseline adjusted mean difference of the drug (300 mg and 1200 mg) and placebo are below 10 msec, a negative thorough QT/QTc study can be claimed. Therefore, our findings are consistent with those reported by the sponsor.

Time	Baseline adjusted mean dif of 300 mg & placebo	1-sided 95% Upper Bound	Baseline adjusted mean dif of 1200 mg & placebo	1-sided 95% Upper Bound	Baseline adjusted mean dif of Moxi & placebo	1-sided 95% Lower Bound (*)
0	1.32	4.78	4.80	8.82	4.62	-0.83
0.5	-0.39	3.47	0.95	4.50	10.63	4.75
1	1.12	4.37	-1.36	1.82	12.04	6.74
1.5	0.26	3.78	-0.05	3.31	13.67	8.42
2	-1.03	2.53	-0.13	3.27	12.03	6.26
3	2.80	5.98	2.56	6.04	15.94	11.10
4	1.47	5.07	2.81	6.35	13.90	8.49
5	0.35	3.81	0.00	3.75	7.11	1.51

6	1.54	5.16	0.63	4.15	10.04	5.21
8	2.80	6.07	0.91	4.19	10.74	5.56
10	1.23	4.73	1.08	4.21	9.90	4.72
12	2.21	5.27	3.50	6.11	5.88	1.14
14	0.72	4.13	1.21	4.70	3.61	-2.17
23	2.98	6.85	5.84	9.28	8.94	3.68

* We applied the most conservative Bonferroni adjustment for α .

Analysis of the aliskerin plasma concentration and ddQTcF data is presented in Figure to Figure 5. Evident in these plots is a lack of a relationship between aliskeri concentrations and change in the QTcF interval.

These results support the lack of effect of steady state exposure of 300 mg and 1200 m Aliskerin on the QT/QTc interval.

Figure 3. Time-Course of Mean QTcF Interval

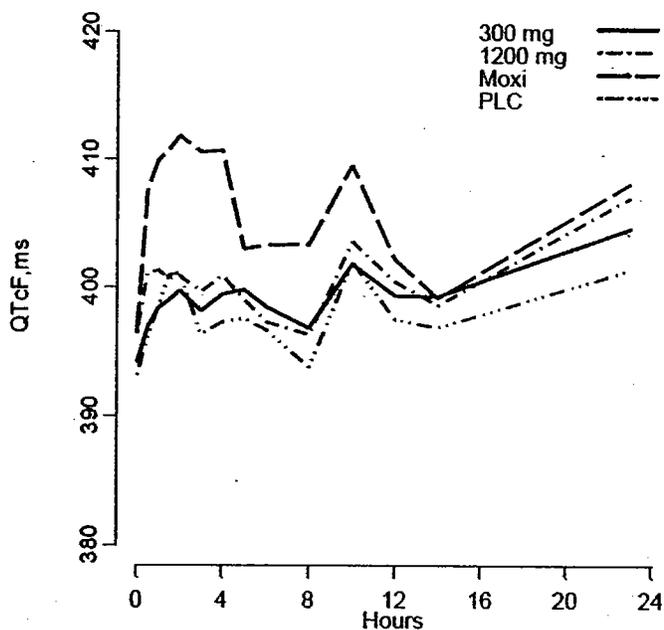


Figure 4. Time Course of Mean ddQTcF Intervals Overlaid with Mean Aliskerin Concentrations

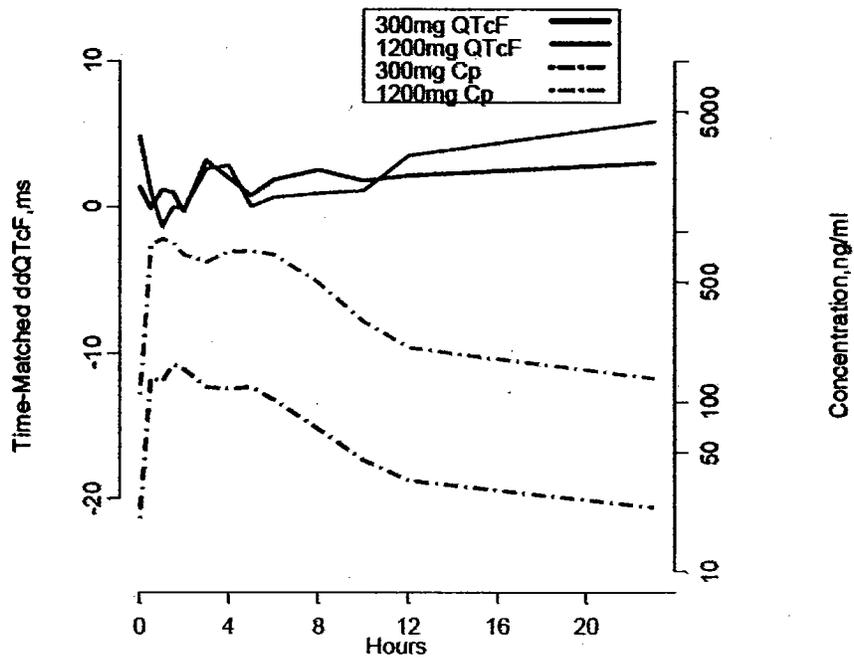
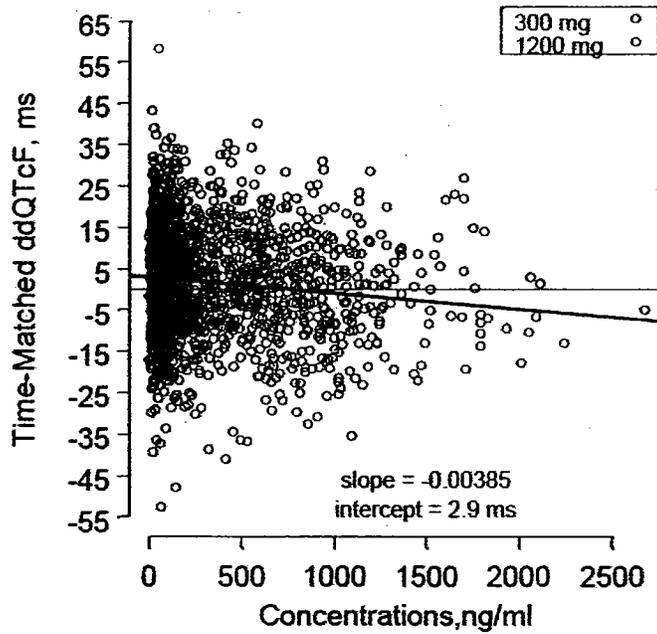


