Sample Collection

Predose blood samples for ethinyl estradiol and norethindrone pharmacokinetic analyses were drawn on Days 8-11 of both treatment periods, and for eplerenone and SC-70303 on Days 8-11 of Period 2 only. On Day 11, blood samples for ethinyl estradiol and norethindrone (Periods 1 and 2) and eplerenone and SC-70303 (Period 2) pharmacokinetic analyses were drawn at -0.5 hours predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16 and 24 hours postdose.

Urine samples were collected during Periods 1 and 2 from -12 –0 hours, 0-12 hours and 12-24 hours relative to the dose on Day 11 for ethinyl estradiol and norethindrone and during Period 2 for eplerenone and SC-70303.

RESULTS:

Ortho-Novum 1/35®-28-day Regimen is an oral contraceptive which contains 35 µg ethinyl estradiol and 1 mg norethindrone. Ethinyl estradiol is extensively metabolized by CYP3A4 to its primary oxidative metabolite, 2-hydroxy ethinyl estradiol. Since eplerenone is also metabolized by CYP3A4, this study evaluated the pharmacokinetics of ethinly estradiol, norethindrone and eplerenone following coadministration.

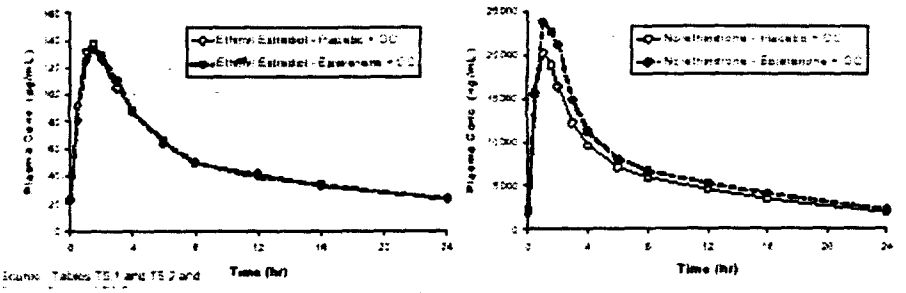
Effect of Eplerenone on Ethinyl Estradiol and Norethindrone Pharmacokinetics

Mean steady-state pharmacokinetic parameters of ethinyl estradiol and norethindrone following coadministration with 100 mg QD eplerenone or placebo are presented in the following table.

Table 1: Arithmetic Mean (%CV) Ethinyl Estradiol and Norethindrone Pharmacokinetic Parameters

Pharmacokinetic Parameter	Ethinyl Estradiol				Norethindrone			
	Placebo + Ortho-Novum 1/35 QD		Eplerenone 100 mg QD + Ortho-Novum 1/35 QD		Placebo + Ortho-Novum 1/35 QD		Eplerenone 100 mg QD + Ortho-Novum 1/35 QD	
	Mean	(%CV)	Mean	(%CV)	Mean	(%CV)	Mean	(%CV)
AUC(0-24) (hr*pg/mL)	1237.15	(31.9%)	1238.91	(33.6%)	144345.3	(28.2%)	169550.5	(29.3%)
MRT (hr)	8.33	(4.7%)	8.37	(5.6%)	7.55	(9.4%)	7.49	(10.7%)
Cmax (pg/mL)	143.15	(32.7%)	140.74	(34.5%)	21606.25	(21.5%)	26163.97	(27.1%)
Tmax (hr)	1.54	(35.1%)	1.66	(31.8%)	1.22	(38.8%)	1.41	(36.5%)
Cmin (pg/mL)	21.23	(42.4%)	22.64	(45.5%)	1921.89	(39.1%)	2335.00	(38.7%)
T1/2 (hr)	14.66	(23.7%)	14.04	(21.2%)	10.00	(25.6%)	10.02	(22.5%)
CL/F (L/hr)	30.08	(21.4%)	30.55	(25.8%)	7.49	(30.5%)	6.48	(34.2%)
CL/F/WT (L/hr/70 kg)	32.75	(24.2%)	33.31	(28.2%)	8.08	(28.1%)	6.93	(28.2%)

Mean Ethinyl Estradiol and Norethindrone Plasma Concentrations



Coadministration of eplerenone with Ortho-Novum 1/35®-28-day Regimen resulted in a negligible decrease in ethinyl estradiol AUC (6%), while Cmax and Cmin were not affected. Coadministration with eplerenone increased Cmax, Cmin and AUC of norethindrone by 20%, 21% and 17%, respectively. Mean norethindrone apparent oral clearance adjusted to 70-kg body weight decreased by 15% in the presence of eplerenone. Both mean Tmax and $T_{1/2}$ of norethindrone were not altered by coadministration with eplerenone.

Table 2: Ratios and 90% Confidence Intervals for Ethinyl Estradiol and Norethindrone Pharmacokinetic Parameters

Pharmacokinetic Parameters	Least Squares Means		Ratio of Means (Eplerenone/ Placebo)	90% CI for Ratio of Means	P-Value
	Eplerenone 100 mg QD + Oral Contraceptive QD	Placebo QD + Oral Contraceptive QD			
	N = 23	N = 23			
Ethinyl Estradiol					
AUC(0-24) (hr*pg/mL)	1187.35	1195.01	0.994	(0.948, 1.041)	0.8152
Cmax (pg/mL)	134.67	138.04	0.976	(0.918, 1.037)	0.4925
Cmin (pg/mL)	21.01	20.04	1.048	(0.976, 1.126)	0.2683
CL/F (L/hr)	29.48	29.29	1.006	(0.961, 1.055)	0.8152
CL/F/WT (L/hr/70 kg)	32.02	31.82	1.006	(0.961, 1.055)	0.8152
Tmax (hr)	1.66	1.54	--	--	0.4348
T(1/2) (hr)	14.04	15.05	--	--	0.2128
Norethindrone					
AUC(0-24) (hr*pg/mL)	162109.9	138965.3	1.167	(1.103, 1.234)	0.0001
Cmax (pg/mL)	25260.52	21090.29	1.198	(1.094, 1.311)	0.0024
Cmin (pg/mL)	2167.81	1786.25	1.214	(1.115, 1.321)	0.0007
CL/F (L/hr)	6.17	7.20	0.857	(0.810, 0.907)	0.0001
CL/F/WT (L/hr/70 kg)	6.70	7.82	0.857	(0.810, 0.907)	0.0001
Tmax (hr)	1.41	1.22	--	--	0.1922
T(1/2) (hr)	10.02	10.00	--	--	0.9620

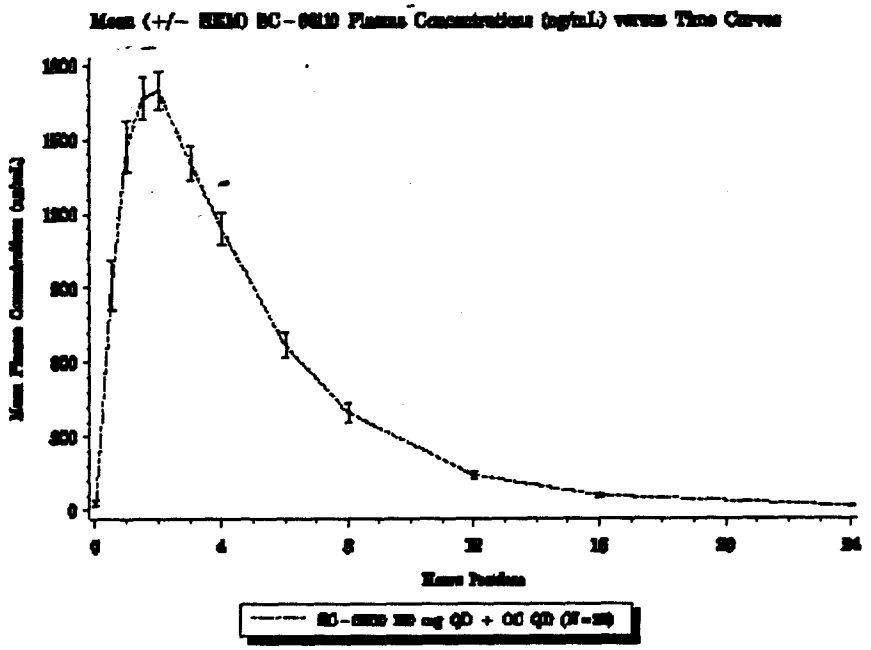
Effect of Ortho-Novum 1/35®-28-day on Eplerenone and SC-70303 Pharmacokinetics

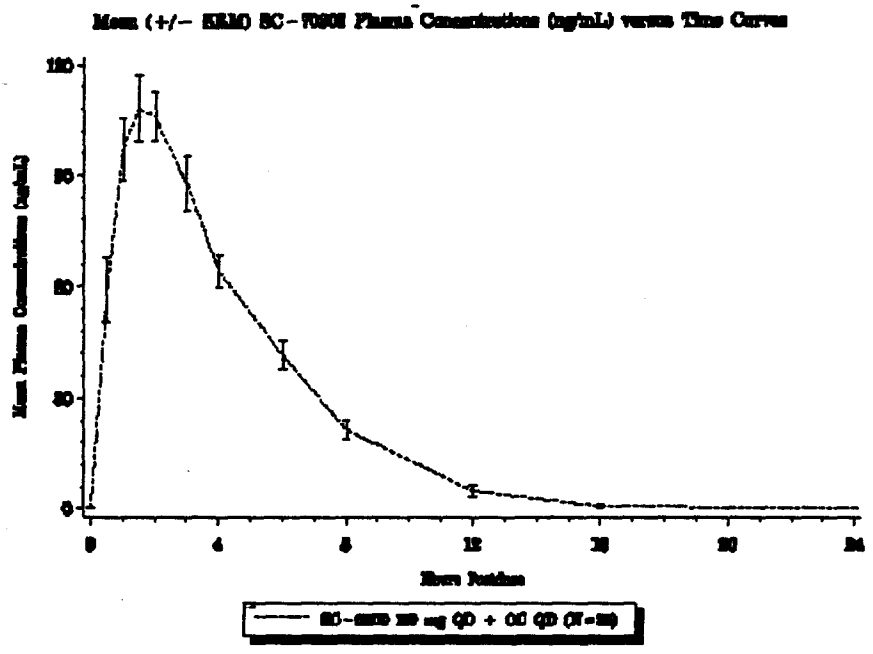
The following table lists the steady-state pharmacokinetic parameters of eplerenone and SC-70303 following coadministration with Ortho-Novum 1/35®-28-day Regimen.

Table 3: Arithmetic Mean (%CV) Eplerenone and SC-70303 Pharmacokinetic Parameters

Pharmacokinetic Parameter	Eplerenone 100 mg QD + Ortho-Novum 1/35 QD			
	Eplerenone		SC-70303	
	Mean	(%CV)	Mean	(%CV)
AUC(0-24) (hr*ng/mL)	9901.47	(26.7%)	564.20	(31.4%)
MRT (hr)	4.58	(18.2%)	3.81	(22.8%)
Cmax (ng/mL)	1857.39	(17.3%)	131.34	(29.2%)
Tmax (hr)	1.70	(46.0%)	1.64	(50.8%)
Cmin (ng/mL)	26.34	(186.5%)	0.00	
T1/2 (hr)	3.11	(26.7%)	2.62	(22.3%)
CL/F (L/hr)	10.89	(30.7%)	NA	N/A
CL/F/WT (L/hr/70 kg)	12.00	(32.9%)	NA	N/A
XU(0-24) (μg)	1676.43	(36.8%)	5493.48	(28.5%)

Eplerenone concentrations when administered alone were not determined in this study. Mean eplerenone AUC0-24 and Cmax in the present study following coadministration with Ortho-Novum 1/35®-28-day Regimen were 9901 ng.h/ml and 1857 ng/ml, respectively. These values were compared to mean eplerenone AUC_{0-24} and Cmax values from other studies where 100 mg QD eplerenone was administered alone; such as the drug interaction study with verapamil where AUC_{0-24} and Cmax were 11562 ng.h/ml and 1892 ng/ml; in the ketoconazole study eplerenone mean AUC_{0-24} and Cmax were 10110 ng.h/ml and 1583 ng/ml, respectively, and in the fluconazole study they were 10374 ng.h/ml and 1577 ng/ml, respectively. Based on the above comparison with other studies, it can be concluded that coadministration with Ortho-Novum 1/35®-28-day Regimen does not affect eplerenone AUC and Cmax.





CONCLUSIONS:

Coadministration of eplerenone with Ortho-Novum 1/35®-28-day Regimen resulted in a negligible decrease in ethinyl estradiol AUC (6%), while Cmax and Cmin were not affected. Coadministration with eplerenone increased norethindrone Cmax, Cmin and AUC by 20%, 21% and 17%, respectively. This increase is not expected to compromise contraception. None of the subjects in this study became pregnant during the study. Mean norethindrone apparent oral clearance adjusted to 70-kg body weight decreased by 15% in the presence of eplerenone. Both mean Tmax and $T_{1/2}$ of norethindrone were not altered by coadministration with eplerenone.

Coadministration with Ortho-Novum 1/35®-28-day Regimen did not affect eplerenone AUC or Cmax.

THE EFFECT OF ST. JOHN'S WORT ON THE PHARMACOKINETIC PROFILE OF EPLERENONE IN HEALTHY ADULT SUBJECTS

STUDY INVESTIGATORS AND SITE:

Protocol Number: NE3-01-02-060

OBJECTIVES:

1. To assess the effect of multiple-dose St. John's Wort coadministration on the single dose pharmacokinetic profile of eplerenone in healthy adult subjects.
2. To assess the safety and tolerability of concomitant administration of multiple doses of St. John's Wort and a single dose of eplerenone in healthy adult subjects.

FORMULATIONS:

Eplerenone – 100 mg tablets (lot number RCT 11748) by Searle.
St. John's Wort - 300 mg tablets (standardized to 0.3% hypericin) by Natrol, Lot number 941507.

STUDY DESIGN:

This study was an open-label, add-on design to examine single-dose eplerenone pharmacokinetic profiles before and after coadministration of multiple doses of St. John's Wort in 18 subjects, 11 M/7 F, age range: 19-41 years weighing between 53 kg to 94 kg. All subjects received the following treatments in the following order: Day 1 = Eplerenone (100 mg single, oral dose); Days 3-16 = St. John's Wort (300 mg TID); Day 17 = Morning dose administration of eplerenone (100 mg single, oral dose) with St. John's Wort (300 mg TID). Subjects received eplerenone doses on Days 1 and 17 following an overnight fast.

ASSAY:

Sample Collection

Plasma samples were analyzed for eplerenone, SC-70303 and SC-71597, and hypericin and pseudohypericin concentrations. Blood samples for eplerenone, SC-70303 and SC-71597 pharmacokinetic analyses were drawn on Days 1 and 17 at predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36 and 48 hours postdose.

RESULTS:

St. John's Wort has been shown to increase the expression of P-glycoprotein and CYP3A4 in humans, thus inducing the metabolism of certain medications such as warfarin, cyclosporin, theophylline, digoxin, HIV protease inhibitors, anticonvulsants, selective serotonin reuptake inhibitors, and oral contraceptives. Since eplerenone is metabolized by CYP3A4, this study was conducted to determine if coadministration of St. John's Wort would have an impact on eplerenone pharmacokinetics.

Effect of St. John's Wort on Eplerenone, SC-70303 and SC-71597 Pharmacokinetics

The following table lists the pharmacokinetic parameters of eplerenone, SC-70303 (open-ring form of eplerenone) and SC-71597 following a single oral dose of 100 mg eplerenone administered alone and in the presence of 300 mg TID St. John's Wort.

