DOUBLE-BLIND, PLACEBO-CONTROLLED, SINGLE DOSE SAFETY AND PHARMACOKINETIC STUDY OF ORAL SC-66110 (EPLERENONE) IN HEALTHY MALE SUBJECTS

STUDY INVESTIGATORS AND SITES:

[redacted]

Protocol No.: EE3-96-02-001

OBJECTIVES:

1. To determine the safety of single, oral doses of eplerenone administered to healthy male subjects.
2. To describe the single dose pharmacokinetic profile of eplerenone.
3. To measure the anti-aldosterone activity of eplerenone in terms of its effect on urinary excretion of Na and K compared to placebo and spironolactone following administration of the orally active mineralocorticoid fludrocortisone.

FORMULATIONS:

Eplerenone – 10, 25, 100, and 200 mg capsules prepared, packaged, and labeled by Searle (Skokie, IL).
Placebo – matching eplerenone by Searle
Spironolactone – 25 mg tablets by Searle Canada (Oakville, Ontario).
Placebo – matching spironolactone tablets by Searle Canada
Fludrocortisone - Florinef®, Squibb BV; Batch No. 95G04; expiry date 31 May 1997
were obtained by [redacted]

STUDY DESIGN:

This was a single center, randomized, double-blind, placebo-controlled, safety and pharmacokinetic study of orally administered single dose eplerenone in 57 healthy male subjects. There were seven parallel dose groups with eight healthy male subjects in each dose group: five of the dose groups received single oral doses of 10, 50, 100, 300, or 1000 mg eplerenone, one dose group received 50 mg of spironolactone, and one dose group received placebo. A total of 57 male subjects (age range:19-49 years) enrolled, 55 (96%) were Caucasian, 1 (2%) was Black, and 1 (2%) was Asian. Of the 57 subjects, 9 were in the eplerenone 300 mg group, and 8 in each of the other six groups. Eplerenone was administered in the morning after a 10-hour overnight fast. All subjects received a 0.5 mg dose of fludrocortisone at the time of study drug administration (0 hour); 0.1 mg

fludrocortisone doses at 2, 4, 6, 8, 10, 12, and 14 hours after study drug administration; and a 0.5 mg fludrocortisone dose 16 hours after study drug administration.

ASSAY:

[redacted]

NP=not provided

Sample Collection

For all subjects, blood samples were obtained 15 minutes prior to study medication administration and 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24, 28, 32, 48, 72, and 96 hours post dose A subset of plasma samples was also assayed for testosterone and aldosterone levels.

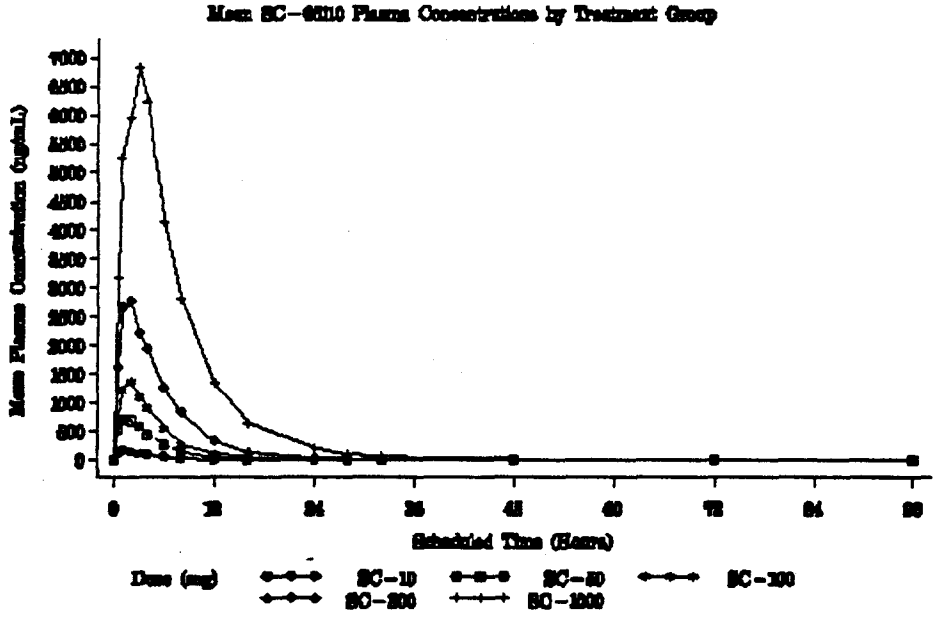
During study participation, urine from each subject was collected for the following periods: predose: -9 to 0 hours, postdose: 0 - 2 hours, 2 - 4 hours, 4 - 6 hours, 6 - 8 hours, 8 - 10 hours, 10 - 12 hours, 12 - 14 hours, 14 - 16 hours, 16 - 24 hours.

RESULTS:

The pharmacokinetic parameters of eplerenone obtained following single dose administration of 10 mg, 50 mg, 100 mg, 300 mg and 1000 mg in a capsule dosage form orally in healthy males are listed in the following table.