Figure 5. Aliskerin Concentration and ddQTcF Relationship



APPENDIX V
PHARMACOMETRICS REVIEW

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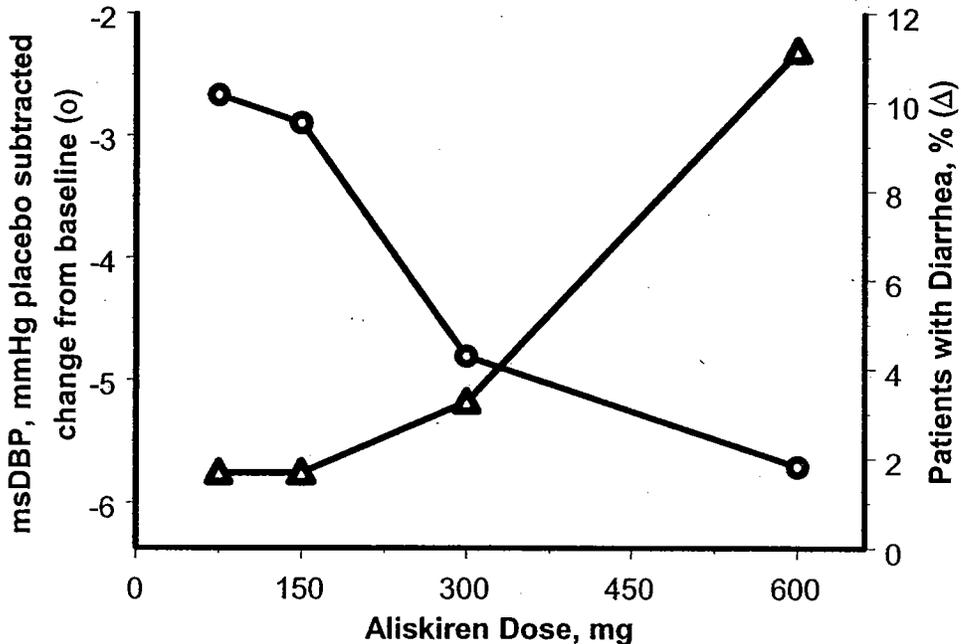
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The pharmacometrics review was aimed at answering the following question:

What is a reasonable starting dose for aliskiren?

Based upon the benefit-risk assessment (Figure 1) derived from dose-response analysis for lowering of LS mean sitting diastolic and systolic blood pressures (effectiveness) and risk for diarrhea (safety), and non-responders by week 4 should be titrated to a maximum of 300 mg daily dose. Aliskiren at 600 mg results in approximately 6 fold increase in risk for diarrhea compared to 75 mg dose. This is also evident in the benefit-risk assessment of responders and patients with diarrhea (Appendix Figure 2). Also, in elderly patients i.e., above 65 years age, no additional benefit in blood pressure reduction is gained by increasing the dose from 75 mg to 300 mg aliskiren.

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

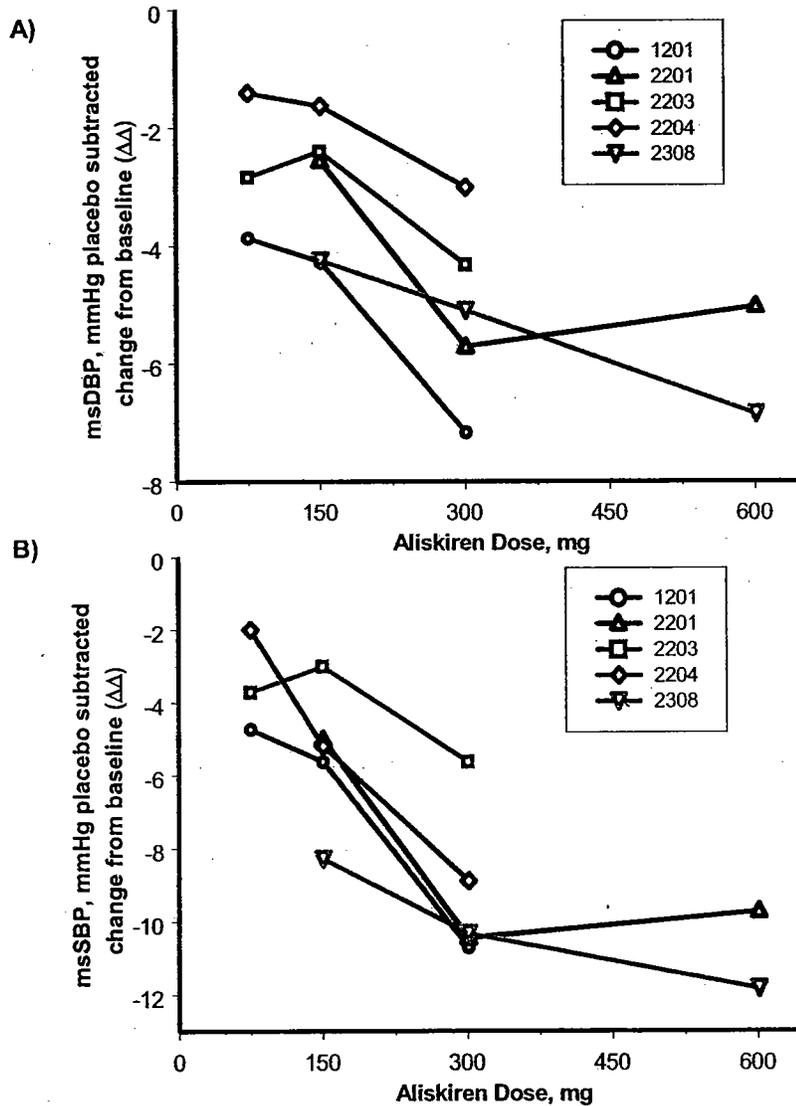


Dose-Response related to effectiveness:

Aliskiren plasma concentrations were not measured in the clinical trials. Hence, concentration-response relationships could not be assessed. The effectiveness of aliskiren was evaluated over a dose range of 75 mg to 600 mg once daily. The dose-response relationship of aliskiren monotherapy was graphically evaluated using data from 5 placebo controlled clinical trials (2201, 2203, 2204, 2308 and 1201). Aliskiren displays a dose dependent lowering of both mean sitting diastolic blood pressure (msDBP) and mean sitting systolic blood pressure (msSBP) (LS means as determined by mixed model for repeated measures or MMRM

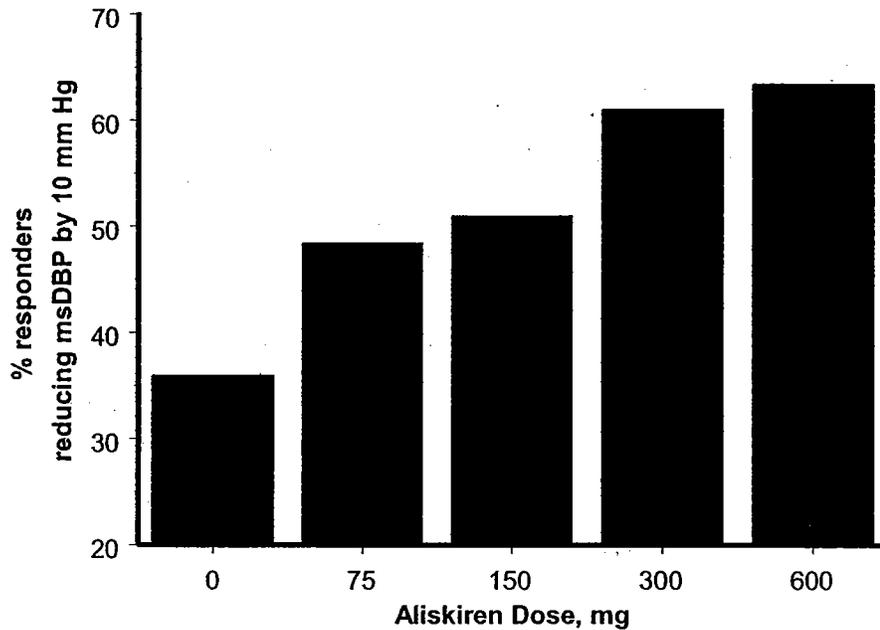
analyses) across all the studies, though not all the reductions were statistically significant (Figure 2).