Table 1: Arithmetic Mean (%CV) Eplerenone, SC-70303 and SC-71597 Pharmacokinetic Parameters

Analyte Pharmacokinetic Parameter	Eplerenone 100 mg SD			Eplerenone 100 mg SD + St. John's Wort 300 mg TID		
	N	Mean	(%CV)	N	Mean	(%CV)
Eplerenone						
AUC(0-∞) (hr*ng/mL)	17	8609.87	(36%)	15	5822.10	(26%)
AUC(0-lqc) (hr*ng/mL)	18	8549.95	(35%)	16	5781.08	(25%)
Cmax (ng/mL)	18	1508.39	(31%)	17	1223.41	(29%)
Tmax (hr)	18	1.86	(47%)	17	1.83	(35%)
T1/2 (hr)	17	3.30	(54%)	16	2.33	(26%)
CL/F (L/hr)	17	13.08	(38%)	15	19.29	(51%)
CL/F/WT (L/hr/70kg)	17	13.66	(51%)	15	20.86	(68%)
XU(0-48) (:g)	18	1921.70	(36%)	17	989.87	(49%)

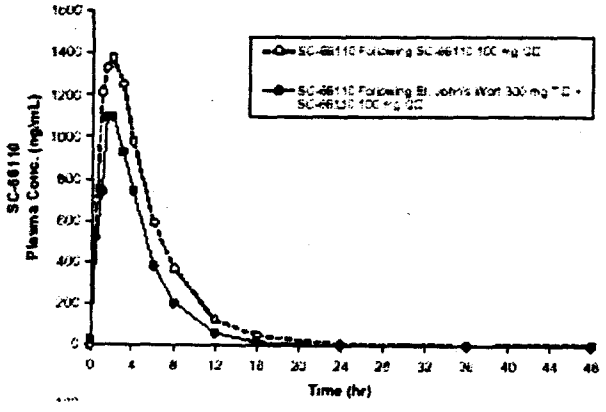
SC-70303						
AUC(0-∞) (hr*ng/mL)	14	577.34	(28%)	13	473.97	(32%)
AUC(0-lqc) (hr*ng/mL)	18	547.78	(41%)	16	375.57	(31%)
Cmax (ng/mL)	18	107.24	(31%)	17	84.89	(30%)
Tmax (hr)	18	1.72	(70%)	17	1.71	(36%)
T1/2 (hr)	14	3.71	(30%)	13	4.58	(56%)
XU(0-48) (:g)	18	4393.03	(40%)	17	2077.76	(39%)
SC-71597						
AUC(0-∞) (hr*ng/mL)	14	5892.55	(26%)	16	4799.82	(19%)
AUC(0-lqc) (hr*ng/mL)	18	5772.79	(24%)	16	4651.29	(19%)
Cmax (ng/mL)	18	682.78	(22%)	17	675.29	(17%)
Tmax (hr)	18	2.82	(42%)	17	2.50	(41%)
T1/2 (hr)	14	5.06	(33%)	17	4.85	(81%)
XU(0-48) (:g)	18	23110.68	(18%)	17	13503.52	(35%)

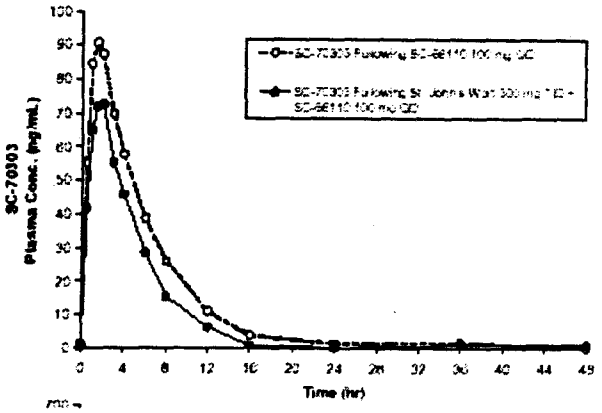
Pretreatment with 300 mg TID St. John's Wort for 14 days altered the single dose pharmacokinetics of eplerenone, SC-70303 and SC-71597 significantly. Mean Cmax and AUC of eplerenone decreased by 19% and 30%, respectively, following coadministration with St. John's Wort. Eplerenone mean apparent oral clearance adjusted for 70-kg body weight increased by 44%, which is probably attributable to decreased bioavailability as evidenced by the 47% decrease in amount of eplerenone excreted in urine over 48 hours following coadministration with St. John's Wort. The decrease in bioavailability is likely due to St. John's Wort induced increase in p-glycoprotein expression. Mean eplerenone $T_{1/2}$ decreased by 1 hour following coadministration.

Coadministration of 300 mg TID St. John's Wort also resulted in 21% and 27%, decreases in SC-70303, open-ring form of eplerenone, Cmax and AUC, respectively. Mean Tmax and $T_{1/2}$ were unchanged and altered slightly (0.6 h), respectively. As seen with eplerenone, SC-70303 amount excreted in urine over 48 hours decreased by 57% in the presence of St. John's Wort.

Pretreatment with St. John's Wort decreased SC-71597 AUC by 17% while Cmax was not affected. Mean SC-71597 decreased by approximately 1 hour with coadministration. Mean amount of SC-71597 excreted in urine over 48 hours decreased by 46%, the magnitude of decrease is similar to that seen with eplerenone following coadministration with St. John's Wort.

Mean Eplerenone, SC-70303 and SC-71597 Plasma Concentrations





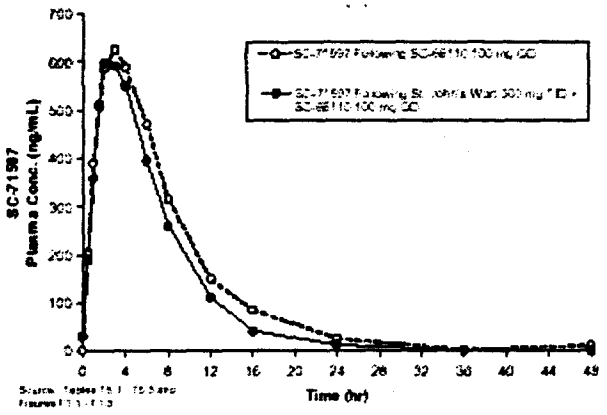


Table 2: Ratios and 90% Confidence Intervals for Eplerenone, SC-70303, and SC-71597 Pharmacokinetic Parameters

Pharmacokinetic Parameter	Least Squares Means				Ratio Coadmin./ Eplerenone	90% Confidence Interval	p-value
	Eplerenone 100 mg SD + St. John's Wort 300 mg TID		Eplerenone 100 mg SD				
	N	LS Mean	N	LS Mean			
EPLERENONE							
AUC (0-∞) (hr*ng/mL)	15	5688.56	17	8205.19	0.693	(0.619, 0.777)	0.0001
AUC (0-lqc) (hr*ng/mL)	16	5680.00	18	8078.26	0.703	(0.634, 0.780)	0.0001
Cmax (ng/mL)	17	1171.00	18	1448.83	0.808	(0.726, 0.900)	0.0031
CL/F (L/hr)	15	17.58	17	12.19	1.442	(1.287, 1.616)	0.0001
CL/F/WT (L/hr/70kg)	15	17.99	17	12.47	1.442	(1.287, 1.616)	0.0001
XU(0-48) (μg)	17	960.48	18	1821.11	0.527	(0.401, 0.694)	0.0010
Tmax (hr)	17	1.89	18	1.86	--	--	0.9011
T(1/2) (hr)	16	2.28	17	3.39	--	--	0.0423
SC-70303							
AUC (0-∞) (hr*ng/mL)	13	464.11	14	542.52	0.855	(0.724, 1.011)	0.1203
AUC (0-lqc) (hr*ng/mL)	16	370.78	18	510.43	0.726	(0.635, 0.831)	0.0008
Cmax (ng/mL)	17	80.35	18	101.96	0.788	(0.710, 0.875)	0.0011
XU(0-48) (μg)	17	1764.96	18	4087.33	0.432	(0.327, 0.570)	0.0001
Tmax (hr)	17	1.72	18	1.72	--	--	0.9950
T(1/2) (hr)	13	4.64	14	4.03	--	--	0.4579
SC-71597							
AUC(0-∞) (hr*ng/mL)	16	4848.29	14	5678.04	0.854	(0.784, 0.930)	0.0069
AUC(0-lqc) (hr*ng/mL)	16	4692.12	18	5620.03	0.835	(0.775, 0.899)	0.0007
Cmax (ng/mL)	17	665.77	18	667.21	0.998	(0.935, 1.065)	0.9545
XU(0-48) (μg)	17	12196.65	18	22729.42	0.537	(0.429, 0.672)	0.0002
Tmax (hr)	17	2.57	18	2.82	--	--	0.2894

T(1/2) (hr)	17	5.00	14	5.88	–	–	0.0296

Effect of Eplerenone on St. John's Wort Pharmacokinetics

Hypericin and pseudohypericin are the active components of St. John's Wort. Following coadministration with eplerenone, hypericin concentrations were constant at approximately 4 ng/ml over the dosing interval of 8 hours. In contrast, pseudohypericin concentration achieved a Cmax of about 4 ng/ml at about 3 hours and declined thereafter. The effect of eplerenone on hypericin and pseudohypericin concentrations is difficult to discern since hypericin and pseudohypericin concentrations were not measured following administration of St. John's Wort alone.

Mean Hypericin and Pseudohypericin Plasma Concentrations Following Coadministration of St. John's Wort 300 mg TID and Eplerenone 100 mg QD, 0-8 Hours Postdose

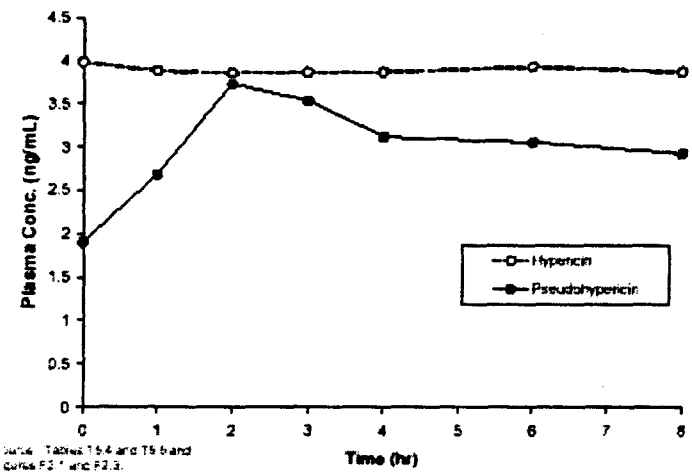


Table 3: Arithmetic Mean (%CV) Hypericin and Pseudohypericin Pharmacokinetic Parameters

Pharmacokinetic Parameter	Eplerenone 100 mg SD + St. John's Wort 300 mg TID (N=17)			
	Hypericin		Pseudohypericin	
AUC(0-8) hr*ng/mL	31.07	(33%)	24.56	(55%)
Cmax (ng/mL)	4.21	(30%)	3.91	(43%)
Tmax (hr)	3.65	(61%)	2.82	(47%)
Cmin (ng/mL)	3.98	(34%)	1.90	(59%)

CONCLUSIONS:

Pretreatment with 300 mg TID St. John's Wort for 14 days altered the single dose pharmacokinetics of eplerenone, SC-70303 and SC-71597 moderately. Mean Cmax and AUC of eplerenone decreased by 19% and 30%, respectively, while SC-70303, open-ring form of eplerenone, Cmax and AUC decreased by 21% and 27%, respectively following coadministration. SC-71597 AUC decreased by 17% while Cmax was not affected. The bioavailability of eplerenone was reduced by 47% as evidenced by the decreased urinary recovery of eplerenone over 48 hours. The lowered bioavailability is probably a result of either induction of CYP 3A4 enzymes by St. John's Wort or increased expression of p-glycoprotein. Similar decreases in urinary recovery were also observed with SC-70303 (57%) and SC-71597 (46%). The decrease in eplerenone exposure up to 30% might not necessitate any dosing adjustment to achieve equivalent reduction in blood pressure. However, hyperforin content in the marketed St. John's Wort products vary over 16-fold. A higher induction and consequently a larger decrease in eplerenone concentrations are possible. Therefore, coadministration of St. John's Wort with eplerenone should be avoided.

AN OPEN-LABEL, RANDOMIZED, SINGLE DOSE, TWO PERIOD CROSSOVER STUDY OF THE EFFECT OF FOOD ON THE PHARMACOKINETIC PROFILE OF ORAL EPLERENONE IN HEALTHY MALE SUBJECTS

STUDY INVESTIGATOR AND SITE:

Report No.: EE3-96-02-005

OBJECTIVE:

To compare the pharmacokinetic profile of eplerenone under fasted and fed conditions

FORMULATIONS:

Eplerenone –100 mg capsule (lot #: RCT 10048) by Searle

STUDY DESIGN:

This was an open-label, randomized, two-way crossover study in which 12 healthy male subjects were randomized to receive a single 100 mg dose of eplerenone on Days 1 and 8 under fasted or fed (immediately following a high-fat breakfast) conditions. Six subjects were to be randomized to each of the two sequences (fed, fasted and fasted, fed). All 12 subjects were male and 20-42 years old (mean = 28.7 years). Eleven (92%) were Caucasian and one (8%) was Black. They were 165.0-185.0 cm tall (mean = 177.67 cm) and weighed 65.2-84.1 kg (mean = 73.63 kg). The components of the high-fat meal were to be: one slice of toasted white bread spread with butter, two fried eggs, two slices of bacon, two ounces of hash browned potatoes, and eight ounces of whole milk. The high-fat meal contained the following nutritional content: 33 g protein, 75 g fat, 58 g carbohydrates, and 1000 calories.

ASSAY:

[redacted]

Sample Collection

On Days 1 and 8, blood samples (10 mL) for pharmacokinetic analysis were to be taken 0.5 hour predose and 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24, 28, 32, 48, 72, and 96 hours postdose.

RESULTS:

The following table lists the single dose eplerenone and SC-70303 pharmacokinetic parameters following administration of a single 100-mg eplerenone dose in the fed and fasted states in healthy male volunteers.

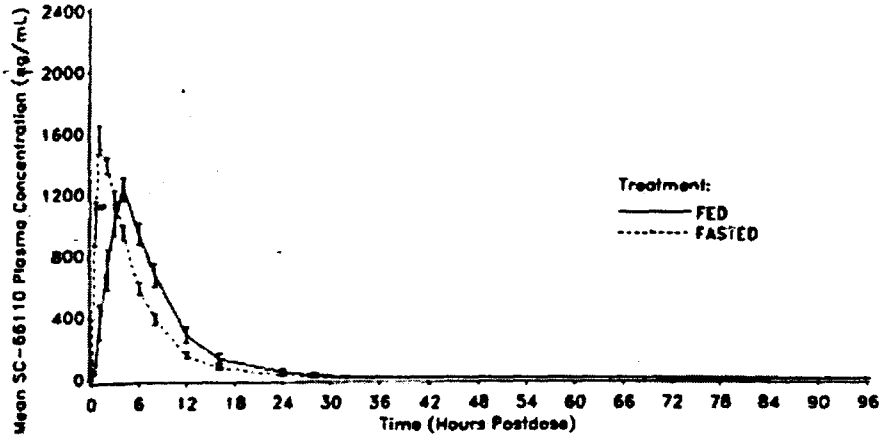
Table 1: Mean Pharmacokinetic Parameters of Eplerenone

		AUC_{0-96} (ng*hr/mL)	Cmax (ng/mL)	$T_{1/2}$ (hr)	Tmax (hr)
Eplerenone	Fed	10171.63	1334.33	3.78	3.75
	Fasted	9202.06	1634.17	3.37	1.29
	p-value	0.325	<0.001	0.100	<0.001
	Ratio (CI)	1.079 (0.945, 1.232)	0.814 (0.758, 0.875)	1.097 (1.000, 1.203)	2.903 (2.412, 3.394)
SC-70303	Fed	470.14	73.86	3.20	3.75
	Fasted	430.62	100.16	3.08	1.13
	p-value	0.445	<0.001	0.709	<0.001
	Ratio (CI)	1.066 (0.921, 1.234)	0.731 (0.670, 0.797)	1.021 (0.924, 1.129)	3.333 (2.744, 3.922)

In general, the high-fat meal delayed the absorption of eplerenone and reduced the maximum concentration absorbed. The maximum mean eplerenone plasma concentration following administration of a single dose of 100 mg eplerenone was reached at four hourspostdose after a high-fat meal (1239.8 ng/mL) and one hour postdose in a fasted condition (1562.7 ng/mL). Coadministration of eplerenone with a high-fat breakfast decreased the Cmax of eplerenone by 19% with a 90% CI of 75.8% to 87.5%. The Tmax of eplerenone occurred about 2.5 hours later in the presence of food. In contrast to Cmax, food increased eplerenone AUC by 8% (90% CI of 94.5% to 1.23%). The $T_{1/2}$ of eplerenone increased by 0.4 hours.

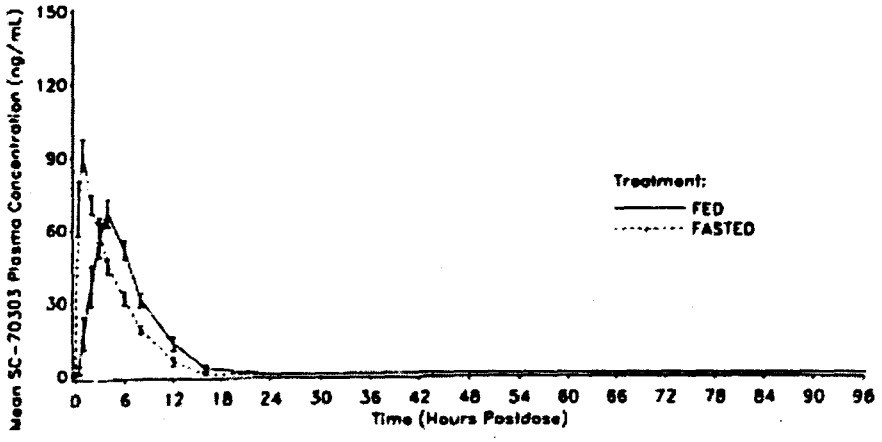
FIGURE 1.1

SC-66110 MEAN (+/- SEM) PLASMA CONCENTRATIONS (ng/mL) BY TREATMENT AND TIME



Note: SC-66110 Dose = 100 mg.

SC-70303 MEAN (+/- SEM) PLASMA CONCENTRATIONS (ng/mL) BY TREATMENT AND TIME



Note: SC-66110 Dose = 100 mg.

Mean concentrations of SC-70303, the open-ring form of eplerenone, were affected to a similar degree as eplerenone indicating that the delay in absorption of eplerenone caused the changes in SC-70303 pharmacokinetics. Coadministration of eplerenone with a high-fat breakfast decreased the Cmax of SC-70303 by 27% with a 90% CI of 67.0% to 79.7%. The Tmax of SC-70303 occurred about 2.6 hours later in the presence of food. Food did not affect SC-70303 AUC (90% CI of 92.1% to 1.23%) or $T_{1/2}$.

CONCLUSIONS:

Compared to the fasted state, coadministration of eplerenone with a high-fat breakfast delayed the absorption of eplerenone resulting in a longer Tmax (4 h vs. 1.5 h) and lower

Cmax (1334 ng/ml vs. 1634 ng/ml). The 90% CI for eplerenone Cmax of 75.8%-87.5% were outside the no food effect limits of 80% to 125%. Food did not affect eplerenone AUC significantly.

Food altered the pharmacokinetics of SC-70303 to a similar degree as eplerenone. Coadministration of eplerenone with a high-fat breakfast decreased the Cmax of SC-70303 by 27%. The Tmax of SC-70303 occurred about 2.6 hours later in the presence of food. Food increased SC-70303 AUC by 7% but $T_{1/2}$ of SC-70303 was not affected.