Table 2: Mean (SD) Pharmacokinetic Parameters of Eplerenone

Eplerenone Parameter	Parameter Value for Each Eplerenone Dose (mean ± SD)				
	10 mg	**50 mg**	**100 mg**	**300 mg**	**1000 mg**
AUC0-96 (ng.hr/mL)	942 ± 494	4017 ± 1440	7943 ± 1878	18451 ± 5483	56435 ± 12840
Cmax (ng/mL)	191 ± 59.2	797 ± 230	1505 ± 221	2968 ± 639	7261 ± 1200
Tmax (hr)	1.3 ± 1.13	1.4 ± 0.83	1.5 ± 0.89	1.5 ± 0.54	2.5 ± 0.92
T1/2 (hr)	2.1 ± 0.69	2.9 ± 1.37	4.9 ± 2.08	3.7 ± 1.38	15.1 ± 8.12
MRT (hr)	3.9 ± 1.60	4.2 ± 1.13	4.9 ± 0.92	5.5 ± 0.86	7.0 ± 1.27
Oral Clearance (L/h)	13.3 ± 6.53	13.7 ± 4.04	13.1 ± 2.27	17.6 ± 5.18	18.4 ± 3.62



Following single dose administration of 10 mg to 1000 mg eplerenone, eplerenone pharmacokinetics was not dose-proportional. Both Cmax and AUC of eplerenone

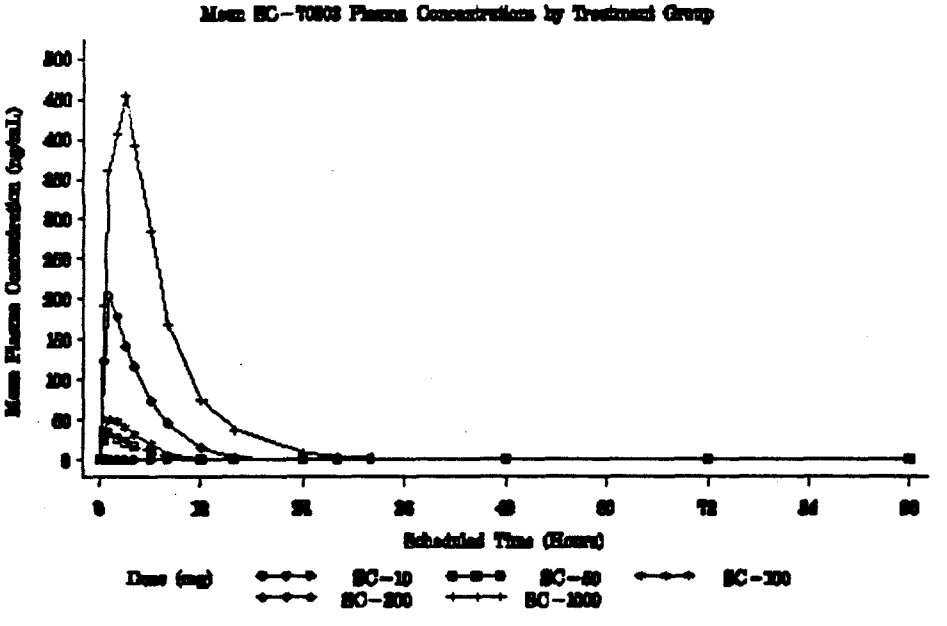
increased less than dose proportionally with increasing dose. The deviation from dose proportionality was not very marked. The decrease in Cmax especially at the highest dose and the 1 hour increase in Tmax indicate solubility/absorption as the reason for the decreased Cmax and AUC. The apparent oral clearance of eplerenone ranged between 13 L/h and 18 L/h. Mean Tmax and $T_{1/2}$ were 1.3-1.5 hr and 2-5 hr, respectively, in the 10-300 mg dose range; and 2.5 hr and 15.1 hr, respectively, for the 1000 mg dose, the increasing $T_{1/2}$ with dose is probably an artifact of better characterization of the terminal phase with the highest dose of 1000 mg compared to the lower doses of 10 to 300 mg. Over the entire 24 hours postdose period, total urinary excretion of eplerenone was 0.8%-1.7% of administered dose.

The pharmacokinetic parameter values for SC-70303 are listed below:

Table 3: Mean ±SD Pharmacokinetic Parameters of SC-70303

SC-70303 Parameter	Parameter Value for Each Eplerenone Dose (mean ± SD)				
	10 mg	50 mg	100 mg	300 mg	1000 mg
AUC0-96 (ng.hr/mL)	*	143 ± 99.5	247 ± 77.4	1065 ± 263	3484 ± 1894
Cmax (ng/mL)	*	36.4 ± 20.1	60.4 ± 15.1	212 ± 61.4	522 ± 196
Tmax (hr)	*	1.0 ± 0.46	1.1 ± 0.63	1.3 ± 0.46	2.5 ± 0.92
T1/2 (hr)	*	2.7 ± 1.07	2.7 ± 0.72	2.8 ± 0.53	2.6 ± 0.69
MRT (hr)	*	2.8 ± 0.91	3.3 ± 0.57	4.2 ± 0.81	5.7 ± 1.13
Oral Clearance (L/h)	*	491 ± 277	445 ± 154	300 ± 86.0	331 ± 95.3