Figure 2: Aliskiren shows dose dependent lowering of blood pressure.



Further, the proportion of responders (drop in msDBP by at least 10 mm Hg by week 8 and the msDBP at trough less than 90 mm Hg) also showed a dose dependency for the pooled data as shown in Figure 3. Approximately 50% of the patients responded to 75 mg Aliskiren monotherapy.

Figure 3: 50% of the patients respond to 75 mg Aliskiren.



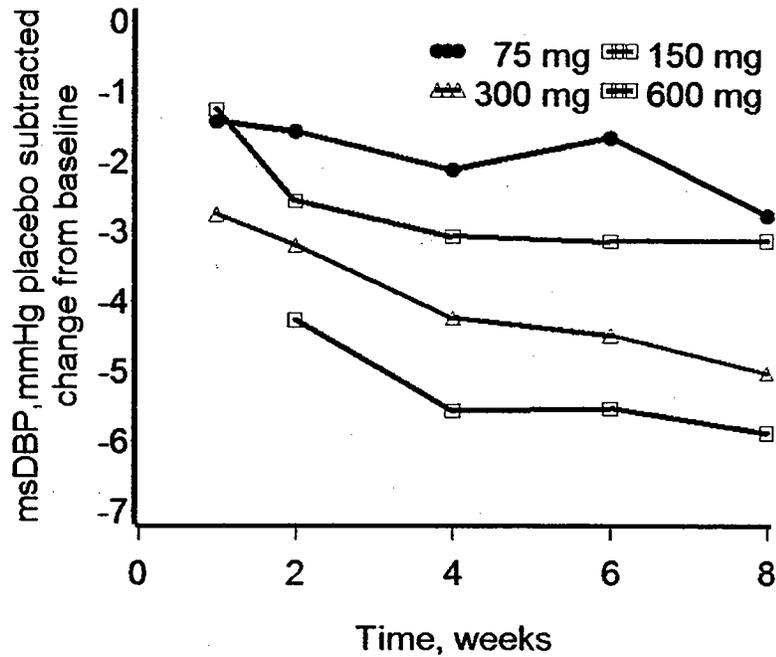
Mean effects on lowering of msDBP for the doses studied generally plateau by week 4 as shown in figure 4. The LS mean effects are obtained by mixed model for repeated measures (MMRM) analysis of the msDBP-time data for the pooled data across the trials as shown below.

$$mSDBP = \beta_0 + \beta_1 \cdot Week + \beta_2 \cdot mSDBP_B + \beta_3 \cdot RX + \beta_4 \cdot Week \cdot RX$$

The detailed results of the MMRM analysis can be found in Appendix Results 1. Also, it can be seen that aliskiren 75 mg consistently reduces the mSDBP compared to placebo at all the visits.

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Figure 4: Blood pressure lowering effects of aliskiren treatment tend to plateau by week 4. (LS Mean msDBP obtained from MMRM analysis).



The dose-response relationship seen across the trials was consistent between gender (Figure 5); but not in elderly patients (age >65 years) as demonstrated in Figures 6 and 7B. However, 75 mg Aliskiren showed reduction in placebo subtracted msDBP. The proportion of responders for 75, 150 and 300 mg doses in elderly is similar (~55%), while in patients with age < 65 years, a dose-dependent increase in percent responders as shown in Figure 7A was seen. Aliskiren 600 mg shows higher response (66%) in elderly. However, the higher dose is associated with higher incidence of diarrhea, which will be discussed later. This lack of dose dependent response in elderly patients is supported by the results of Study 2324, which was aimed at evaluating the blood pressure lowering effects for the change from baseline to endpoint in mean 24-hour ABPM in patients ≥ 65 years age with essential hypertension. Study 2324 did not demonstrate dose response relationship between treatment with aliskiren 75 mg and 300 mg

Figure 5: Aliskiren dose-response across gender is similar. (LS Mean msDBP obtained from MMRM analysis).

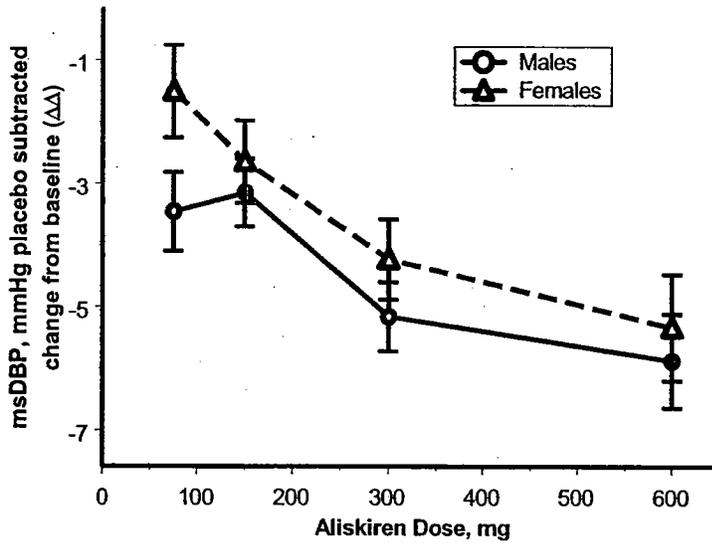


Figure 6: Aliskiren dose higher than 75 mg does not provide substantial benefit in elderly. (LS Mean msDBP obtained from MMRM analysis).