COMMENTS:

1. This food effect study was performed using eplerenone 100 mg capsule. The to-be-marketed product are tablets.
2. The 19% decrease in Cmax and the increased Tmax of 4 hours is not expected to have a clinically significant effect. Moreover, in another study (NE3-99-02-030) food did not affect AUC or Cmax of eplerenone. Eplerenone tablets can be administered without regard to food.

THE STUDY OF BIOEQUIVALENCY OF TABLETS AND CAPSULES OF EPLERENONE IN HEALTHY SUBJECTS

STUDY INVESTIGATOR AND SITE:

Report No.: NE3-99-02-029

OBJECTIVES:

To examine the single-dose bioequivalence of eplerenone tablets versus capsules of 25 mg, 50 mg and 100 mg strengths in healthy adult subjects.

FORMULATIONS:

The following formulations were supplied by Searle:
Eplerenone 100 mg film-coated tablets (lot number RCT 11063, lot size: —
Eplerenone 100 mg capsules (lot number RCT 11062, lot size: —)
Eplerenone 50 mg film-coated tablets (lot number RCT 11061, lot size: —
Eplerenone 50 mg capsules (lot number RCT 11060, lot size: —)
Eplerenone 25 mg film-coated tablets (lot number RCT 11059, lot size: —
Eplerenone 25 mg capsules (lot number RCT 11056, lot size: —

STUDY DESIGN:

This was an open-label, randomized, single-dose, two-sequence, six-treatment, and six-period crossover design study conducted in 36 healthy adult subjects, 10 F/26 M, age range: 20-45 years. Subjects were randomized in equal numbers to one of the following two sequences:

	Period 1 Day 1	Period 2 Day 5	Period 3 Day 9	Period 4 Day 13	Period 5 Day 17	Period 6 Day 21
Sequence I	A	B	C	D	E	F
Sequence II	B	A	D	C	F	E

A = 25 mg Capsules D = 50 mg Tablets
B = 25 mg Tablets E = 100 mg Capsules
C = 50 mg Capsules F = 100 mg Tablets

On study Days 1, 5, 9, 13, 17 and 21, subjects received a single eplerenone dose following an overnight fast.

ASSAY:

Sample Collection

Blood samples were collected on Days 1, 5, 9, 13, 17 at the following time-points: predose (-30 minutes) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24 and 48 hours postdose. Urine samples were collected and pooled at -12 to 0 hours on Day 1 and 0-24 and 24-48 hours postdose on all dosing days.

RESULTS:

The following table lists the arithmetic means of eplerenone and SC-70303 pharmacokinetic parameters following a single oral dose of eplerenone 25 mg, 50 mg and 100 mg capsules and tablets.

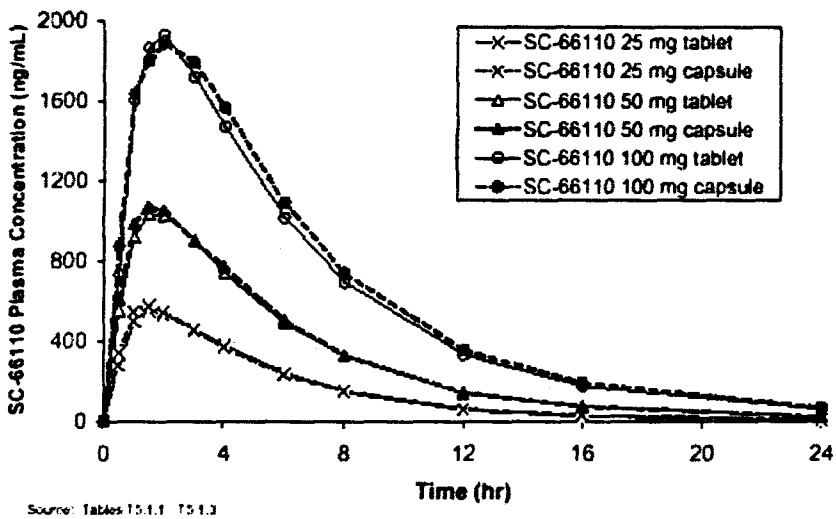
Table 1: Arithmetic Mean (%CV) Eplerenone and SC-70303 Pharmacokinetic Parameters

Parameter	Eplerenone 25 mg Tab		Eplerenone 25 mg Cap		Eplerenone 50 mg Tab		Eplerenone 50 mg Cap		Eplerenone 100 mg Tab		Eplerenone 100 mg Cap	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
EPLERENONE												
AUC(0-lqc) (hr*ng/mL)	36	3403.12 (29.44%)	36	3420.16 (42.72%)	35	7267.47 (31.01%)	36	7289.87 (27.76%)	36	14420.02 (34.09%)	36	15261.77 (31.94%)
AUC(0-∞) (hr*ng/mL)	36	3500.49 (29.43%)	35	3638.99 (42.72%)	35	7455.92 (31.50%)	36	7467.28 (28.30%)	36	14759.36 (34.29%)	36	15604.78 (32.30%)
Cmax (ng/mL)	36	617.74 (17.36%)	36	611.42 (25.59%)	35	1202.19 (16.88%)	36	1195.91 (15.17%)	36	2077.71 (16.75%)	36	2081.34 (18.43%)
Tmax (hr)	36	1.51 (44.30%)	36	1.90 (102.41%)	35	1.51 (44.22%)	36	1.61 (50.92%)	36	1.64 (41.65%)	36	1.76 (44.17%)
T1/2 (hr)	36	3.27 (30.77%)	35	3.49 (55.74%)	35	3.89 (31.04%)	36	3.93 (31.19%)	36	4.30 (30.89%)	36	4.54 (28.71%)
CL/F (L/hr)	36	7.79 (30.91%)	35	7.85 (34.04%)	35	7.38 (31.54%)	36	7.21 (27.05%)	36	7.52 (31.41%)	36	7.04 (30.19%)
XU(0-48) (µg)	36	413.4 (44.99%)	36	454.4 (53.50%)	36	1031.4 (49.47%)	36	1049.0 (47.49%)	36	2264.4 (48.42%)	36	2253.2 (47.54%)
SC-70303												
AUC(0-lqc) (hr*ng/mL)	36	83.11 (31.38%)	36	84.00 (55.43%)	35	218.91 (25.52%)	36	223.69 (24.99%)	36	467.26 (26.67%)	36	496.76 (24.29%)
AUC(0-∞) (hr*ng/mL)	36	135.01 (28.48%)	36	144.73 (43.79%)	35	280.14 (30.56%)	36	279.59 (21.92%)	36	528.75 (24.51%)	36	557.03 (22.75%)
Cmax (ng/mL)	36	22.53 (21.73%)	36	22.76 (27.35%)	35	49.82 (20.47%)	36	49.02 (27.45%)	36	86.53 (26.09%)	36	86.31 (21.81%)
Tmax (hr)	36	1.46	36	1.40	35	1.49	36	1.54	36	1.57	36	1.71

		(53.35%)		(69.65%)		(43.56%)		(54.48%)		(44.51%)		(53.46%)
T1/2 (hr)	33	4.00 (38.36%)	36	4.43 (54.72%)	35	3.94 (44.11%)	36	3.81 (29.65%)	36	3.74 (29.58%)	36	3.84 (25.92%)
XU(0-48) (µg)	36	1414.4 (39.05%)	36	1480.8 (48.57%)	36	3052.3 (41.30%)	36	3012.7 (43.57%)	36	6420.1 (44.58%)	36	6474.2 (43.24%)

Following a single dose of 25 mg, 50 mg and 100 mg eplerenone tablets, mean Cmax of eplerenone from the tablets were 618 ng/ml,1202 ng/ml and 2078 ng/ml, respectively, and mean AUC was 3500 ng.h/ml, 7456 ng.h/ml and 14759 ng.h/ml, respectively. Mean Cmax of eplerenone 25 mg, 50 mg and 100 mg capsules were 611 ng/ml, 1196 ng/ml and 2081 ng/ml, respectively, and mean AUC were 3639 ng.h/ml, 7467 ng.h/ml and 15605 ng.h/ml, respectively.

Mean SC-66110 Plasma Concentrations, 0-24 Hours Postdose



Source: Tables 15.1.1 15.1.3

Both the capsule and tablet formulations of eplerenone were bioequivalent for the plasma pharmacokinetic parameters for each of the doses (25 mg, 50 mg and 100 mg). Mean Cmax and AUC of eplerenone from the 25 mg, 50 mg and 100 mg eplerenone tablets were bioequivalent to 25 mg, 50 mg and 100 mg eplerenone capsules. The 90% CI limits for both Cmax and AUC of eplerenone were contained within the bioequivalence limits of 0.8 and 1.25.

Similarly, mean Cmax and AUC of SC-70303 (open-ring form of eplerenone) from 25 mg, 50 mg and 100 mg eplerenone tablets were bioequivalent 25 mg, 50 mg and 100 mg eplerenone capsules.

Table 4: Ratios and 90% Confidence Intervals for Eplerenone and SC-70303 Pharmacokinetic Parameters

Pharmacokinetic	Least Squares Means	Ratio	90%	p-value

Parameter	Eplerenone Tablet		Eplerenone Capsule		Tablet/ Capsule	Confidence Interval	
	N	Mean	N	Mean			
25 mg							
Eplerenone							
AUC(0-lqc) (hr*ng/mL)	36	3259.68	36	3105.82	1.050	(0.9235, 1.1927)	0.527
AUC(0-∞) (hr*ng/mL)	36	3353.94	35	3409.91	0.984	(0.9070, 1.0666)	0.732
Cmax (ng/mL)	36	608.11	36	572.75	1.062	(0.9225, 1.2219)	0.476
XU(0-48) (μg)	36	367.22	36	406.84	0.903	(0.7793, 1.0453)	0.246
SC-70303							
AUC(0-lqc) (hr*ng/mL)	36	79.03	36	74.25	1.064	(0.9575, 1.1831)	0.326
AUC(0-∞) (hr*ng/mL)	36	129.78	36	134.35	0.966	(0.8870, 1.0520)	0.498
Cmax (ng/mL)	36	22.02	36	21.98	1.002	(0.9522, 1.0544)	0.947
XU(0-48) (μg)	36	1308.78	36	1354.36	0.966	(0.8587, 1.0874)	0.627
50 mg							
Eplerenone							
AUC(0-lqc) (hr*ng/mL)	35	7004.17	36	7033.69	0.996	(0.9640, 1.0285)	0.827
AUC(0-∞) (hr*ng/mL)	35	7177.48	36	7194.32	0.998	(0.9672, 1.0290)	0.899
Cmax (ng/mL)	35	1186.62	36	1182.27	1.004	(0.9642, 1.0447)	0.878
XU(0-48) (μg)	35	950.05	35	938.10	1.013	(0.8911, 1.1509)	0.868
SC-70303							
AUC(0-lqc) (hr*ng/mL)	35	212.40	36	217.56	0.976	(0.9332, 1.0212)	0.374
AUC(0-∞) (hr*ng/mL)	35	270.79	36	273.77	0.989	(0.9474, 1.0326)	0.670
Cmax (ng/mL)	35	48.61	36	47.31	1.027	(0.9769, 1.0806)	0.370
XU(0-48) (μg)	35	2938.40	35	2813.61	1.044	(0.9261, 1.1777)	0.545
100 mg							
Eplerenone							
AUC(0-lqc) (hr*ng/mL)	36	13683.47	36	14563.12	0.940	(0.9159, 0.9638)	<0.001
AUC(0-∞) (hr*ng/mL)	36	13986.77	36	14867.22	0.941	(0.9184, 0.9636)	<0.001
Cmax (ng/mL)	36	2048.92	36	2044.51	1.002	(0.9644, 1.0413)	0.925
XU(0-48) (μg)	36	2004.25	36	2015.03	0.995	(0.8961, 1.1040)	0.931
SC-70303							
AUC(0-lqc) (hr*ng/mL)	36	452.34	36	483.24	0.936	(0.9079, 0.9650)	<0.001
AUC(0-∞) (hr*ng/mL)	36	514.59	36	544.10	0.946	(0.9224, 0.9696)	<0.001
Cmax (ng/mL)	36	83.61	36	84.40	0.991	(0.9368, 1.0475)	0.777
XU(0-48) (μg)	36	5924.66	36	5983.12	0.990	(0.9223, 1.0630)	0.817

The test for dose proportionality for eplerenone over the dose range of 25 mg to 100 mg indicated that eplerenone AUC increased dose proportionally while eplerenone Cmax from both tablet and capsule formulations exhibited a less than dose proportional increase, especially at 100 mg. The slightly reduced Cmax at the 100 mg dose could be a result of reduced solubility of eplerenone at higher doses.

Dose Proportionality of Eplerenone and SC-70303, 25 mg through 100 mg

Pharmacokinetic Parameter	Least Squares Means			P-Value
	Eplerenone 25 mg	Eplerenone 50 mg	Eplerenone 100 mg	
	N = 36	N = 36	N = 36	
Eplerenone				
Capsule				
AUC(0-lqc) (hr*ng/mL)	3420.16	3644.94	3815.44	0.046
AUC(0-∞) (hr*ng/mL)	3669.54	3733.64	3901.19	0.205
Cmax (ng/mL)	611.42	597.96	520.33	<0.001
Tablet				

AUC(0-lqc) (hr*ng/mL)	3403.12	3655.57	3605.01	0.171
AUC(0-∞) (hr*ng/mL)	3500.49	3751.33	3689.84	0.214
Cmax (ng/mL)	617.74	601.64	519.43	<0.001
SC-70303				
Capsule				
AUC(0-lqc) (hr*ng/mL)	84.00	111.84	124.19	<0.001
AUC(0-∞) (hr*ng/mL)	144.73	139.79	139.26	0.555
Cmax (ng/mL)	22.76	24.51	21.58	0.066
Tablet				
AUC(0-lqc) (hr*ng/mL)	83.11	109.73	116.82	<0.001
AUC(0-∞) (hr*ng/mL)	135.01	140.12	132.19	0.462
Cmax (ng/mL)	22.53	24.85	21.63	0.028

In contrast to eplerenone, the test for dose proportionality of SC-70303 over eplerenone dose range of 25 mg to 100 mg indicated a slightly more than dose proportional increase in SC-70303 AUC while SC-70303 Cmax increased dose proportionally.

CONCLUSIONS:

Both the capsule and tablet formulations of eplerenone were bioequivalent for the plasma pharmacokinetic parameters for 25 mg, 50 mg and 100 mg. Mean Cmax and AUC of eplerenone from the 25 mg, 50 mg and 100 mg eplerenone tablets were bioequivalent to 25 mg, 50 mg and 100 mg eplerenone capsules. The 90% CI limits for both Cmax and AUC of eplerenone were contained within the bioequivalence limits of 0.8 and 1.25.

Similarly, mean Cmax and AUC of SC-70303 (open-ring form of eplerenone) from 25 mg, 50 mg and 100 mg eplerenone tablets were bioequivalent to mean SC-70303 Cmax and AUC 25 mg, 50 mg and 100 mg eplerenone capsules.

The test for dose proportionality for eplerenone over the dose range of 25 mg to 100 mg indicated that eplerenone AUC increased dose proportionally while eplerenone Cmax from both tablet and capsule formulations exhibited a less than dose proportional increase, especially at 100 mg. In contrast to eplerenone, the test for dose proportionality of SC-70303 over eplerenone dose range of 25 mg to 100 mg indicated a slightly more than dose proportional increase in SC-70303 AUC while SC-70303 Cmax increased dose proportionally over 25 mg to 100 mg eplerenone doses.

THE EFFECT OF FOOD, ANTACID AND GRAPEFRUIT JUICE ON THE PHARMACOKINETIC PROFILE OF EPLERENONE IN HEALTHY SUBJECTS

STUDY INVESTIGATOR AND SITE:

Report No.: NE3-99-02-030

OBJECTIVES:

To examine the effect of coadministration of a high-fat meal, antacid and grapefruit juice on the single-dose pharmacokinetic profile of eplerenone 100 mg tablets in healthy adult subjects.

FORMULATIONS:

A. Eplerenone –100 mg film-coated tablets (lot number RCT 11100) by Searle
B. Mylanta®. Maximum Strength (MS) Liquid (lot number CCF034)
C. Grapefruit juice (Donald Duck Brand manufacturing lot number CHHC0383).

STUDY DESIGN:

This was an open-label, randomized, single-dose, four-period, four-sequence, four-treatment crossover design study conducted in 16 healthy adult subjects, 3 F/13M, age range: 20-39 years. All study participants received a single 100 mg dose of eplerenone on the morning of Days 1, 5, 9 and 13. All study participants received a single 100 mg dose of eplerenone on the morning of Days 1, 5, 9 and 13. Subjects randomized to **Treatment A** received 100 mg eplerenone under fasting conditions. Subjects randomized to **Treatment B** received 100 mg eplerenone with high-fat (75 grams of fat) meal] consumed two slices of toasted white bread spread with butter, two eggs fried in butter, two slices of bacon, two ounces of hash browns and eight ounces of whole milk immediately prior to administration of eplerenone. Subjects randomized to **Treatment C** received 100 mg eplerenone ingested with 180 mL of room-temperature water and 30 mL of liquid antacid (Mylanta® MS). A second dose of 30 mL liquid Mylanta®MS only was administered 1-hour following the initial dose. Subjects randomized to **Treatment D** received 100 mg eplerenone with 250 mL of double-strength grapefruit juice. Subjects were not required to consume water with this dose. Subjects crossed over to alternate treatments following a washout interval of 4 days.

ASSAY:

[redacted]

Sample Collection

Blood samples for measuring plasma concentrations of eplerenone and SC-70303 were drawn on Days 1, 5, 9 and 13 for all subjects at the following time points: predose (-30 minutes) and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36 and 48 hours postdose.

RESULTS:

The following table lists the pharmacokinetic parameters of eplerenone and SC-70303 (open-ring form of eplerenone) following a single 100 mg dose of eplerenone administered alone or coadministered with a high-fat meal, antacid or grapefruit juice.

Table 1: Arithmetic Mean Eplerenone and SC-70303 Pharmacokinetic Parameters

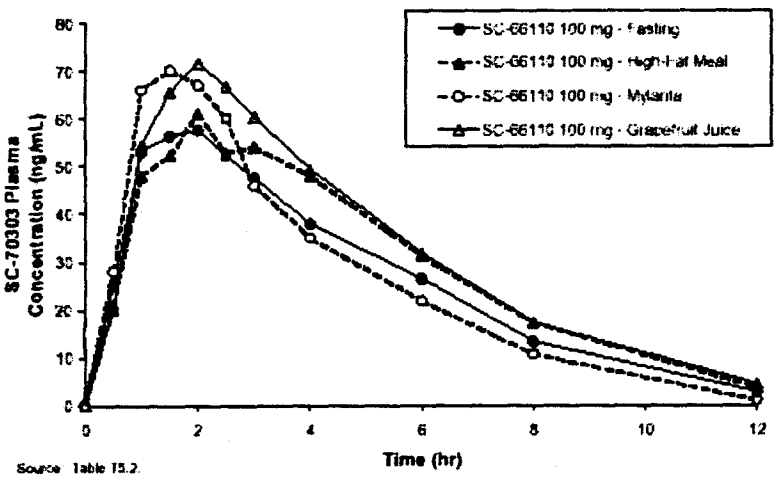
	Eplerenone 100 mg Fasting	Eplerenone 100 mg + High-Fat Meal	Eplerenone 100 mg + Mylanta® MS	Eplerenone 100 mg + Grapefruit Juice
	N = 16	N = 16	N = 16	N = 16
Eplerenone				
AUC(0-lqc) (hr*ng/mL)	8321.9	8698.2	7878.2	9978.4
AUC(0-∞) (hr*ng/mL)	8416.3	8804.4	7958.7	10072.5
Cmax (ng/mL)	1462.9	1548.9	1628.5	1875.0
Tmax (hr)	1.9	2.6	1.7	2.0
Kel	0.3	0.3	0.3	0.3
T1/2 (hr)	2.8	2.7	2.5	2.9
AUMC (0-∞) (hr^2*ng/mL)	41745.6	47073.6	35687.8	51852.9
MRT (hr)	4.8	5.1	4.3	4.9
Cmax/AUC(0-lqc) (1/hr)	0.2	0.2	0.2	0.2
CL/F (L/hr)	12.9	12.4	13.6	10.8
CL/F/WT (L/hr/70 kg)	12.3	11.9	12.9	10.3
SC-70303				
AUC(0-lqc) (hr*ng/mL)	294.8	337.2	290.8	369.4
AUC(0-∞) (hr*ng/mL)	365.6	381.0	337.0	413.2
Cmax (ng/mL)	64.3	73.8	83.4	85.7
Tmax (hr)	1.7	2.7	1.4	1.9
Kel	0.2	0.3	0.3	0.3
T1/2 (hr)	3.3	2.7	2.6	2.7
AUMC (0-∞) (hr^2*ng/mL)	2128.5	1964.4	1481.7	2068.0
MRT (hr)	5.5	5.0	4.3	4.8
Cmax/AUC(0-lqc) (1/hr)	0.2	0.2	0.3	0.2

Effect of High-fat Meal on Eplerenone and SC-70303 Pharmacokinetics:

Coadministration of a high-fat meal with eplerenone did not affect eplerenone pharmacokinetics significantly. Eplerenone AUC and Cmax were unaffected by administration of a high fat meal. Eplerenone Tmax increased by 0.7 h but T1/2 was not affected by food. The 95% CI for the ratios of eplerenone mean Cmax and AUC were contained within the no food effect limits of 0.8 and 1.25.

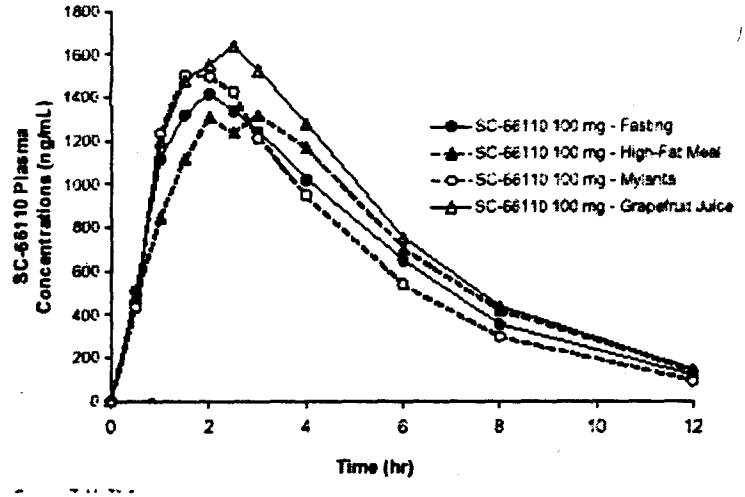
There was a more pronounced effect on SC-70303, open-ring form of eplerenone, pharmacokinetics upon coadministration of a high-fat meal with eplerenone. SC-70303 AUC and Cmax were both higher by 15%. SC-70303 Tmax increased by 1 h and T1/2 decreased by 0.6 h in the presence of food. The 90% CI for the ratios of SC-70303 mean Cmax was outside the no food effect limits of 0.8 and 1.25. The 95% CI for SC-70303 Cmax was 1.02-1.31.

Mean Eplerenone Plasma Concentrations, 0-12 Hours Postdose



Source Table 15.2.

Mean SC-70303 Plasma Concentrations, 0-12 Hours Postdose



Effect of Antacid on Eplerenone and SC-70303 Pharmacokinetics:

Coadministration of eplerenone with antacid, Mylanta®MS, MS (contains equal amounts of aluminum hydroxide and magnesium hydroxide, and smaller amounts of simethicone), increased eplerenone Cmax by 11% but AUC was unaffected. Eplerenone CL/F adjusted for 70 kg body weight was unaffected by coadministration of antacid. The 95% CI for eplerenone Cmax and AUC were contained within the bioequivalence limits of 0.8-1.25.

Coadministration of eplerenone with antacid had a more pronounced effect on peak SC-70303 concentrations. Mean SC-70303 Cmax increased by 33% while the AUC of SC-70303 was unaffected. SC-70303 $T_{1/2}$ decreased by 0.7 h in the presence of antacid compared to the fasted state. The 95% CI for SC-70303 Cmax was 1.17-1.51, while 95% CI for SC-70303 AUC was contained within the bioequivalence limits of 0.8-1.25.

Table 2: Ratios and 95% Confidence Intervals for Eplerenone and SC-70303 Pharmacokinetic Parameters

Treatment Group/ PK Parameter	Eplerenone		Ratio Test/ Fasting	95% CI for Ratio	SC-70303		Ratio Test/ Fasting	95% CI for Ratio
	Geometric LSM				Geometric LSM			
	Test	Fasting			Test	Fasting		
	N = 16	N = 16			N = 16	N = 16		
High-Fat Meal								
Cmax (ng/mL)	1489.9	1426.7	1.044	(0.945, 1.154)	70.1	60.9	1.150	(1.012, 1.307)
AUC(0-lqc) (h*ng/mL)	8314.4	7998.7	1.039	(0.960, 1.125)	318.2	276.4	1.151	(1.066, 1.243)
AUC (0-∞) (h*ng/mL)	8409.9	8090.6	1.039	(0.960, 1.126)	363.8	346.9	1.049	(0.945, 1.164)
CL/F (L/hr)	11.9	12.4	0.962	(0.888, 1.042)	--	--	--	--
CL/F/WT (L/h/70 kg)	11.3	11.8	0.962	(0.888, 1.042)	--	--	--	--
Liquid Antacid Mylanta®MS								
Cmax (ng/mL)	1587.7	1426.7	1.113	(1.007, 1.229)	81.0	60.9	1.329	(1.169, 1.510)
AUC(0-lqc) (h*ng/mL)	7593.4	7998.7	0.949	(0.877, 1.028)	274.2	276.4	0.992	(0.919, 1.072)
AUC (0-∞) (h*ng/mL)	7672.8	8090.6	0.948	(0.875, 1.027)	320.3	346.9	0.923	(0.832, 1.025)
CL/F (L/hr)	13.0	12.4	1.054	(0.973, 1.142)	--	--	--	--
CL/F/WT (L/h/70 kg)	12.4	11.8	1.054	(0.973, 1.142)	--	--	--	--
Grapefruit Juice								
Cmax (ng/mL)	1836.8	1426.7	1.287	(1.165, 1.422)	84.0	60.9	1.378	(1.213, 1.566)
AUC(0-lqc) (h*ng/mL)	9584.0	7998.7	1.198	(1.107, 1.297)	349.6	276.4	1.265	(1.171, 1.366)
AUC (0-∞) (h*ng/mL)	9675.4	8090.6	1.196	(1.104, 1.295)	394.5	346.9	1.137	(1.024, 1.262)
CL/F (L/hr)	10.3	12.4	0.836	(0.772, 0.906)	--	--	--	--
CL/F/WT (L/h/70 kg)	9.8	11.8	0.836	(0.772, 0.906)	--	--	--	--

Effect of Grapefruit Juice on Eplerenone and SC-70303 Pharmacokinetics:

Coadministration of eplerenone with grapefruit juice significantly affected the pharmacokinetics of both eplerenone and SC-70303. Mean Cmax and AUC of eplerenone increased by 29% and 20%, respectively, and eplerenone apparent oral clearance adjusted for 70 kg body weight decreased by 17% in the presence of grapefruit juice. Both Tmax and $T_{1/2}$ of eplerenone were unaffected by grapefruit juice. The 95% CI for eplerenone

Cmax and AUC were 1.17-1.42 and 1.10-1.30, respectively, which are over the bioequivalence limits of 0.8-1.25.

Coadministration of grapefruit increased mean SC-70303 Cmax and AUC by 38% and 27, respectively. Grapefruit juice decreased SC-70303 T1/2 decreased by 0.6 hours. The 95% CI for ratio of SC-70303 Cmax and AUC in the presence of grapefruit juice to the fasted state were 1.21-1.57 and 1.17-1.37, respectively,

CONCLUSIONS

Coadministration of a high-fat meal with eplerenone did not affect eplerenone pharmacokinetics significantly. Food increased eplerenone AUC and Cmax by 4%. This is in contrast to the 19% decrease in Cmax and a Tmax of 4 h observed in a previous single dose food-effect study (EE3-96-02-005).

Coadministration with antacid did not affect eplerenone Cmax and AUC significantly. The 95% CI for eplerenone Cmax and AUC were contained within the bioequivalence limits of 0.8-1.25.

Coadministration of eplerenone with 250 ml of double strength grapefruit juice significantly affected the pharmacokinetics of both eplerenone and SC-70303. Mean Cmax and AUC of eplerenone increased by 29% and 20%, respectively. The 95% CI for eplerenone Cmax and AUC were 1.17-1.42 and 1.10-1.30, respectively, which are over the bioequivalence limits of 0.8-1.25. The increase in relative bioavailability of eplerenone in the presence of grapefruit juice is likely due to inhibition of CYP 3A4 in the small intestine resulting in decreased first pass metabolism of eplerenone a substrate of CYP 3A4.The increased eplerenone concentrations in the presence of grapefruit juice is not expected to be clinically significant.

THE BIOEQUIVALENCY STUDY OF DIFFERENT PARTICLE SIZE TABLETS OF EPLERENONE IN HEALTHY SUBJECTS

STUDY INVESTIGATOR AND SITE:

Report No.: NE3-00-02-043

OBJECTIVES:

To examine the single-dose bioequivalence of 100 mg eplerenone tablets manufactured with approximately 90 µM, 176 µM, 230 µM and 357 µM particle sizes in healthy adult subjects.

FORMULATIONS:

Searle provided the following formulations:
Eplerenone 100 mg film-coated tablets (R99686) tablets 90 µM (lot number RCT 11488) (Reference)
Eplerenone 100 mg film-coated tablets (R99686) tablets — D90 = 176 µM) (lot number RCT 11489)
Eplerenone 100 mg film-coated tablets (R99686) tablets — D90 = 230 µM) (lot number RCT 11490)
Eplerenone 100 mg film-coated tablets (R99686) tablets — D90 = 357 µM) (lot number RCT 11491)

STUDY DESIGN:

This was an open-label, randomized, single-dose, four-sequence, four-treatment, and four-period crossover design study conducted in 40 healthy adult subjects, 20 F/ 20 M, age range:19-45 years.

	Period 1 Day 1	Period 2 Day 5	Period 3 Day 9	Period 4 Day 13
Sequence I	A	D	B	C
Sequence II	B	A	C	D
Sequence III	C	B	D	A
Sequence IV	D	C	A	B

A = 100 mg Eplerenone tablets - 90 µM particle size (reference)
B = 100 mg Eplerenone tablets - D90 = 176 µM particle size (test)
C = 100 mg Eplerenone tablets - D90 = 230 µM particle size (test)
D = 100 mg Eplerenone tablets - D90 = 357 µM particle size (test)

On study Days 1, 5, 9, and 13, subjects received a single eplerenone dose, one of 4 formulations according to the randomization scheme, following an overnight fast.

ASSAY:

Sample Collection

Blood samples for eplerenone and SC-70303 pharmacokinetic analyses were drawn on Days 1, 5, 9, and 13 for all subjects at the following time-points: predose (-30 minutes), and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24 and 48 hours postdose.

Urine samples were collected and pooled at -12 to 0 hours on Day –1, immediately prior to dosing on day 1, and 0-24 and 24-48 hours postdose on all dosing days.

RESULTS:

Mean single dose pharmacokinetic parameters of eplerenone and SC-70303 obtained following administration of 100-mg eplerenone from 4 formulations which differ in eplerenone particle size are presented in the following table.

Table 1: Arithmetic Mean Eplerenone and SC-70303 Pharmacokinetic Parameters

	Eplerenone 100 mg Tablet			
	90 µM tablet	D90 = 176 µM tablet	D90 = 230 µM tablet	D90 = 357 µM tablet
	N = 40	N = 40	N = 40	N = 40
Eplerenone				
AUC(0-lqc) (hr*ng/mL)	11678.94	11568.39	12205.06	12672.50
AUC(0-∞) (hr*ng/mL)	11848.32	11776.66	12485.57	13090.27
Cmax (ng/mL)	1918.84	1762.43	1656.69	1408.36
Tmax (hr)	1.73	1.96	2.38	2.49
Kel (1/hr)	0.215	0.209	0.202	0.140
CL/F (L/hr)	9.35	9.33	9.17	8.88
XU(0-48) (µg)	1913.83	1760.86	2061.64	1924.96
SC-70303				
AUC(0-lqc) (hr*ng/mL)	399.04	396.74	422.41	404.02
AUC(0-∞) (hr*ng/mL)	458.71	444.38	475.73	467.23
Cmax (ng/mL)	84.79	75.03	68.68	54.11
Tmax (hr)	1.49	1.84	2.26	2.33
Kel (1/hr)	0.220	0.214	0.206	0.164
XU(0-48) (µg)	5783.91	5155.20	6260.99	6262.43

Particle size of eplerenone had a significant effect on rate of absorption as evidenced by a decrease in Cmax with increasing particle size but had no effect on AUC of eplerenone. Increasing the particle size from 90 µM, 176 µM, 230 µM and 357 µM decreased mean eplerenone Cmax by of 9%, 14% and 27% respectively, while the AUC was relatively

unchanged 11679 ng.h/ml, 11568 ng.h/ml, 12206 ng.h/ml and 12673 ng.h/ml, respectively. Eplerenone Tmax increased from 1.7 h to 2.5 hours with increasing particle size. Except for a lower amount of eplerenone recovered from urine with the 176 µM formulation, similar amounts of eplerenone were recovered from urine from the other formulations.

Similar to the effect on eplerenone, particle size of eplerenone also had a significant effect on SC-70303 Cmax. Increasing the particle size from 90 µM, 176 µM, 230 µM and 357 µM resulted decreased mean SC-70303 Cmax by12%, 19% and 36%, respectively, while SC-70303 AUC was relatively unchanged 399 ng.h/ml, 397 ng.h/ml, 422 ng.h/ml and 404 ng.h/ml, respectively. SC-70303 Tmax increased from 1.5 h to 2.3 hours with increasing particle size. The 230 µM and 357 µM formulations yielded higher SC-70303 urinary recoveries compared to the 90 µM and 176 µM formulations.