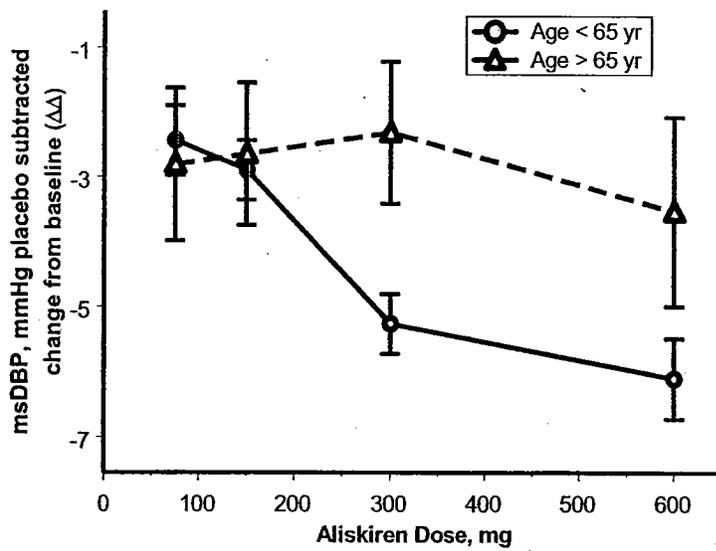
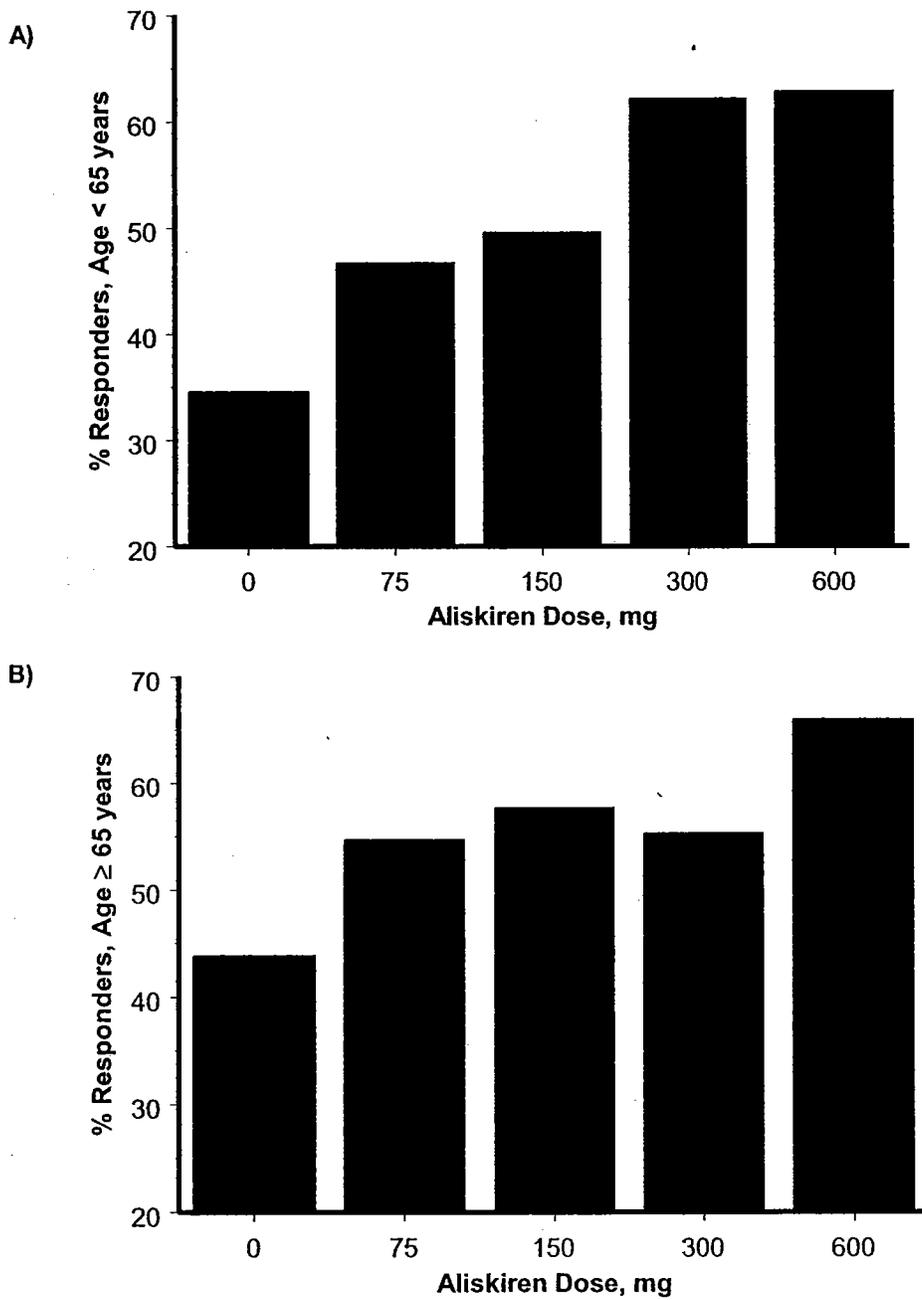


Figure 7: In elderly patients no dose-dependent increase in % responders is seen over 75 – 300 mg doses of Aliskiren.



Dose-Response related to safety:

Diarrhea was the most frequent adverse event seen in the placebo controlled clinical trials with aliskiren treatment (3.42%) compared to placebo (1.92%). Diarrhea in the database was defined as either one of the following preferred terms “Abnormal faeces”, “Defaecation urgency”, “Diarrhoea”, “Diarrhoea haemorrhagic” and “Frequent bowel movements”.

A dose dependent response to diarrhea was observed with Aliskiren treatment as shown in Figure 8. Logistic regression models were used to explore the relationship between aliskiren dose and diarrhea. Dose was found to be a strong predictor of diarrhea. The probability of diarrhea doubles when aliskiren dose increases from 75 mg to 300 mg, while an increase in aliskiren dose from 75 mg to 600 mg is associated with approximately 6 fold increase in probability of diarrhea. Gender and age (above and below 65 years) were not found to significantly predict diarrhea as shown in Figure 9.

Figure 8: Percent patients with diarrhea doubles with 300 mg Aliskiren.