Mean SC-66110 Plasma Concentrations, 0-24 Hours Postdose

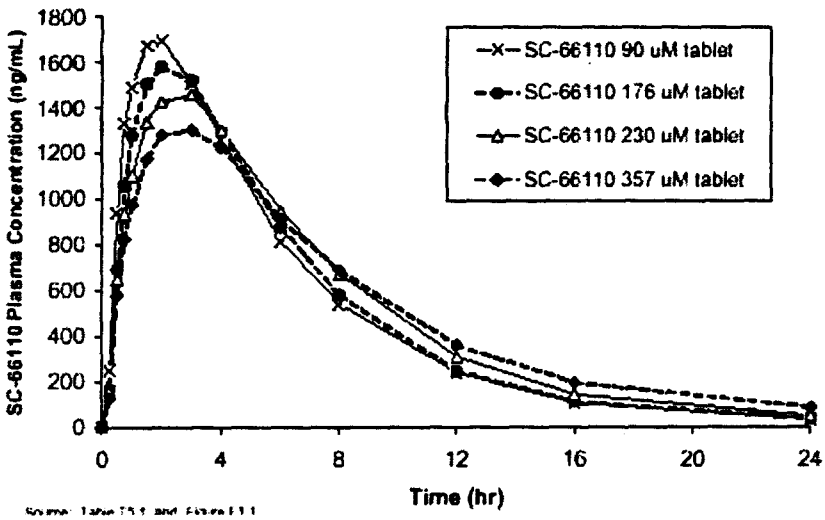


Table 2: Ratios and 90% Confidence Intervals for Eplerenone and SC-70303 Pharmacokinetic Parameters

	Formulation		Least Squares Means		Ratio of Means Test/Ref	90% CI for Ratio	P-Value
	Test	Ref	Test	Ref			
Eplerenone							
AUC(0-lqc) (hr*ng/mL)	B	A	11085.71	11127.59	0.996	(0.961, 1.032)	0.861
AUC(0-∞) (hr*ng/mL)	B	A	11269.18	11272.58	1.000	(0.965, 1.036)	0.989
Cmax (ng/mL)	B	A	1721.64	1881.50	0.915	(0.883, 0.948)	<0.001
Tmax (hr)	B	A	1.96	1.73	–	–	0.284
AUC(0-lqc) (hr*ng/mL)	C	A	11478.19	11127.59	1.032	(0.996, 1.069)	0.150
AUC(0-∞) (hr*ng/mL)	C	A	11717.37	11272.58	1.039	(1.003, 1.077)	0.072
Cmax (ng/mL)	C	A	1624.87	1881.50	0.864	(0.834, 0.895)	<0.001
Tmax (hr)	C	A	2.38	1.73	–	–	0.003

AUC(0-lqc) (hr*ng/mL)	D	A	11792.81	11127.59	1.060	(1.023, 1.098)	0.008
AUC(0-∞) (hr*ng/mL)	D	A	12179.55	11272.58	1.080	(1.043, 1.119)	<0.001
Cmax (ng/mL)	D	A	1372.15	1881.50	0.729	(0.704, 0.756)	<0.001
Tmax (hr)	D	A	2.49	1.73	--	--	<0.001
SC-70303							
AUC(0-lqc) (hr*ng/mL)	B	A	382.28	383.45	0.997	(0.953, 1.043)	0.911
AUC(0-∞) (hr*ng/mL)	B	A	434.94	441.75	0.985	(0.946, 1.025)	0.522
Cmax (ng/mL)	B	A	72.72	82.30	0.884	(0.838, 0.931)	<0.001
Tmax (hr)	B	A	1.84	1.49	--	--	0.115
AUC(0-lqc) (hr*ng/mL)	C	A	397.85	383.45	1.038	(0.992, 1.085)	0.178
AUC(0-∞) (hr*ng/mL)	C	A	454.68	441.75	1.029	(0.989, 1.071)	0.240
Cmax (ng/mL)	C	A	66.66	82.30	0.810	(0.768, 0.854)	<0.001
Tmax (hr)	C	A	2.26	1.49	--	--	<0.001
AUC(0-lqc) (hr*ng/mL)	D	A	378.79	383.45	0.988	(0.944, 1.033)	0.654
AUC(0-∞) (hr*ng/mL)	D	A	450.18	441.75	1.019	(0.979, 1.061)	0.446
Cmax (ng/mL)	D	A	52.99	82.30	0.644	(0.611, 0.679)	<0.001
Tmax (hr)	D	A	2.33	1.49	--	--	<0.001

A = Eplerenone 100 mg 90 µM tablet B = Eplerenone 100 mg D90 = 176 µM tablet
C = Eplerenone 100 mg D90 = 230 µM tablet D = Eplerenone 100 mg D90 = 357 µM tablet

Formulations with particle sizes of 176 µM and 230 µM were bioequivalent to the 90 µM particle size formulation (reference) with respect to eplerenone; 90% CI for both Cmax and AUC were contained within bioequivalence limits of 0.8-1.25. The formulation with the largest particle size, 357 µM, was not bioequivalent to the 90 µM formulation; 90% CI for eplerenone Cmax was below the lower bioequivalence limit of 0.8. The 90% CI for ratio of eplerenone AUC however, was bioequivalent.

Similar to eplerenone, formulation with particle sizes of 176 µM was bioequivalent to the 90 µM particle size formulation (reference) with respect to SC-70303; 90% CI for both Cmax and AUC were contained within bioequivalence limits of 0.8-1.25. However, formulations with a larger particle size, 230 µM and 357 µM were not bioequivalent to the 90 µM formulation; 90% CI for SC-70303 Cmax was below the lower bioequivalence limit of 0.8. The 90% CI for ratio of eplerenone AUC from the 230 µM and 357 µM formulations were bioequivalent to 90 µM formulation.

CONCLUSIONS

Particle size had a significant influence on eplerenone and SC-70303 Cmax; Cmax decreased with increasing particle size of drug substance.

Eplerenone tablets formulated with drug substance to D90 = 176 µM were bioequivalent to tablets made with 90 µM particle size with respect to both eplerenone and SC-70303 after single dose administration. Tablets formulated with eplerenone to D90 = 230 µM were bioequivalent to 90 µM particle size with respect to eplerenone, but not the open-ring form, SC-70303. Tablets formulated with drug substance to D90 = 357 µM were not bioequivalent to tablets with 90 µM particle size with respect to both eplerenone and SC-70303 after single dose administration.

WAIVER FOR A BIOEQUIVALENCE STUDY COMPARING CLINICAL AND COMMERCIAL (TO BE MARKETED) FORMULATIONS

The sponsor has demonstrated in vivo bioequivalence of 25 mg, 50 mg and 100 mg eplerenone capsules and 25 mg, 50 mg and 100 mg eplerenone tablets in Study NE3-99-02-029. The composition of the capsules used in the bioequivalence study is similar to the composition of the capsule formulations used in the pivotal clinical trial EE3-96-02-010. However, the tablets used in the bioequivalence study were clinical trial tablets used in pivotal clinical trial IE3-00-02-049. In pivotal clinical trial IE3-00-02-049 the sponsor used 25 mg, 50 mg and 100 mg eplerenone tablets with composition similar to the commercial tablets. The Phase III clinical trial tablets and the commercial tablets differ in shape only. The composition of Phase III and proposed commercial tablets is provided in the following table.

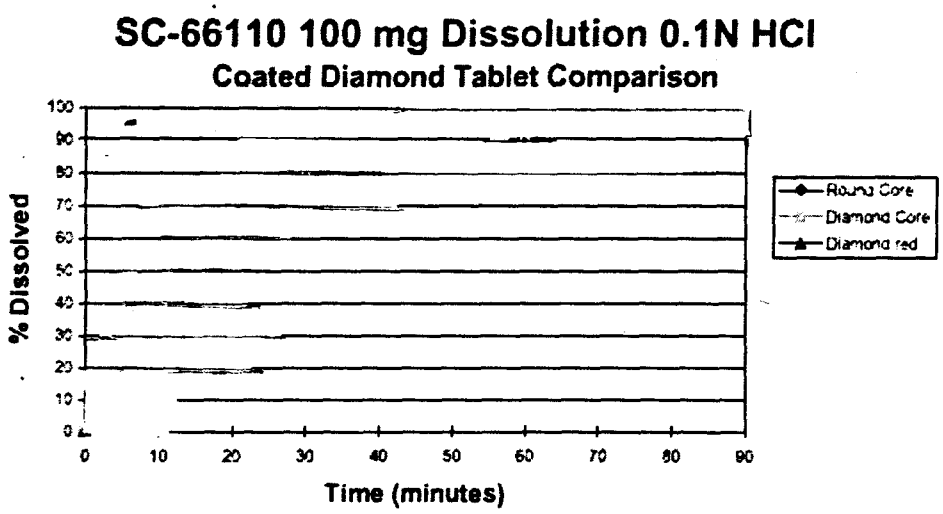
Table 1. Composition of Phase III and proposed commercial tablets.

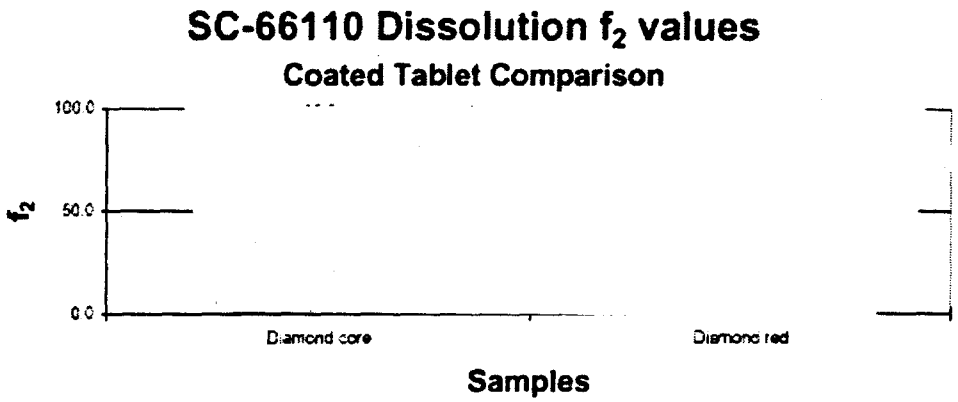
INGREDIENT	(%)
Eplerenone Lactose Microcrystalline Cellulose Croscarmellose Sodium Hydroxypropyl Methylcellulose, Sodium Lauryl Sulphate NF Talc USP Magnesium Stearate, NF	
red for proposed commercial 100 mg pink for proposed commercial 50 mg yellow for proposed commercial 25 mg	

The shape of the to-be-marketed film coated tablet differs from the pivotal clinical trial tablets. Therefore the effect of coating and shape on dissolution were evaluated using 100 mg strength of the following tablets.

25 mg, 50 mg and 100 mg Round-Shaped Core
100 mg Diamond-Shaped Core
25 mg, 50 mg and 100 mg Diamond-Shaped Coated Tablets

Six tablets of each type were studied using the proposed dissolution conditions of 1000 mL 0.1 N HCl, USP Apparatus 2 at 50 rpm. The dissolution profiles are shown in the following figure.





Dissolution from the round core, diamond core and coated diamond core 100 mg tablets were similar as evidenced by a f2 value greater than 50.

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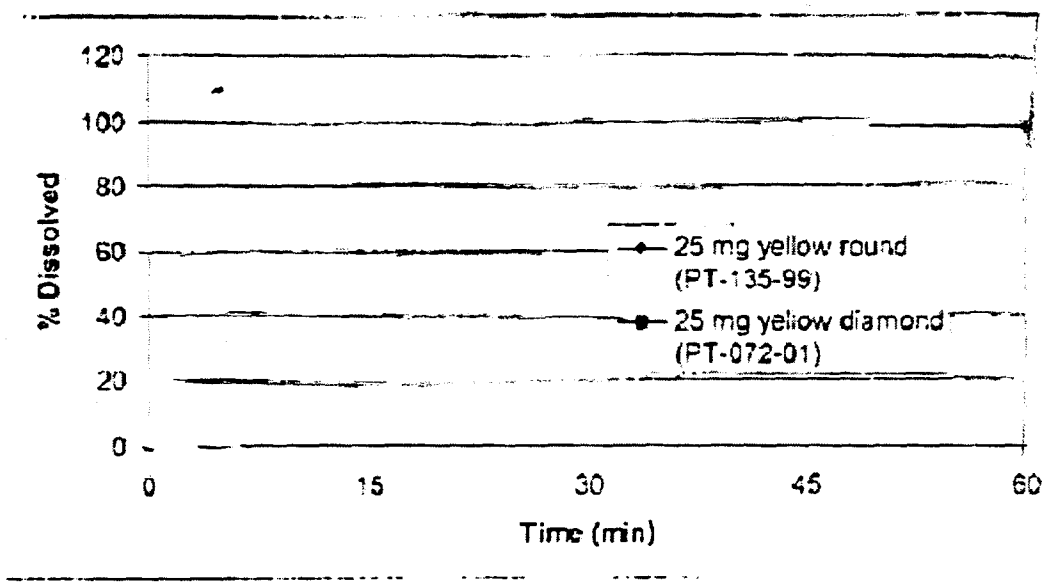
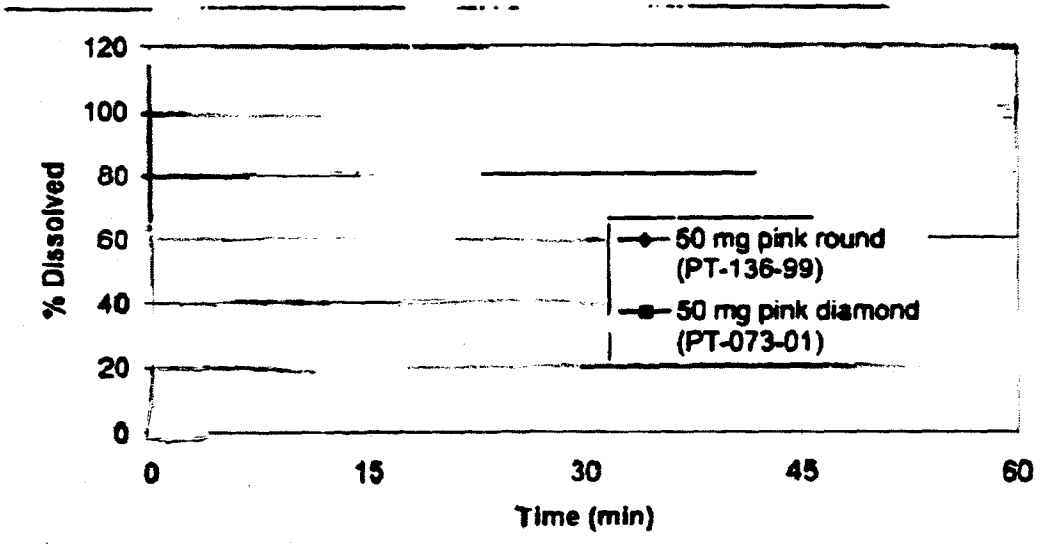
Dissolution Profiles for Eplerenone 25 mg Yellow Round and 25 mg Yellow Diamond-Shaped Tablets



Dissolution Profiles for Eplerenone 50 mg Pink Round and 50 mg Pink Diamond-Shaped Tablets



Dissolution from the round core and diamond core 25 mg and 50 mg strengths were similar with mean dissolution greater than [redacted]% in 15 minutes.

CONCLUSIONS:

The sponsor has demonstrated in vivo bioequivalence between the pivotal clinical trial capsules and Phase III tablets. The Phase III clinical trial tablets and the commercial

tablets of eplerenone are similar except for shape. The difference in shape between the Phase III tablets and the commercial tablets had no effect on release characteristics of eplerenone drug substance as demonstrated by the similarity in the in vitro dissolution profiles of the 2 tablets. An in vivo bioequivalence waiver is granted for the shape change between the clinical and commercial tablets of eplerenone.

DISSOLUTION METHOD DEVELOPMENT:

Rationale for Selection of Dissolution Method and Media for Eplerenone (SC-66110) Tablets

Eplerenone solubility in various dissolution media at 37° C was assessed in order to determine if sink conditions criteria exist in that medium. One gram of drug substance was added to 100 mL of media to determine the solubility of eplerenone at 37° C.

The following table lists the results of solubility testing of eplerenone in different media.

Table 1: Solubility of Eplerenone in Different Media

Media	Dissolved mg/mL	×100 mg dose in 1000 mL
S. Intestinal fluid (USP)	0.35	3.5
0.05 M PO4 pH 6.8	0.40	4.0
Water	0.43	4.3
0.1 N HCl	0.45	4.5
0.05 M PO4 pH 7.4	0.46	4.6
S. Gastric fluid (USP)	0.47	4.7
1% Bile Salts solution	0.48	4.8
0.3% SDS	0.67	6.7
0.5% SDS	0.76	7.6
1% CTAB	0.76	7.6
0.75% SDS	0.86	8.6
2% SDS	0.90	9.0
1% SDS	0.93	9.3
3% SDS	0.93	9.3
4% SDS	0.96	9.6

Eplerenone solubility was greater than 3 times the highest dose of 100 mg in 1000 mL in all of the media tested.

Based on solubility and physiological relevance, 4 media were selected for further investigation (0.1 N HCl, 0.05 M Phosphate (PO_4), 1% Bile Salts and 1% SDS). These 4 media were evaluated using tablets from process development studies and tablets manufactured by the proposed commercial process.

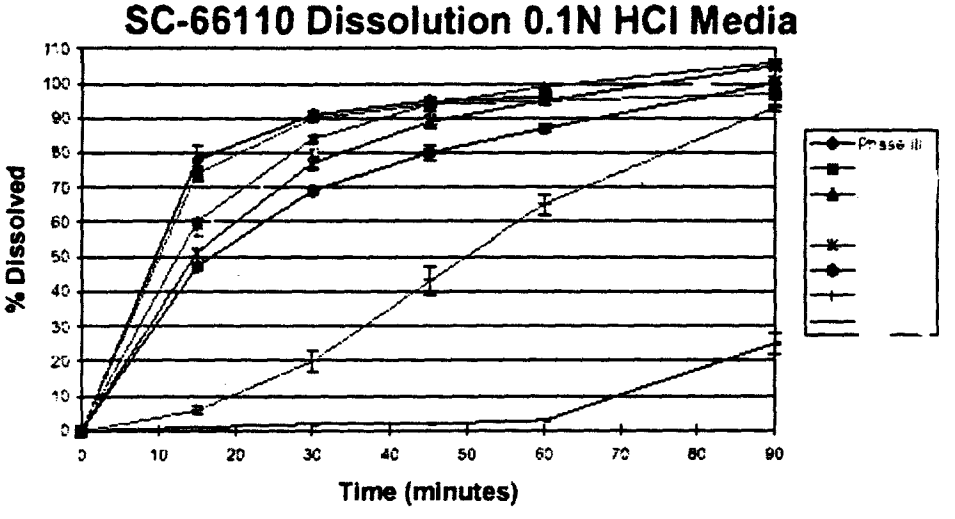
The dissolution experiments were conducted using six 100-mg tablets per run. Tablets made outside of nominal conditions were used to test for discrimination by the dissolution method being developed. The tablets used for assessing the discriminatory power of different dissolution media are listed in the following table.

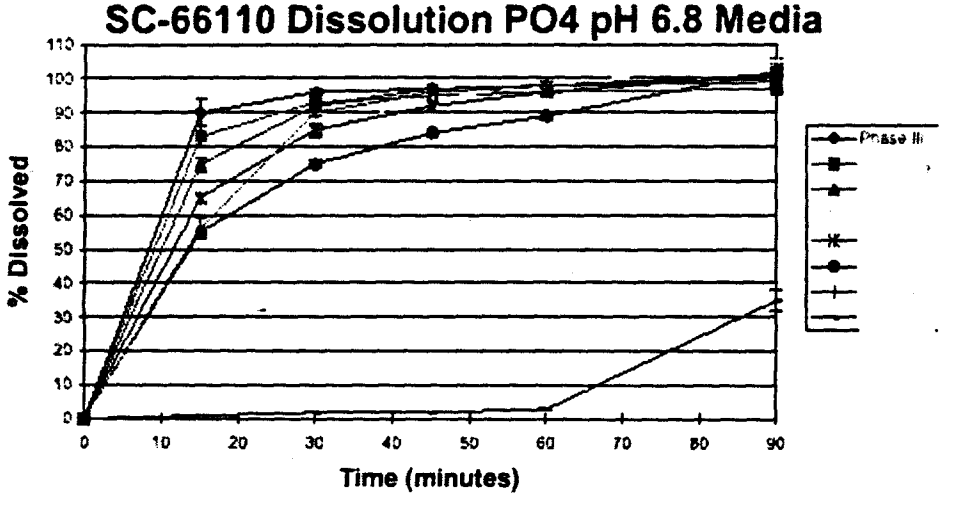
Table 2: Tablets used in dissolution method development

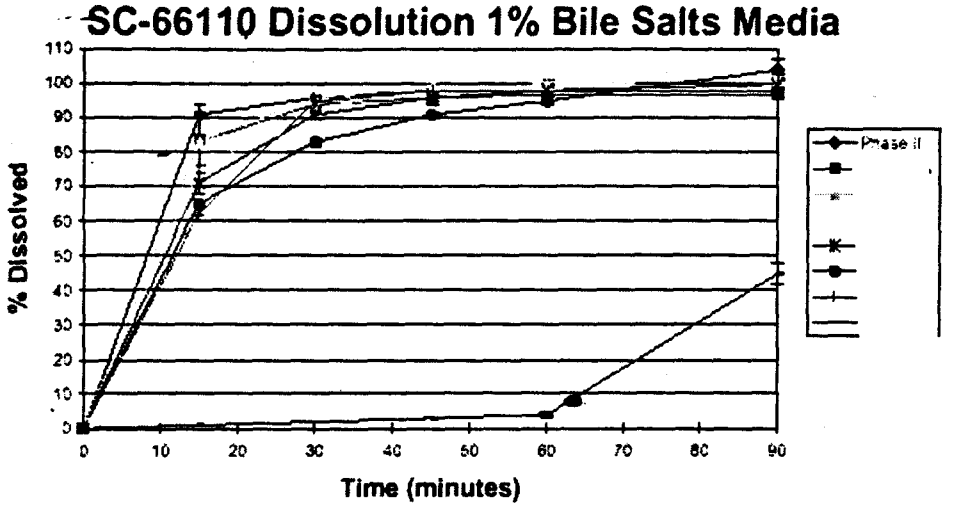
Tablet	Adjusted Parameter	Nominal Parameter	Scale
Phase III			

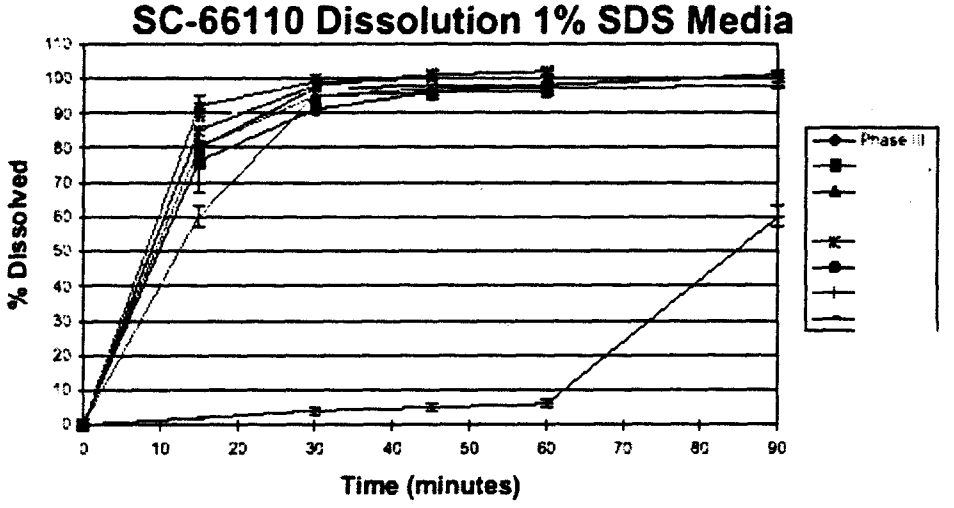
The dissolution conditions used for the investigation were USP apparatus II (paddles) at 50 rpm with time points of 15, 30, 45 and 60 minutes.

The dissolution profiles for 1% SDS, 0.1 N HCl, 50 mM phosphate pH 6.8, and 1% bile salts using tablets listed in Table 2 are shown in the following Figures.

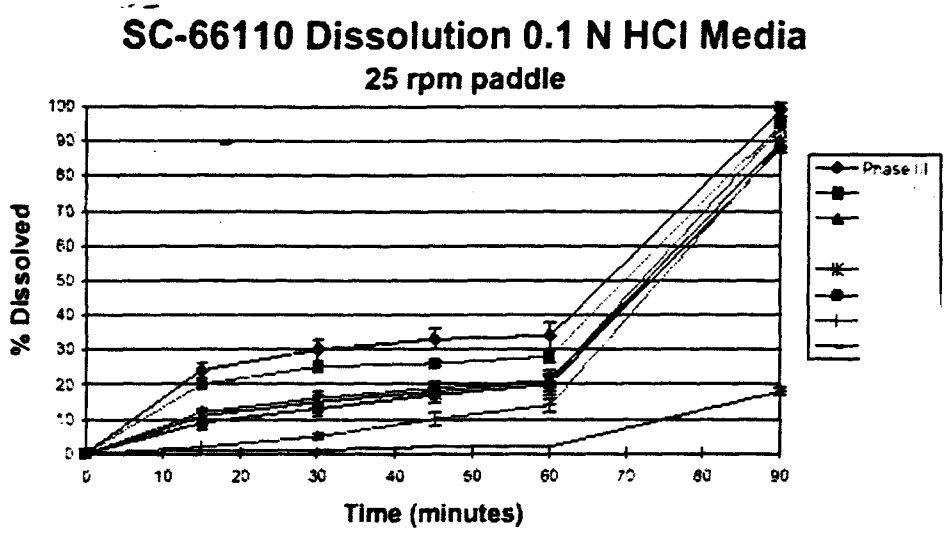


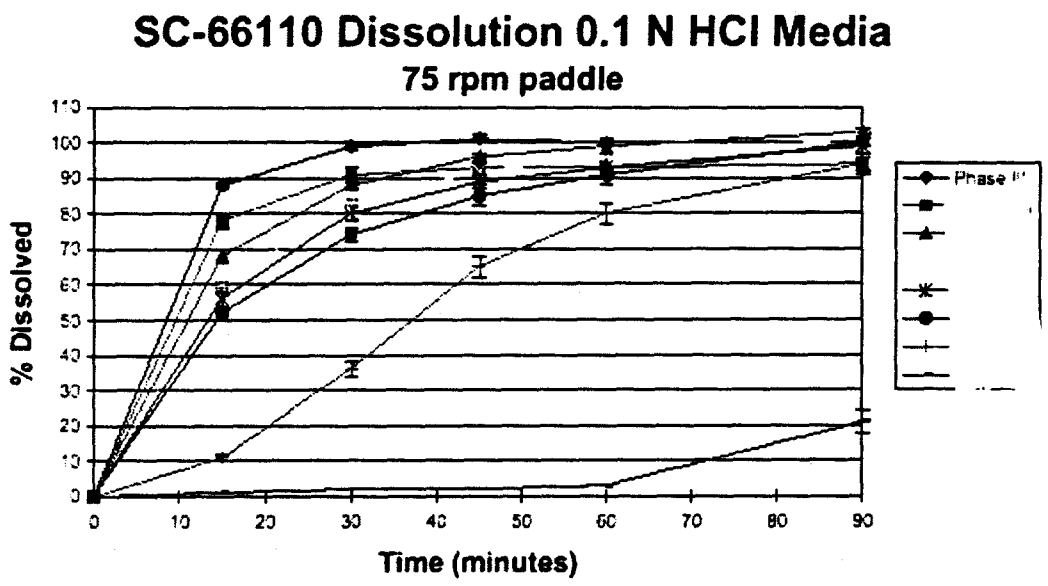






Additionally, the effects of paddle speed at 25 and 75 rotations/minute were investigated using 0.1 N HCl as the dissolution media. Cone shaped mounding was observed for all tablets tested showing insufficient hydrodynamics at 25 rpm for this type of formulation. Profiles obtained at a paddle speed of 25 rpm and 75 rpm are shown in the following Figure.





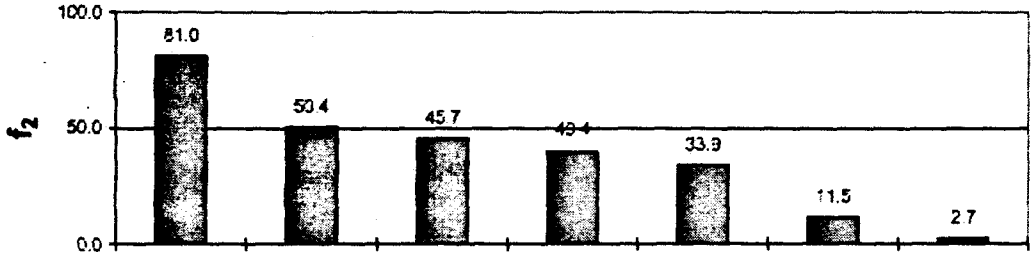
Dissolution profiles in each medium were compared using the similarity factor (f2):

$$f_2 = 50LOG\{[1+\frac{1}{n}\sum_{t=1}^{n}(Rt-Tt)^2]^{-0.5}\times 100\}$$

where R_t and T_t are the percent dissolved at each time point. Data collected at time points of 15, 30, 45, and 60 minutes were used in the f2 calculations. An f_2 value between 50 and 100 suggests the two dissolution profiles are similar. The Phase III tablet profile was used as the reference. The results of the f2 tests are shown as bar graphs in following Figures.

SC-66110 Dissolution f_2 values

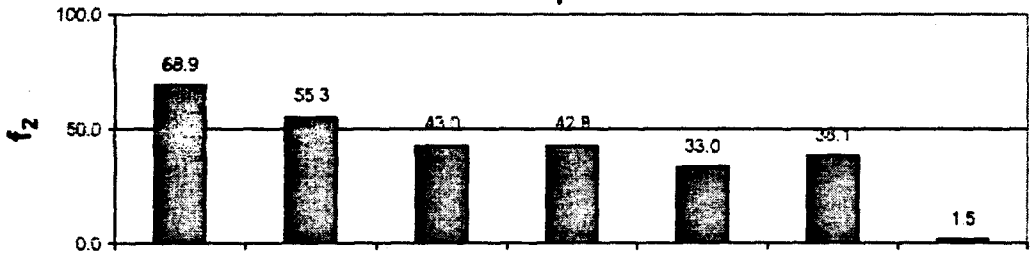
0.1N HCl



Samples

SC-66110 Dissolution f_2 values

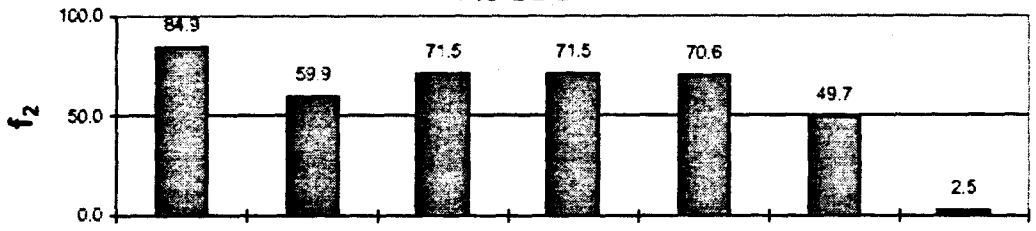
50 mM PO4 pH 6.8



Samples

SC-66110 Dissolution f_2 values

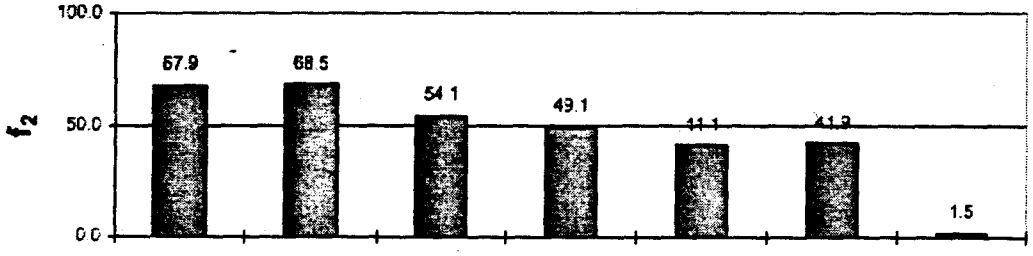
1% SDS



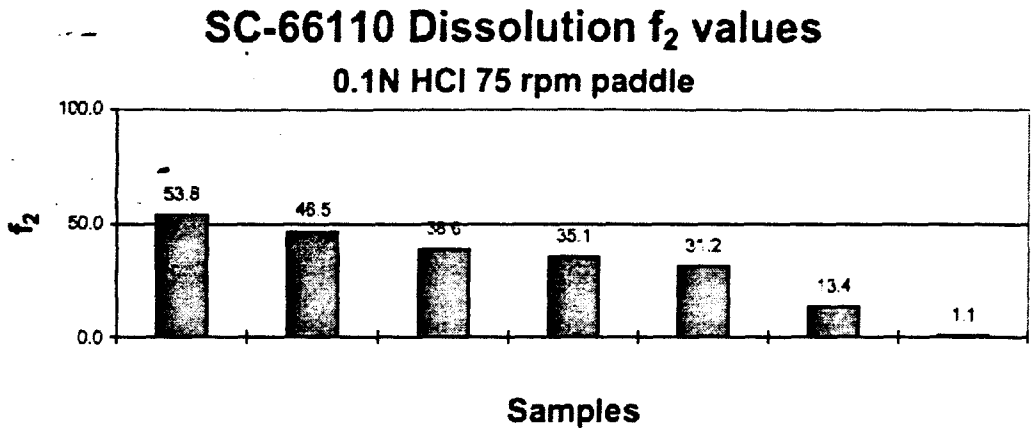
Samples

SC-66110 Dissolution f_2 values

Bile Salts



Samples



Discrimination between the tablets with various modifications was best obtained with 0.1 N HCl and 50 mM phosphate buffer pH 6.8, at 50 rpm.

The sponsor selected 0.1 N HCl as the dissolution media based on its discriminating ability, physiological relevance, and its common regulatory acceptance.

The sponsor proposed final dissolution method is as follows:
Apparatus: USP Apparatus II (paddles)
Medium: 0.1 N HCl
Volume: 1000 mL
Rotation Speed: 50 rpm
Specification: NLT [redacted]% (Q) at 30 minutes

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics finds the sponsor proposed dissolution method of USP Apparatus II (paddles) at 50 rpm and 1000 ml of 0.1 N HCl dissolution media and dissolution specification of NLT [redacted]% (Q) at 30 minutes acceptable.

PHARMACOKINETIC-PHARMACODYNAMIC RELATIONSHIP

BACKGROUND:

Dose response relationship was explored using pharmacodynamic data from 2 pivotal controlled studies, Protocol EE3-96-02-010 and Protocol 049. Further, data from both studies (010 and 049) were merged and analyzed simultaneously. Since blood samples for pharmacokinetic analysis of eplerenone were not collected in either study, concentration-effect relationship could not be developed for the primary end point - trough cuff diastolic blood pressure. However, the pharmacokinetic model developed in adults was used to simulate expected plasma concentrations of eplerenone and a PK/PD relationship between eplerenone concentrations and ambulatory blood pressure (ABPM) was attempted. The details of the 2 pivotal clinical trials, 010 and 049 are briefly described below.

Study Title: EFFICACY AND SAFETY EVALUATION OF A RANGE OF DOSES OF EPLERENONE IN THE TREATMENT OF MILD TO MODERATE HYPERTENSION

Protocol #: EE3-96-02-010

OBJECTIVES:

1. To identify a dose-response relationship between eplerenone doses and trough cuff sitting diastolic blood pressure (primary end point and trough cuff sitting systolic blood pressure (secondary end point).
2. To evaluate the effect of placebo on trough cuff sitting diastolic and systolic blood pressures with time.