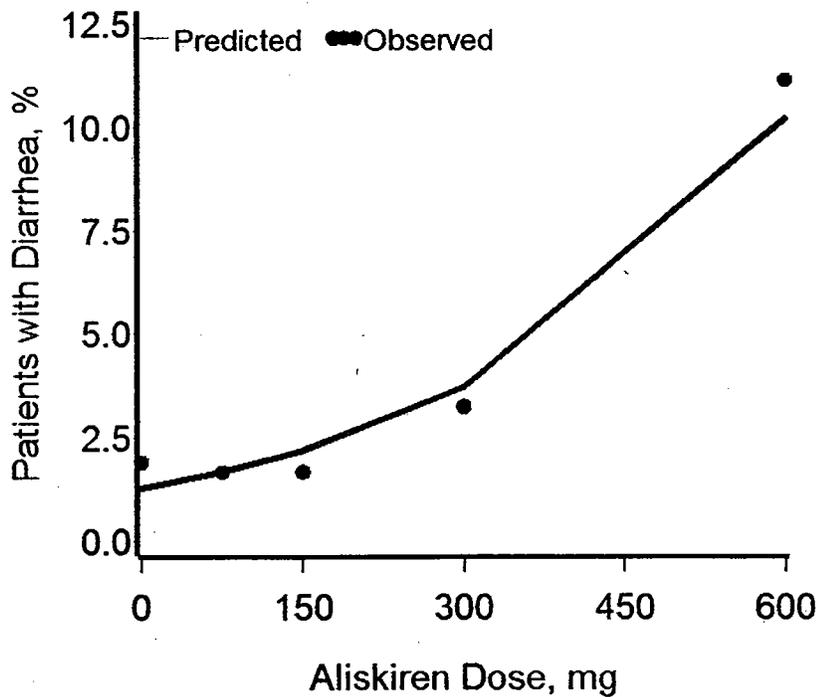
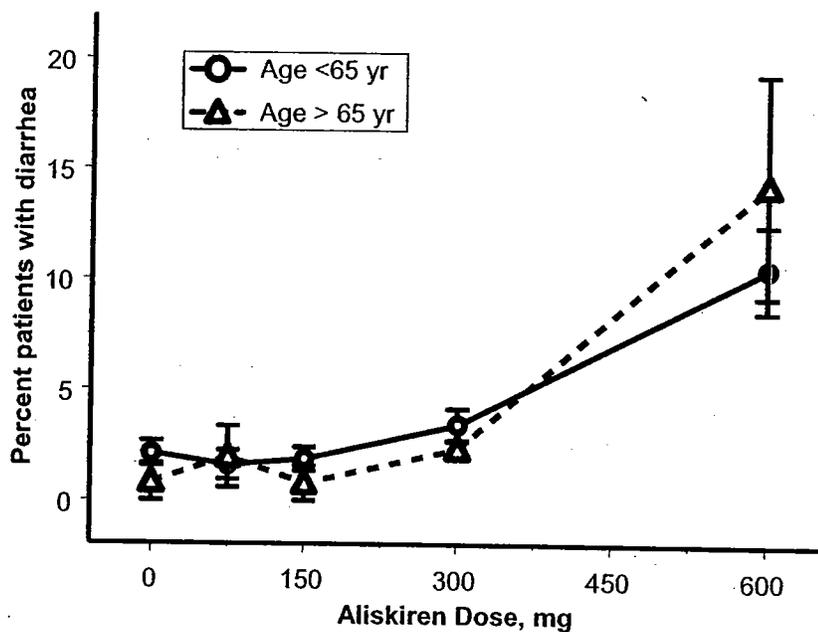
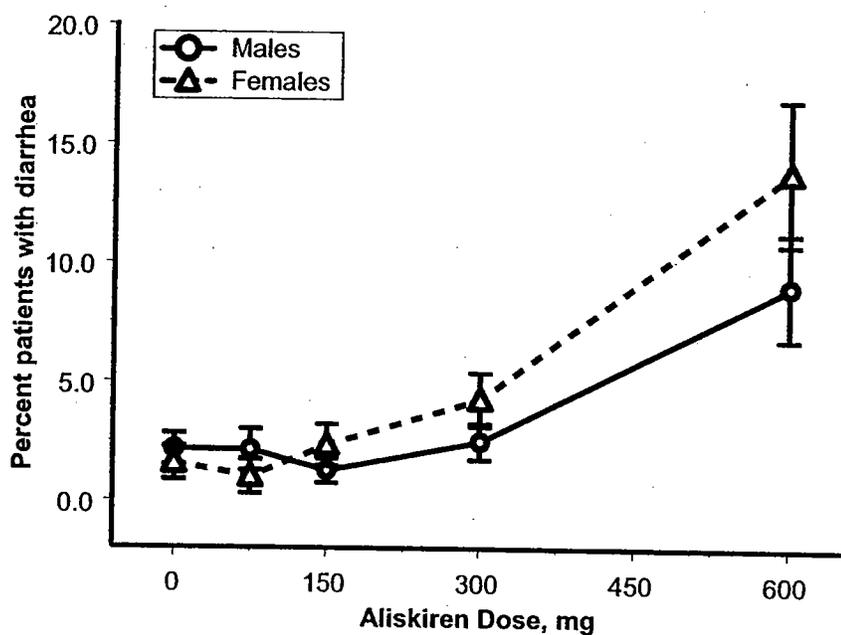


Figure 9: The risk for diarrhea is similar across the subgroups of gender and age.



Recommendation:

- Aliskiren 75 mg dose shows effectiveness in decreasing the msDBP by week 8 and 50% of patients at this dose show a reduction of msDBP by 10 mm Hg. —
— Non-responders at week 4 may benefit from dose titration to a maximum of 300 mg daily dose of aliskiren. The response should be assessed every 4 weeks before titration to higher dose.
- Aliskiren doses higher than 75 mg up to 300 mg do not show any additional benefit in blood pressure reduction in elderly patients (age \geq 65 years) —
—

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Appendix V a:

Figure 1: Dosing with 75 mg Aliskiren results in reduction of both msDBP and msSBP. (LS Mean msDBP obtained from MMRM analysis).

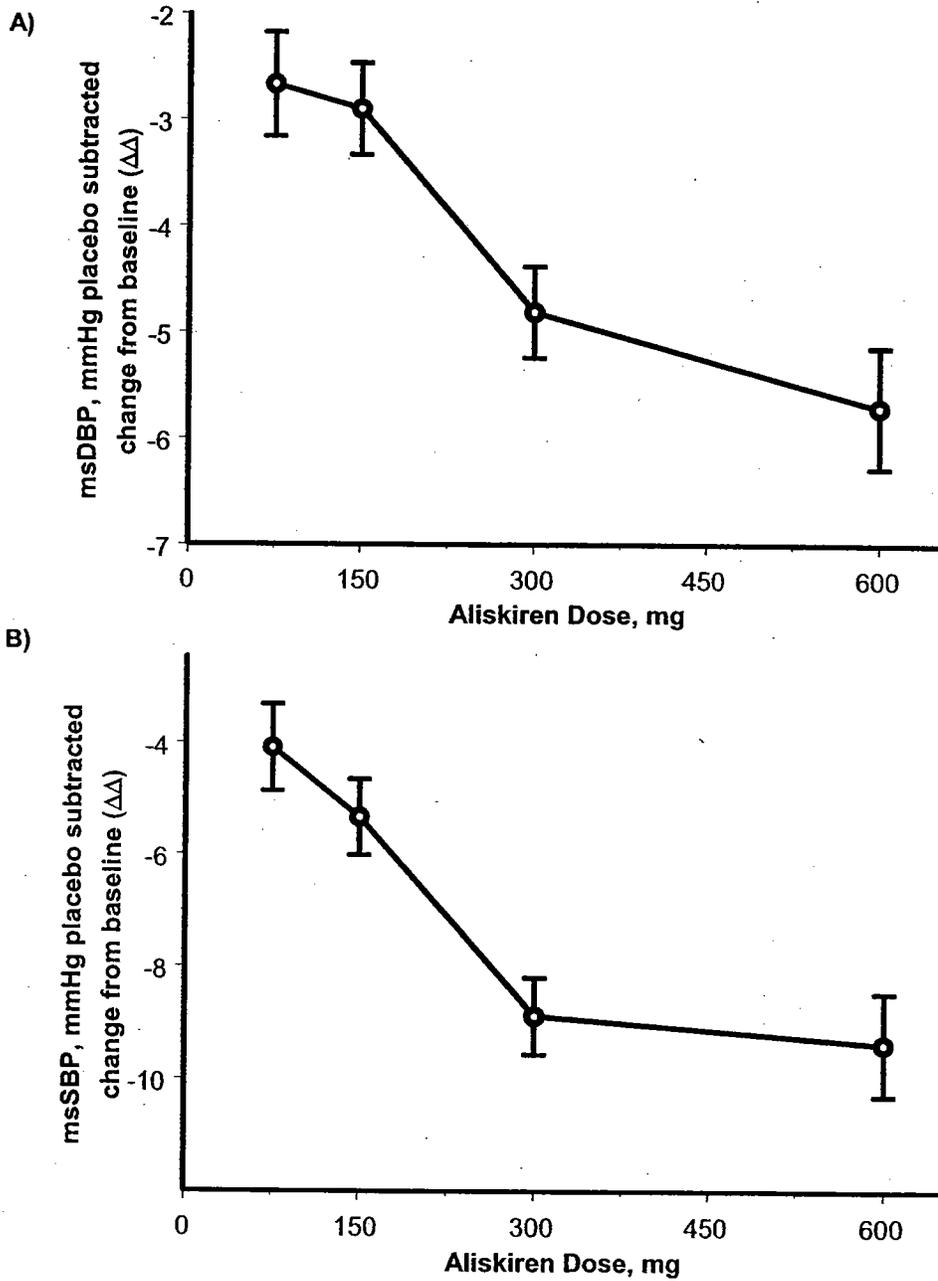


Figure 2: and patients should be titrated to a maximum of 300 mg daily dose of Aliskiren.

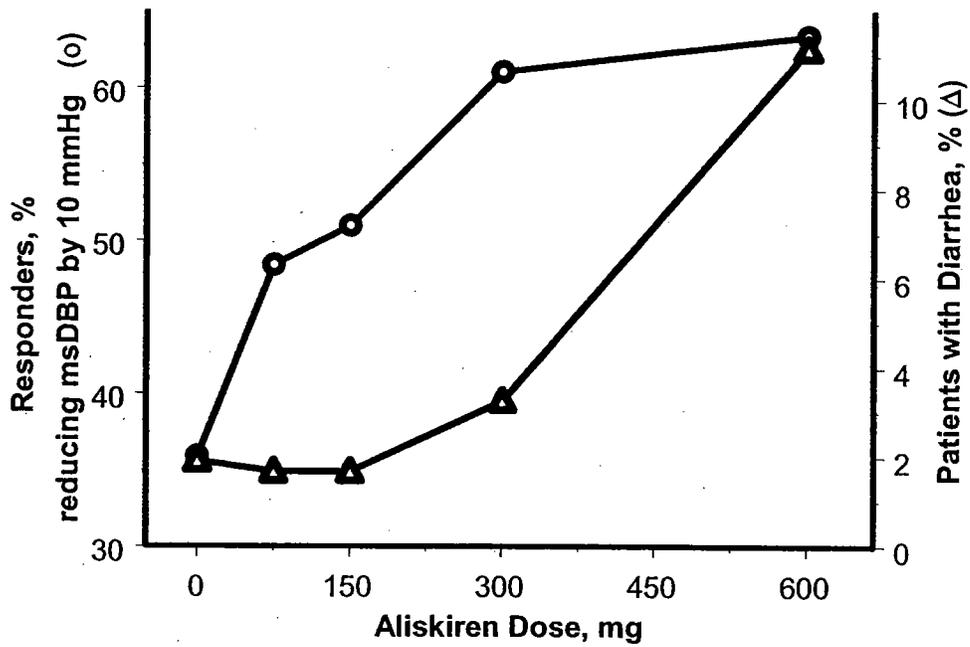
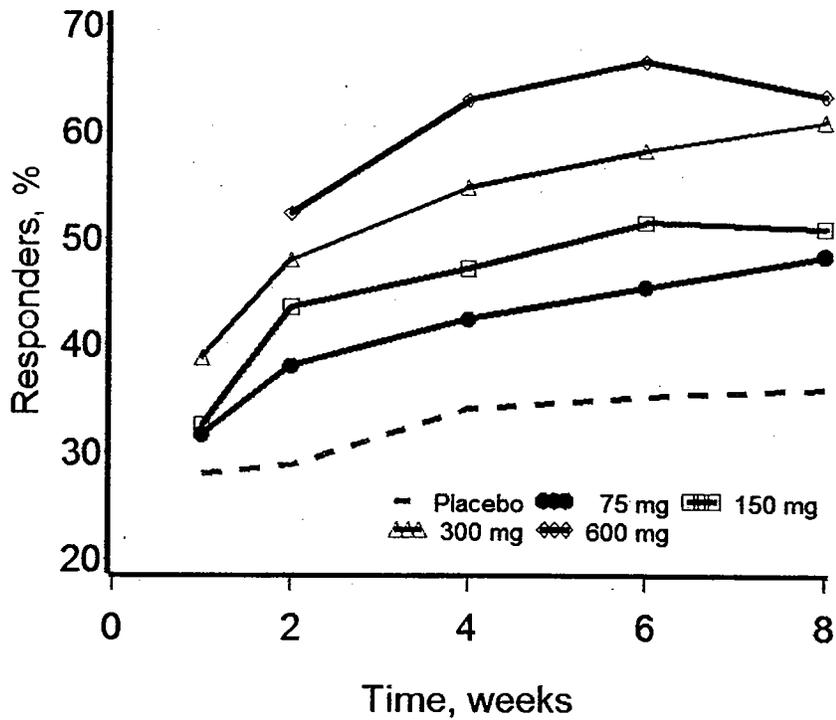


Figure 3: and non-responders should be titrated to a maximum of 300 mg daily dose of Aliskiren.



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 Draft Labeling

 Deliberative Process

APPENDIX VI DISSOLUTION

The sponsor is proposing the following dissolution method and specifications:

Apparatus	USP Apparatus I (basket)
Speed	100 rpm
Medium	0.1N HCl
Volume	500 mL
Temperature	37° C ± 0.5° C
Q	— after 30 minutes

Below is the data submitted by the sponsor that would be appropriate for assessment (FMI formulation data only). The sponsor did perform an F2 similarity comparison between the MF (market formulation) and FMI (final market image) formulation that is intermingled with the data needed for assessment; but the F2 similarity data is not required since they conducted a bioequivalence study between the over-encapsulated MF formulation used in clinical trials 2203 and 2204 and the FMI formulation. The difference between the MF and FMI formulation is that some of the MF formulations had no non-functional film coating on them or had less film coating. The assessment performed below is for the purposes of setting dissolution methods and specifications with the FMI formulation. All tables and graphs for both strengths are utilizing Apparatus I (basket) at 100-rpms. All media volume used is 500 mL.

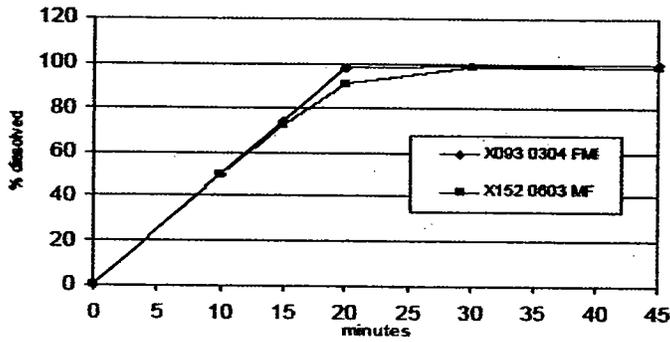
Batches X093 0304 (150 mg) and X107 0304 (300 mg) will be assessed below since they are the FMI formulation; but the MF formulation in the figures below will not. Batch X093 0304 (150 mg) was used in clinical studies 1201 (pivotal trial) and 2302. Batches X105 0304 and X298LA are FMI formulations as well for the 150 mg strengths. Batch X107 0304 (300 mg) was utilized in clinical studies 2203 (pivotal trial), 2208, and 2217.