STUDY DESIGN:

This was a multicenter, randomized, double-blind, placebo lead-in, parallel group study comparing the safety and effectiveness of a range of doses of eplerenone to placebo. Spironolactone 50 mg BID (twice a day) was included as the active reference drug. Patients with mild to moderate hypertension defined as a sitting, cuff assessed, diastolic blood pressure (DBP) of 95 mm Hg and <114 mm Hg and a 24-hour mean DBP of 85 mm Hg as assessed by an Ambulatory Blood Pressure Monitoring (ABPM) device. The study consisted of three periods: a 2-week Pretreatment Screening Period, a 4-week Single-Blind Placebo Lead-In Period, and an 8-week Double-Blind Treatment Period. Qualified patients in the Double-Blind Treatment Period were randomized to placebo, one of 3 daily doses of eplerenone (50 mg, 100 mg, or 400 mg) administered once a day (QD) or in divided doses (BID), or spironolactone 50 mg BID. 417 patients were randomized to the double-blind segment of the study and received at least one dose of study medication. These patients were distributed as follows: placebo (n=52); eplerenone 50 mg QD (n=54); eplerenone 100 mg QD (n=48); eplerenone 400 mg QD (n=54);

eplerenone 25 mg BID (n=53); eplerenone 50 mg BID (n=53); eplerenone 200 mg BID (n=48); and spironolactone 50 mg BID (n=47).

The primary effectiveness variable was the change from Baseline in cuff DBP (sitting) measured at trough plasma levels after 8 weeks of double-blind treatment. The secondary efficacy variables after 8 weeks of double-blind treatment were the change from Baseline in trough cuff systolic blood pressure (SBP) (sitting), and the change from Baseline in 24-hour mean DBP and mean SBP.

Study Title: A DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF RANGING DOSES OF EPLERENONE FOR THE TREATMENT OF MILD TO MODERATE HYPERTENSION

Protocol #: IE3-00-02-049

OBJECTIVES:

1. To evaluate the efficacy of eplerenone as compared to placebo by measuring mean change from Baseline in seated trough cuff diastolic BP (SiDBP) at Week 12.
2. To evaluate the mean change from Baseline in seated trough systolic BP (SiSBP).
3. To evaluate the mean change from Baseline in 24-hour DBP and SBP assessed by ambulatory BP monitoring (ABPM).

STUDY DESIGN:

This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study designed to compare the efficacy and safety of a range of doses of eplerenone versus placebo in patients with mild to moderate hypertension. The study consisted of a 2-week Pretreatment Screening Period followed by a four-week Single-Blind, Placebo Run-In Period, prior to randomization to a 12-week Double-Blind, Randomized Treatment Period. Patients at least 18 years of age with essential hypertension (SiDBP =95 mmHg and < 110 mmHg and SiSBP < 180 mmHg) and who met specific inclusion criteria were eligible for entry into the Pretreatment Screening Period. A total of 400 patients were randomized into the study. Of these, 90 received placebo, 45 received eplerenone 25 mg QD, 87 received eplerenone 50 mg QD, 90 received eplerenone 100 mg QD, and 88 received eplerenone 200 mg QD.

PK-PD MODELING OBJECTIVES:

1. To characterize the dose-response relationship between eplerenone daily dose and reduction in trough sitting diastolic (primary end point) and sitting systolic blood pressures in hypertensive patients in clinical studies –010 and 049.

2. To characterize the dose-response relationship between eplerenone daily dose and increase in thyroid stimulating hormone concentrations (TSH) in hypertensive patients in clinical studies-010 and 049.

PK-PD MODELING AND METHODS:

Blood samples were not collected from individuals in both clinical trials, Study 010 and 049. Therefore, a dose response relationship was explored between eplerenone daily dose and SiDBP, SiSBP and TSH concentrations. Blood pressure and dosing information from the 2 pivotal studies, 010 and 049 were combined and analyzed simultaneously using nonlinear mixed effects modeling was performed using NONMEM (ver. 5,). S-plus was used for graphical display.

NULL MODEL:

A null model assuming no effect of drug (drug effect=0) was tested. This model assumes that all changes in blood pressure are due to variability in base line. This was done to test the null model of zero slope for the concentration-effect relationship. The model is described below,

$$BL_i = TVBL * \exp(\eta_{iBL})$$

where BLi is the null effect baseline in individual 'i'. TVBL is the typical value of null baseline with random effect η_i. The η_i's are assumed to have zero means and covariance matrix, Ω. The square roots of the diagonal elements of Ω are interpreted as approximate coefficients of variation (CVs).

$$EFFECT_i = BL_i + \varepsilon_{ij}$$

$EFFECT_i$ is the blood pressure in individual 'i'. Residual intra-subject random error is denoted by ε_{ij} which is assumed to be independent, have a zero mean, and a variance of σ^2, where σ is the approximate CV. ε_{ij} is an additive component.

PLACEBO MODEL:

This model assumes that all changes in blood pressure are either due to baseline variability and/or effect of time. Placebo effect was estimated for SiDBP and SiSBP as a linear function of time in days using the following equation:

$$EFFECT_{ij} = BL_i + PL_i * RDAY + \varepsilon_{ij}$$

Where RDAY is the dosing day relative to start of randomization (Day 0).

DRUG EFFECT MODEL:

Both Emax and linear drug effect models were tested for characterizing the dose-response relationship between eplerenone daily dose and SiDBP and SiSBP.

The final expression of the linear drug effect model including placebo effect is described below,

$$EFFECT_{ij} = BL_i * (1 + SLP_i * Dose_i) + PL_i * RDAY + \varepsilon_{ij}$$

Where $EFFECT_{ij}$ is j^{th} measurement of SiDBP and SiSBP, BL_i is baseline SiDBP and SiSBP, SLP_i is the slope of the effect vs eplerenone dose curve in the i^{th} patient. PL_i is the slope of the placebo effect relationship with time, RDAY. ε_{ij} is an additive component. Interindividual variability for both slope of drug-effect relationship and placebo effect relationship were modeled using the additive error model.

The final expression of the Emax drug effect model including placebo effect is described below,

$$EFFECT_{ij} = BL_i * \left(1 + \frac{E\max_i \cdot Dose_i}{ED_{50i} + Dose_i}\right) + PL_i * RDAY + \varepsilon_{ij}$$

Where $EFFECT_{ij}$ is j^{th} measurement of SiDBP and SiSBP, BL_i is baseline SiDBP and SiSBP, $Emax_i$ is the maximum effect in SiDBP and SiSBP. ED_{50i} is the dose that results in half-maximal effect (Emax/2) in individual 'i'. ε_{ij} is an additive component. Interindividual variability for Emax and placebo effect relationships were modeled using the additive error model while baseline and ED_{50} were modeled using a proportional error model.

The first order conditional estimation (FOCE) method of estimation was used for all analysis. Goodness of fit of the various models were set a priori to a significance level of 0.01 determined by the χ^2 distribution, that is a difference (ΔELS) of greater than 6.63 (-2·log likelihood).

RESULTS AND DISCUSSION

Modeling of dose-response indicated a dose related decrease in SiDBP and SiSBP. The modeling of SiDBP (primary efficacy endpoint) and SiSBP (secondary efficacy endpoint) are described separately.

Trough Sitting Diastolic Blood Pressure (SiDBP):

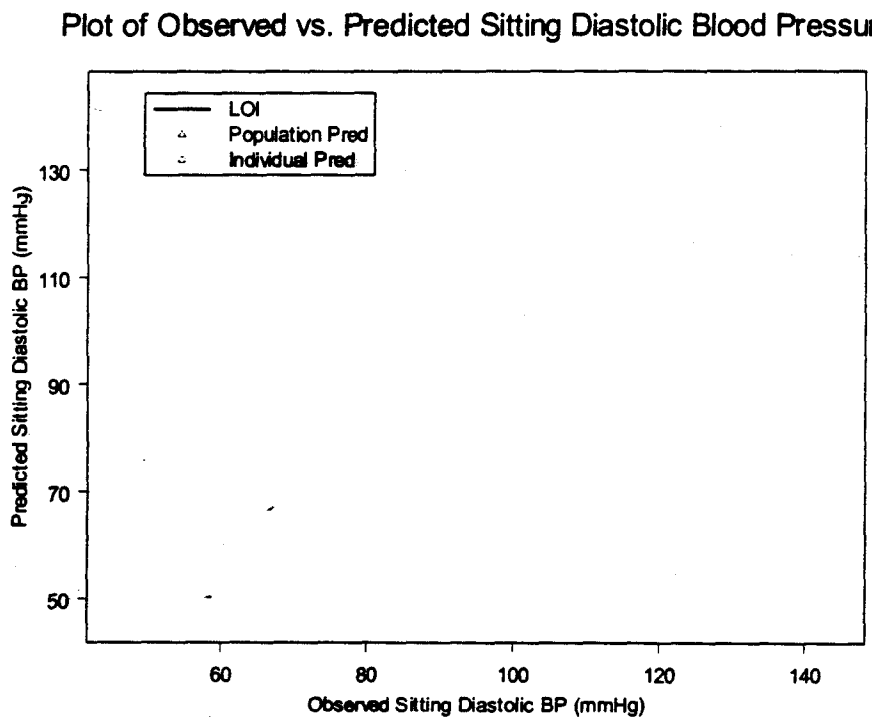
Modeling of eplerenone dose versus SiDBP indicated that eplerenone had a significant effect on blood pressure. The objective function values associated with the different models tested are listed in the following table.

#	MODEL FOR TROUGH SITTING DBP	OBJ FUNC	Δ OBJ FUNC	SIG
1	Null Model	53764.748		
2	Placebo Model	51576.655	-2188.093	**
3	Linear Model	50740.301	-836.354	**
4	Log-linear Model	50400.190	-1176.465	**
5	EMAX Model	50378.221	-1198.434	**
6	EMAX Model – test for BID and QD	50377.571	-0.65	NS
7	Step Function	50399.919	-1176.736	**
8	Emax Model – effect of sex on SiDBP baseline	50377.975	-0.246	NS
9	Emax Model – effect of sex on SiDBP Emax	50377.243	-0.978	NS
10	Emax Model – effect of body wt. on SiDBP BL	50377.481	-0.74	NS
11	Emax Model – effect of Age on SiDBP BL	50377.480	-0.75	NS

**Significance defined a priori at p = 0.01 (ΔELS=6.63)

Comparison of models indicated that the Emax model best fit the data compared to the linear or log-linear pharmacodynamic model or step function model (effect in the absence or presence of drug).

The observed versus Emax model predicted SiDBP is presented in the following figure (LOI=line of identity).



The parameter estimates obtained with the Emax model with associated standard error of estimate and inter-individual variability is listed below.

FINAL MODEL FOR SITTING DIASTOLIC BLOOD PRESSURE MODEL

BASE LINE =TBL*EXP(ETA_BL)
EMAX =TEMAX + ETA_EMAX
ED50 =TED50*EXP(ETA_ED50)
PLACEBO =TPL + ETA_PL

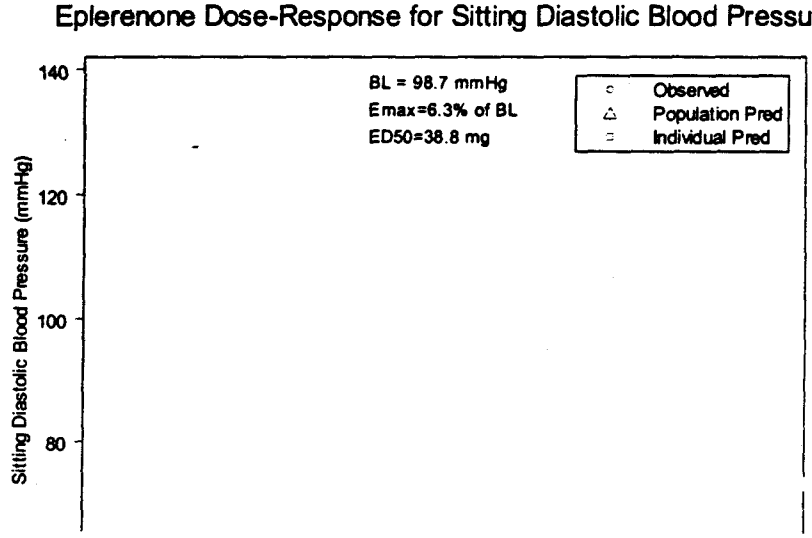
EFFECT = BASE LINE*(1+(EMAX*DOSE/ED50+DOSE)) + PLACEBO*RDAY

Parameter	Typical Value (SE%)	Interindiv Variability (SE%)
Baseline (mmHg)	98.7 (0.2%)	0.2% (6.4%)
Emax (% of Baseline)	-0.0629 (7.5%)	105% (15.3%)
ED_{50} (mg)	38.8 (13.8%)	404% (77.8%)
Placebo Slope (mmHg/RDAY)	0.00954 (48.5%)	932% (48.5%)
Residual Variability (Additive)		
σ standard deviation (mmHg)	4.72 (3.5%)	

**Significance defined a priori at p = 0.01 (ΔELS=6.63)

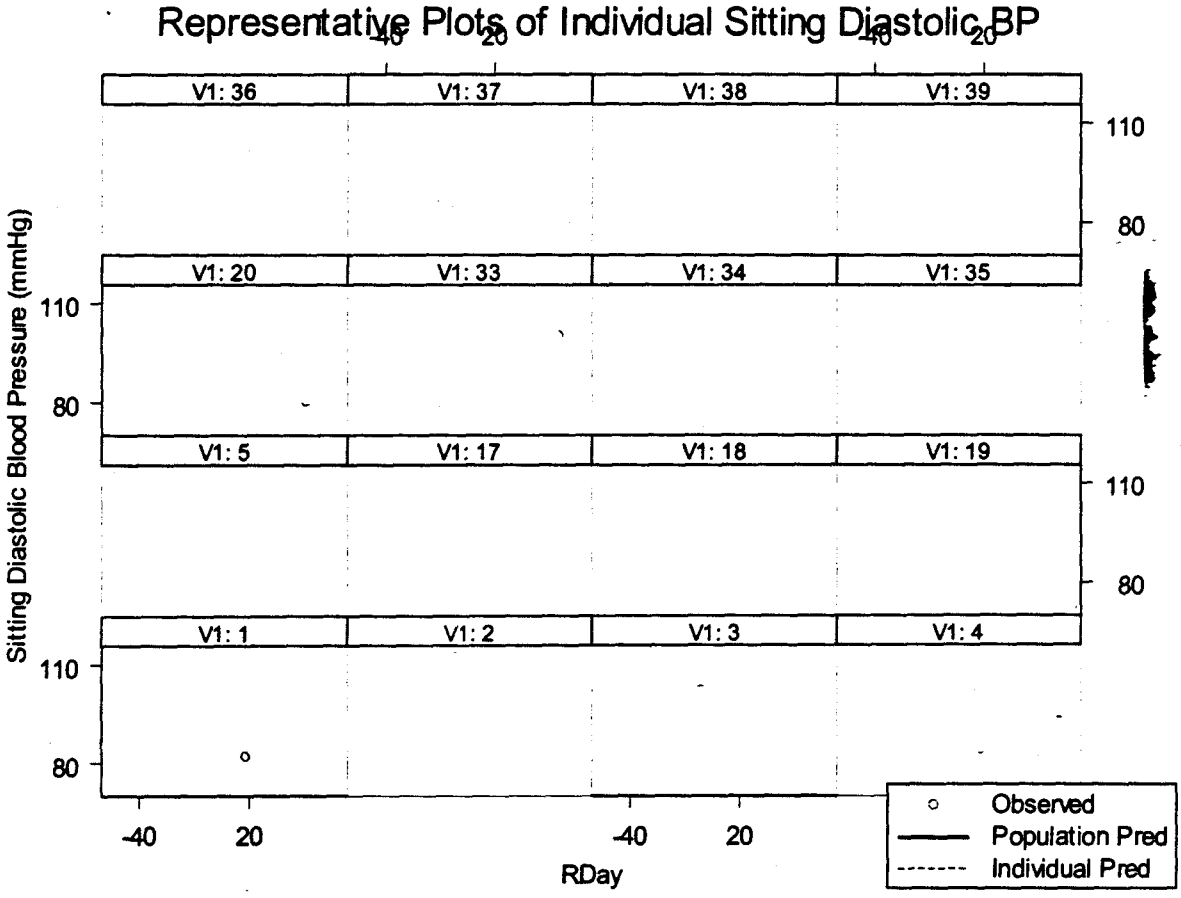
The typical value of SiDBP baseline was 98.7 mmHg. The typical value for Emax and ED_{50} for SiDBP was 6.29% reduction from baseline and 39 mg, respectively. The standard error of the estimates were low for both Emax and ED_{50} (8% and 14%, respectively). However, the inter-individual variability for both Emax and ED_{50} were high, 105% and 404%, respectively. In the placebo group, SiDBP increased with time at a rate of 0.0095 mmHg/Day. The standard deviation of the residual variability was 5 mmHg.

The results of the covariate analysis indicated that age, body weight and sex did not have an effect on SiDBP baseline. Covariate analysis also indicated that the Emax between males and females were similar. The runs assessing the effect of body weight and age on SiDBP Emax terminated at an objective function value of 50380.



As is evident from the above figure, the Emax dose-response for SiDBP indicates a shallow decrease in SiDBP with increasing doses with minimal differences in SiDBP lowering effect above the ED_{50} of 39 mg. Therefore, a 100 mg dose would yield a reduction in SiDBP of 4.5% of baseline and a 200 mg dose would yield a reduction in SiDBP of 5.3% of baseline. None of the covariates tested (? ? ?) showed statistically significant influence on the model parameters. Graphical display showed no clear trends between the covariates and the individual parameter estimates.

Representative blood pressure plots of individuals with population prediction and individual prediction are presented in the following figure.



Trough Sitting Systolic Blood Pressure (SiSBP):

Modeling of eplerenone dose versus SiSBP indicated that eplerenone had a significant effect on blood pressure. The objective function values associated with the different models tested is listed in the following table.

#	MODEL FOR TROUGH SITTING SBP	OBJ FUNC	Δ OBJ FUNC	SIG
1	Null Model	66407.813		
2	Placebo Model	64225.687	-2182.126	**
3	Linear Model	63356.215	-869.472	**
4	Log-linear Model	63139.936	-1085.751	**
5	EMAX Model	63140.220	-1085.467	**
6	EMAX Model – test for BID and QD	63136.203	-4.017	NS
7	Step Function	63145.480	-1080.207	**
8	Emax Model – effect of sex on baseline SiSBP	63134.924	-5.296	NS
9	Emax Model – effect of sex on Emax SiSBP	63137.446	-2.774	NS
10	Emax Model – effect of Age on baseline SiSBP	63047.635	-92.585	**

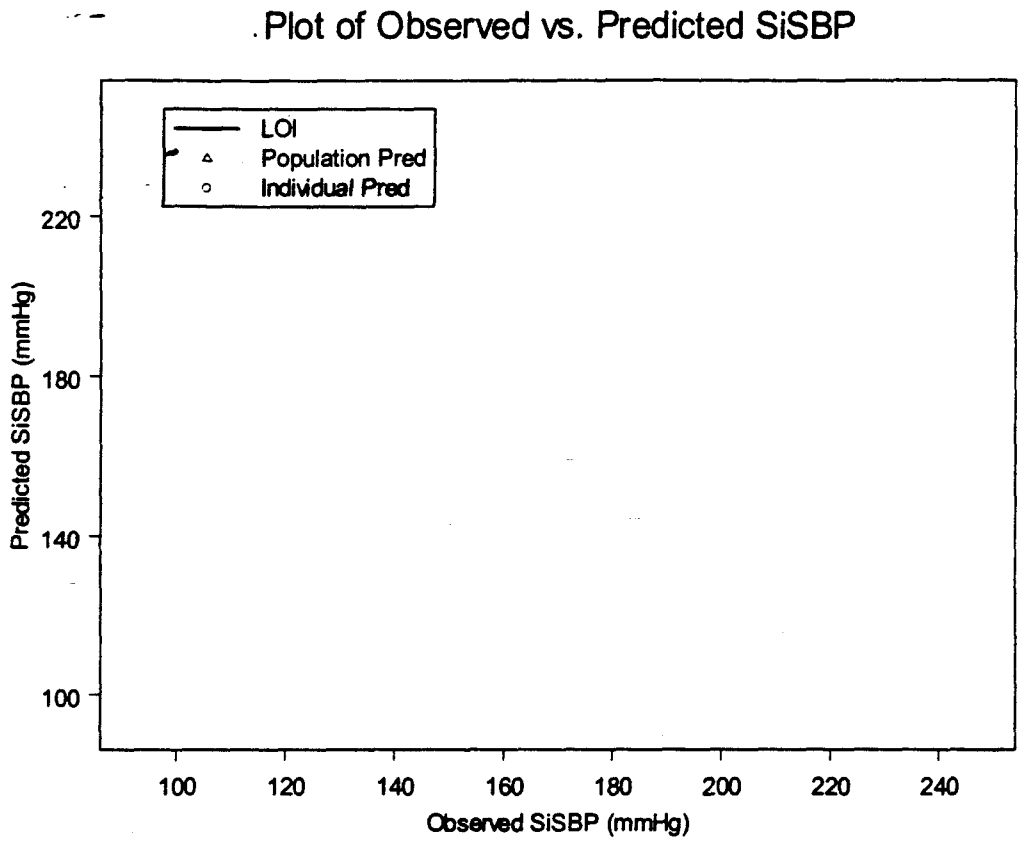
**Significance defined a priori at p = 0.01 (ΔELS=6.63)

Comparison of models indicated that the log-linear model and the Emax model best described the data compared to the linear pharmacodynamic model or step function model (effect in the absence or presence of drug). The objective function values of the log-linear model and the Emax model were similar, indicating that both models characterize dose-SiSBP relationship equally well. The key difference between the models are that with the Emax model the reduction in SiSBP plateaus after the ED_{50} while in the log-linear model reduction in SiSBP continues to increase with log of dose, without a plateau.

The reviewer chose the Emax model to describe SiSBP data based on the fact that the Emax model best described SiDBP compared to the log-linear model. It is inconceivable to have the Emax model describe reduction in SiDBP with a plateau in effect, while SiSBP reduction continues with increasing doses of eplerenone.

Analysis of the effect of covariates, age, body weight and sex on baseline SiSBP and Emax indicated that age had a significant influence on baseline SiSBP. Baseline SiSBP increased with an exponent of 0.135/year. The typical value of baseline SiSBP in a 45 year old adult was 148 mmHg. Covariate sex did not have an effect on either baseline SiSBP or Emax. NONMEM runs of body weight on baseline SiSBP and Emax and age on Emax terminated with objective function values higher than the base Emax model.

The following figure is a plot of observed SiSBP versus Emax model (+age effect on baseline SiSBP) predicted SiSBP.



The parameter estimates obtained with the Emax model with covariate age influence on baseline SiSBP with inter-individual variability is listed below. (Standard error of the estimates were not estimable).

FINAL MODEL FOR SITTING SYSTOLIC BLOOD PRESSURE MODEL WITH EFFECT OF AGE ON BASELINE SiSBP

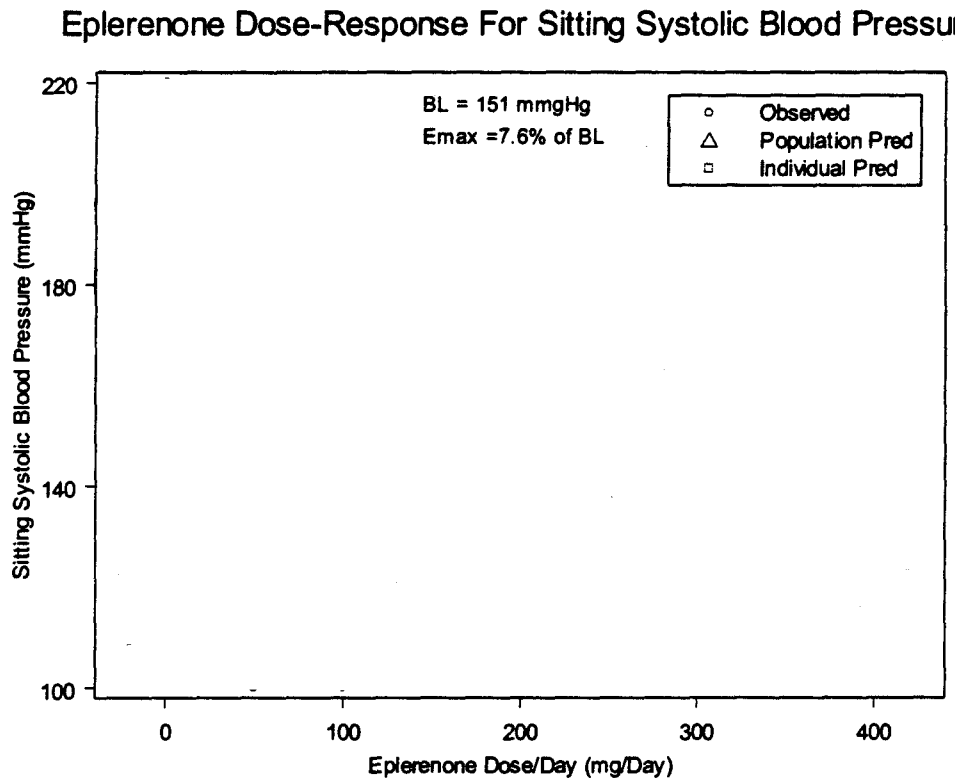
FAGE = AGE/45 Years
BASE LINE =TBL*EXP(ETA_BL)*FAGE**(EXPONENT)
EMAX =TEMAX + ETA_EMAX
ED50 =TED50*EXP(ETA_ED50)
PLACEBO =TPL + ETA_PL
EFFECT = BASE LINE*(1+(EMAX*DOSE/ED50+DOSE)) + PLACEBO*RDAY

Parameter	Typical Value	Interindiv Variability
Baseline (mmHg)	148	0.496%
Emax (% of Baseline)	-0.0762	90.8%
ED_{50} (mg)	27.5	39%
Placebo Slope (mmHg/RDAY)	0.0325	488%

Effect of Age (mmHg/year)	0.135	
Residual Variability (Additive)		
σ standard deviation (mmHg)	8.148	

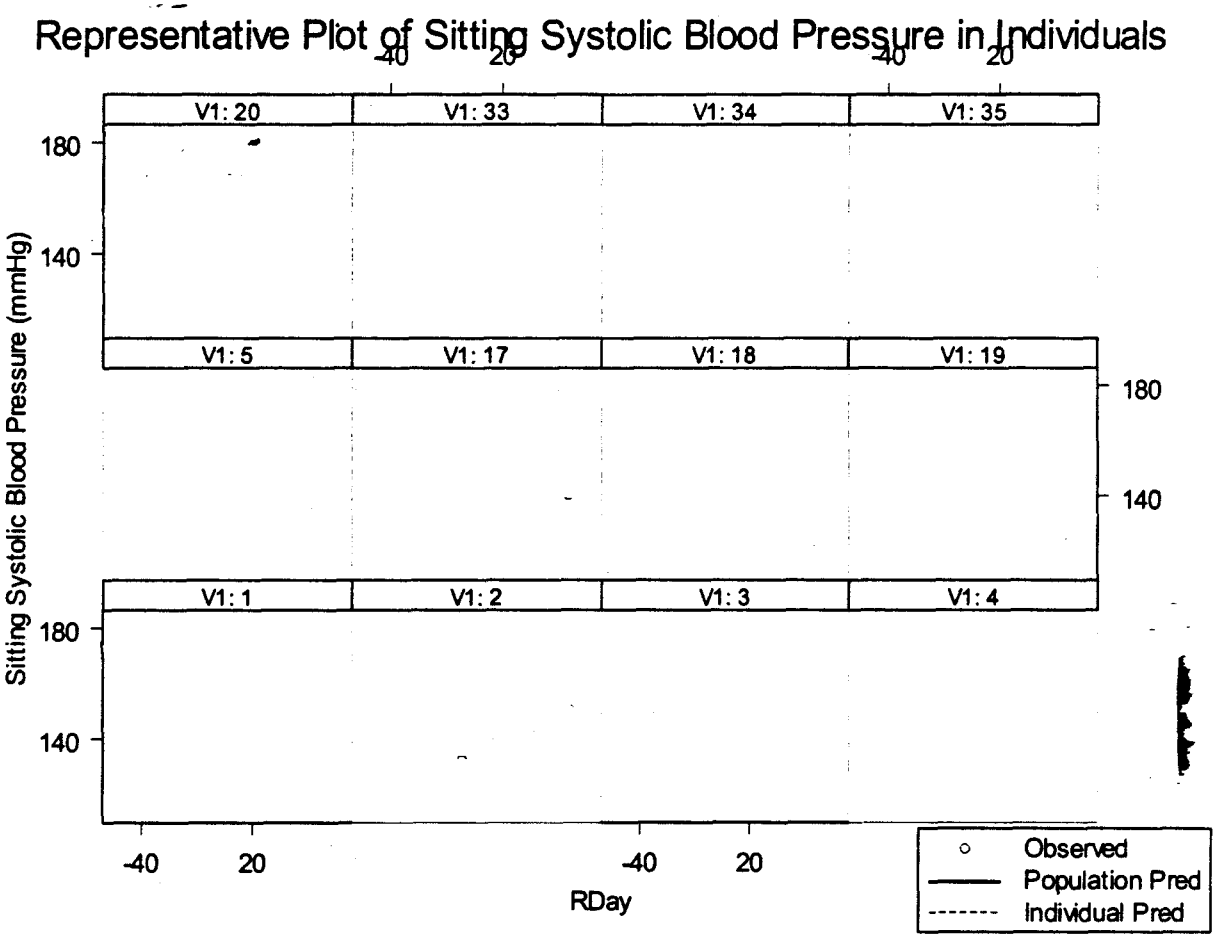
**Significance defined a priori at p = 0.01 (ΔELS=6.63)

The typical value of SiSBP baseline in a 45 year old individual is 148 mmHg. The typical value for Emax and ED_{50} for SiDBP was 7.62% reduction from baseline and 28 mg, respectively. However, the inter-individual variability for both Emax and ED_{50} were high, 91% and 488%, respectively. In the placebo group, SiDBP increased with time at a rate of 0.0325 mmHg/Day. The standard deviated of the residual variability was 8 mmHg.



The Emax dose-response for SiDBP indicates a shallow decrease in SiSBP with increasing doses, with minimal differences in SiSBP lowering effect above the ED_{50} of 27 mg. Therefore, a 100 mg dose would yield a reduction in SiSBP of 6% of baseline and a 200 mg dose would yield a reduction in SiSBP of 6.7% of baseline.

Representative blood pressure plots of individuals with population prediction and individual prediction are presented in the following figure.



EFFECT OF EPLERENONE ON THYROID STIMULATING HORMONE (TSH) CONCENTRATIONS:

A plot of the eplerenone dose versus TSH concentrations does not indicate any monotonous pattern of increase or decrease in TSH concentrations with increasing eplerenone dose as is evident in the following plot.

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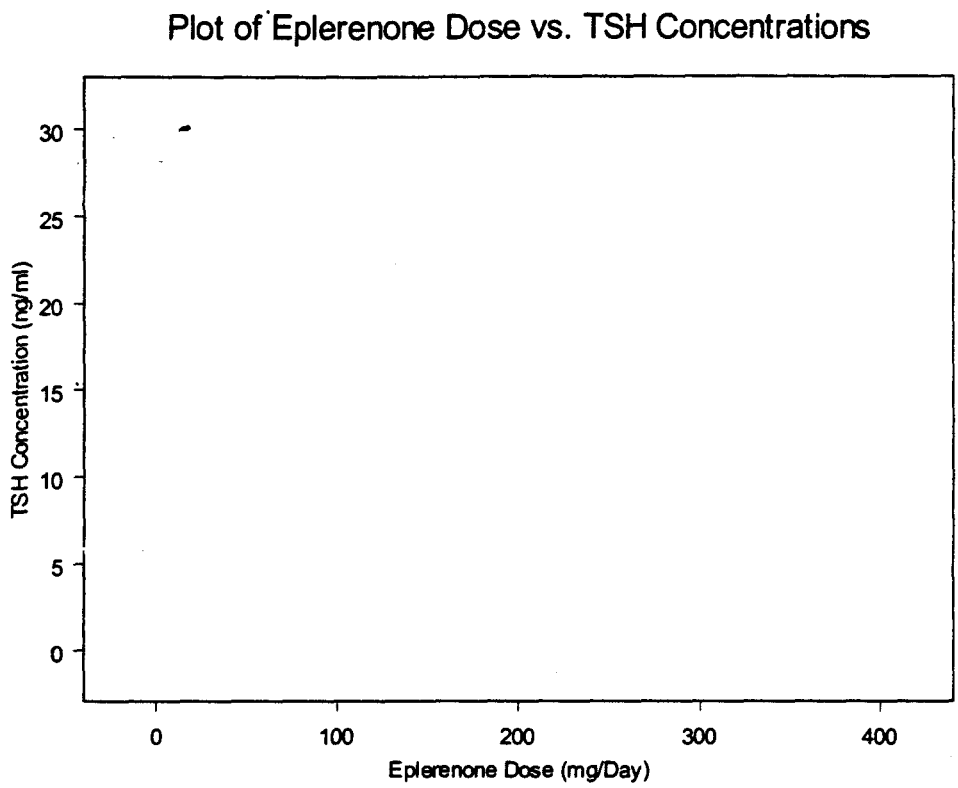

Modeling of dose-TSH relationship yielded poor population predictions. Therefore, modeling of eplerenone dose and TSH concentrations was abandoned. From the plot, it appears that TSH concentrations in the placebo group bracket the TSH concentrations in all groups of eplerenone and there is an absence of a clear trend in effect. The TSH concentrations in clinical studies –010 and 049 were monitored over 8 to 12 weeks only. It is possible that a clearer trend in effect on TSH concentrations might be more evident with a longer monitoring period.

CONCLUSIONS:

The Emax model best described eplerenone dose and SiDBP and SiSBP data of clinical studies-010 and 049. The typical values of SiDBP baseline, Emax and ED_{50} were 98.7 mmHg, 6.29% reduction from baseline and 39 mg, respectively. A 100 mg dose would yield a reduction in SiDBP of 4.5% of baseline and a 200 mg dose would yield a reduction in SiDBP of 5.3% of baseline. In the placebo group, SiDBP increased with time at a rate of 0.0095 mmHg/Day.

The typical values of SiSBP baseline (in a 45 year old), Emax and ED_{50} were 148 mmHg, 7.62% reduction from baseline and 28 mg, respectively. Similar to SiDBP the dose-response for SiSBP indicates a shallow decrease in SiSBP with increasing doses, with minimal differences in SiSBP lowering effect above the ED_{50} of 28 mg. Therefore, a 100

mg dose would yield a reduction in SiSBP of 6% of baseline and a 200 mg dose would yield a reduction in SiSBP of 6.7% of baseline. In the placebo group, SiDBP increased with time at a rate of 0.0325 mmHg/Day.

Based on the ED50 estimate (about 40 mg for SiDBP) the proposed dosing regimen with a starting dose of 50 mg seemed reasonable.

The effect of eplerenone dose on TSH concentrations was not modeled because of lack of obvious trend between eplerenone dose and TSH concentration. It is not clear if eplerenone has an effect on TSH concentrations.

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/s/

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Jogarao Gobburu
8/23/02 08:55:18 AM
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