Dissolution Data for SPP100 FMI 150 mg tablets

SPP100 150 mg, batch X093 0304, (0.01N HCl)

Run	10 min.	15 min.	20 min.	30 min.	45 min.	60 min.
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean (%)	50.1	74.1	97.8	98.9	99.3	99.3
Min. (%)						
Max. (%)						
Srel. (%)	5.2	3.4	0.8	1.0	1.1	1.1

**Comparative dissolution profile of SPP100 150 mg MF/FMI
(0.01N HCl, 100rpm)**

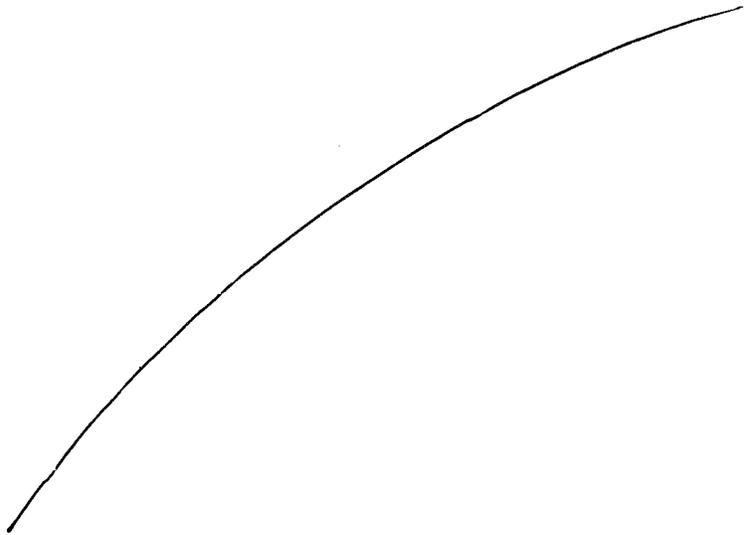


SPP100 150 mg, batch X105 0304, (0.01N HCl)

Run	10 min	15 min	20 min	30 min	45 min	60 min
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean (%)	42.9	64.8	83.0	101.2	99.9	101.2
Min. (%)						
Max. (%)						
Srel. (%)	6.5	4.8	4.8	1.7	1.8	1.6

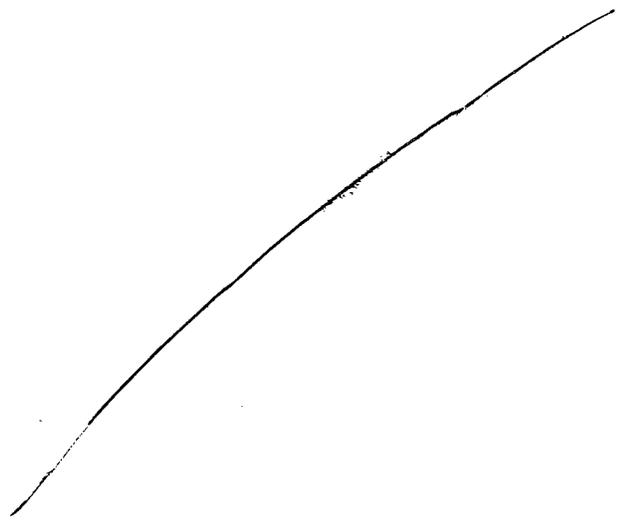
Dissolution data for SPP100 150mg, batch X105 0304, (phosphate buffer, pH 4.5)

Run	10 min	15 min	20 min	30 min	45 min	60 min
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Dissolution data for SPP100 150mg, batch X105 0304, (phosphate buffer, pH 6.8)

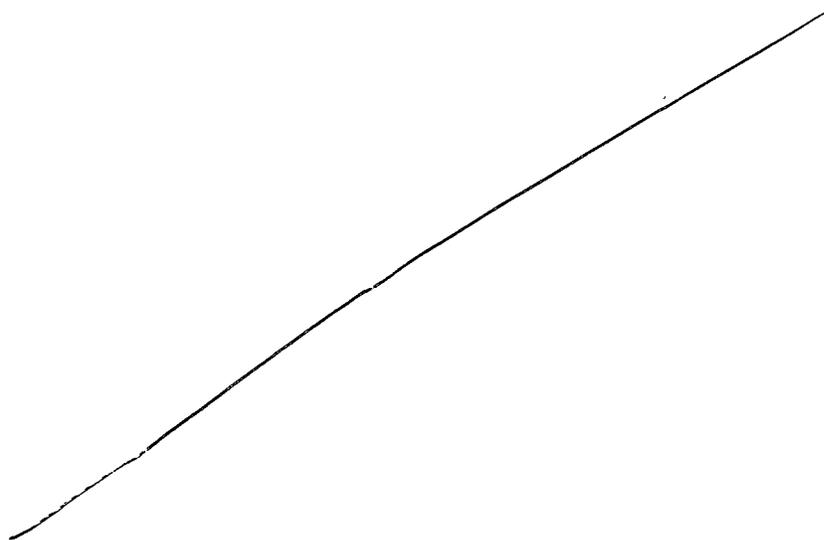
Run	10 min	15 min	20 min	30 min	45 min	60 min
-----	--------	--------	--------	--------	--------	--------



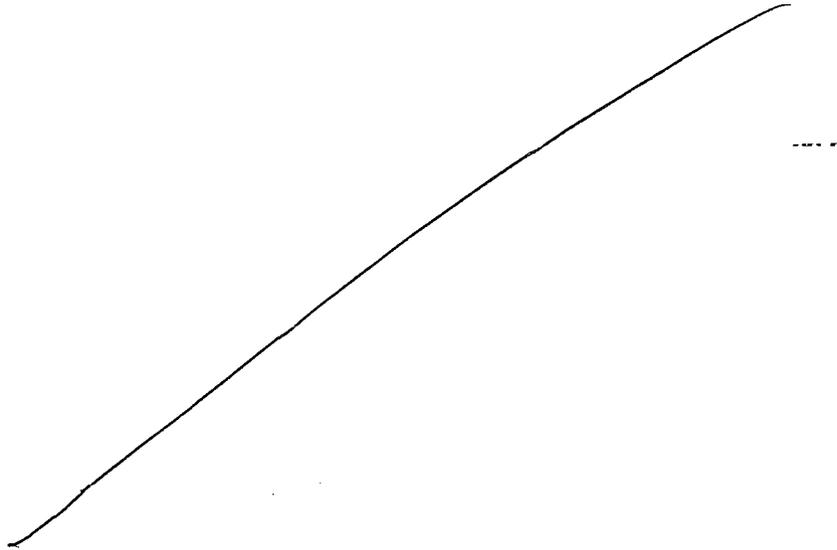
Dissolution data for SPP100 150mg, batch X298LA, (0.01N HCl)

Run	10 min	15 min	20 min	30 min	45 min	60 min
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean (%)	41.9	63.9	82.2	98.5	98.7	98.8
Min. (%)						
Max. (%)						
Srel. (%)	4.3	4.6	5.5	0.8	0.8	0.8

Dissolution data for SPP100 150mg, batch X298LA, (phosphate buffer, pH 4.5)



Dissolution data for SPP100 150mg, batch X298LA, (phosphate buffer, pH 6.8)



Dissolution Data for SPP100 FMI 300 mg tablets

Dissolution data for SPP100 300mg, batch X107 0304, (0.01N HCl)

Run	10 min.	15 min.	20 min.	30 min.	45 min.	60 min.
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean (%)	38.1	55.3	69.7	93.9	98.8	98.8
Min. (%)						
Max. (%)						
Srel. (%)	7.6	6.8	5.9	4.1	1.2	1.2

1 Page(s) Withheld

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Draft Labeling

Deliberative Process

The sponsor has submitted tables for different batches of the FMI formulation. After reviewing all the SPP100 dissolution data for both the 150 and 300 mg strengths, the proposed method and specification is acceptable.

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Appendix VII
COVER SHEET AND OCPB FILING/REVIEW FORM

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Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission			
	Information		Information
NDA Number	21985	Brand Name	Tekturna
OCPB Division (I, II, III)	DPE 1	Generic Name	Aliskiren
Medical Division	HFD-110	Drug Class	Renin Inhibitor
OCPB Reviewer	Lydia Velazquez	Indication(s)	Hypertension; may be used alone or in combination with other hypertensive medications
OCPB Team Leader	Patrick Marroum	Dosage Form	Tablets – 150 and 300 mg
		Dosing Regimen	150 to 300 mg Daily
Date of Submission	10 February 2006	Route of Administration	Oral
Estimated Due Date of OCPB Review	November 22, 2006	Sponsor	Novartis
PDUFA Due Date	December 13, 2006	Priority Classification	1S
Division Due Date	November 22, 2006		

CLIN. PHARM. AND BIOPHARM. INFORMATION

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			Not adequate. Not inclusive and representative of all CPB studies to assess for review. Sponsor is aware and looking into it-no delivery date of new TOC given yet
Tabular Listing of All Human Studies	X			Partial table
HPK Summary	X			Not representative of all CPB studies in the NDA
Labeling	X	3		In PDF and Word format, Annotated label not representative of studies performed and does not provide correct link to where analysis are located (sponsor is looking into where the analysis is located).
Reference Bioanalytical and Analytical Methods	X	25		
I. Clinical Pharmacology				
Mass balance:	X	2		Healthy Males, 150 mg and 300 mg
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:	X	1		
Pharmacokinetics (e.g., Phase I) -				
<i>Healthy Volunteers-</i>				
single dose:	X	6		1 Dose Proportionality, 1 Food Effect, 1 Geriatrics, Japanese males, PK/PD, 1 DDI
multiple dose:	X	15		13 DDI, 1 QT Study, 1 ascending doses
<i>Patients-</i>				
single dose:				
multiple dose:	X	5		3 m/m HTN, 1 renal, 1 CHF
Dose proportionality -				
fasting / non-fasting single dose:	X	1		Fasting state
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				

In-vivo effects on primary drug:	X	17		Dual Effects: Furosemide, Lanoxin, Valsartan, Amlodipine, Metformin, Ramipril, Hydrochlorothiazide, Warfarin, SD Atenolol, SD Celecoxib, SD Lovastatin NOTE: Atenolol, Atorvastatin, Celecoxib, Acenocoumarol (to be submitted later-sponsor will get back to us as far as timeline) Effect on Aliskiren: Ketoconazole, Isbesartan
In-vivo effects of primary drug:	X	8		Dual Effects: Furosemide, Lanoxin, Valsartan, Amlodipine, Metformin, Ramipril, Hydrochlorothiazide, Cimetidine
In-vitro:	X	3		CYP 450 studies
Subpopulation studies -				
ethnicity:	X	2		1. Japanese (healthy males), SD and MD _____ sponsor to locate location of analysis
gender:	X	1		_____ sponsor to locate analysis
pediatrics:				
geriatrics:	X	1		SD, healthy volunteers
renal impairment:	X	1		MD, dual study (DDI-Irbesartan)
hepatic impairment:	X	1		SD
Type 2 Diabetes	X	1		SD
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	5		1 MD, healthy-enalapril comp---1 MD, renal-enalapril comp-effects on proteinuria 1 MD, CHF-ramipril comp--- Not submitted yet (timeline for delivery TBD by sponsor) - SD, 1 in healthy males, 1 in healthy M/F
Phase 3 clinical trial:	X	3		1 MD, m/m HTN-HCTZ combo---1 MD, m/m HTN-ramipril combo---1 MD, m/m HTN-Irbesartan combo
Population Analyses -				Unable to tell so far due to incomplete representation and incomplete description/reference of submitted studies/statements (sponsor aware and is looking into it-could not answer the question at this time)
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:	X	1		Capsule vs Powder vs IV
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X	1		BA of 5 different formulations
Bioequivalence studies -	X			To be submitted in April, 2006
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	X	2		Food Effect (1 testing formulations-capsule vs EC tablet)
Dissolution:	X			Dissolution summary for 150 mg, no studies, data and development program (totally missing), will submit in April 2006 to include 300 mg data
(IVVC):				
Bio-wavier request based on BCS				
BCS class	X			Referenced; but not located
III. Other CPB Studies				
Genotype/phenotype studies:				

Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Permeability	X	2		Caco-2 cells
Efflux	X	2		MDR(MDR1, MRP2, MXR); PSC833
QT Study	X	1		MD, Healthy
Total Number of Studies		81		25 analytical reports, 2 mass balance, 1 protein binding, 1 dose proportionality, 25 DDI, 3 CYP 450, 7 special populations (2 ethnicity, 1 gender, 1 geriatrics, 1 renal 1 hepatic, and 1 Type 2 Diabetes), 8 PK/PD, 2 BA (relative and 1 absolute), 2 food effect, 2 permeability, 2 efflux, and 1 QT study. Still missing BF study (not counted in total).
Filability and QBR comments				
		"X" IF YES	COMMENTS	
Application filable ?		X		
Comments sent to firm?			<p>1. Section 6 Table of Contents (TOC) not reflective of CPB studies in the submission. The table only states 25 studies; but have found many studies throughout the NDA. Not confident that all studies to be assessed for review have been found by the reviewer since sponsor has not provided appropriate TOC or links. <u>Sponsor aware of this and assessing in order to submit a new TOC.</u></p> <p>2. Annotated labeling not providing appropriate links to find studies/data and links not transporting the reviewer to the site. <u>Sponsor aware and currently looking into it.</u></p> <p>3. Dissolution development plan and studies completely missing <u>(submitting April 2006).</u></p> <p>4. Sponsor will be submitting a bioequivalence study report for review in April 2006.</p> <p>5. Found 6 additional studies (Studies 2230, 2234, 2235, 2101, 2212, and 2318) to be submitted later; but unsure of date, <u>sponsor will get back to us regarding submission date.</u></p>	
QBR questions (key issues to be considered)				
Other comments or information not included above				
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

CC: NDA 21-985, HFD-110 (FrommE), HFD-860 (MehtaM, MarroumP, VelazquezL), CDR Central Document Room

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

/s/

Lydia Velazquez
1/10/2007 10:42:43 AM
BIOPHARMACEUTICS

Original NDA review

Rajnikanth Madabushi
1/10/2007 10:44:29 AM
PHARMACOLOGIST

Jogarao Gobburu
1/10/2007 11:25:07 AM
BIOPHARMACEUTICS

Patrick Marroum
1/11/2007 10:33:20 AM
BIOPHARMACEUTICS