* Not computed because most concentrations were below the assay detection limit

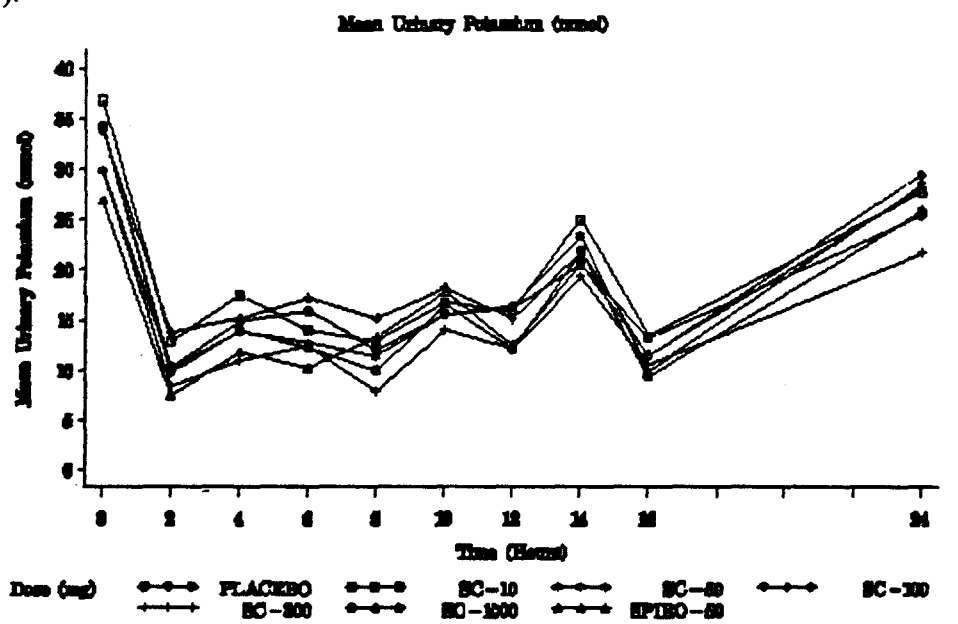


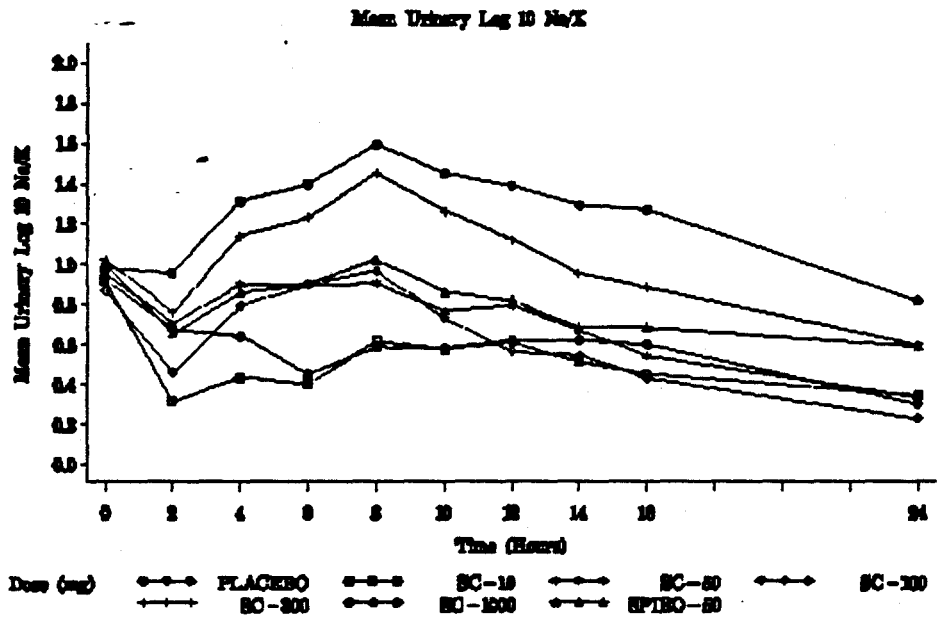
The concentrations of SC-70303, the inactive, open lactone ring form of eplerenone, were about 5% to 7% of eplerenone concentrations. The closed-ring form (SC-66110) and the open-ring form (SC-70303) are in chemical equilibrium: eplerenone is converted to SC-70303 under basic conditions, while SC-70303 is converted to eplerenone under acidic conditions. SC-70303 AUC was dose proportional over the range of 10 mg to 1000 mg however, Cmax of SC-70303 increased less than dose proportionally with increasing dose. The pharmacokinetic parameters of SC-70303 following the 10 mg dose were not calculable because of low concentrations. mean Tmax and $T_{1/2}$ were 1.0-1.3 hr and 2.7-2.8 hr, respectively, in the 50-300 mg eplerenone dose range; and 2.5 hr and 2.6 hr, respectively, for the 1000 mg dose. The largest amounts of eplerenone and SC-70303 were excreted in 2-4 hours postdose urine.

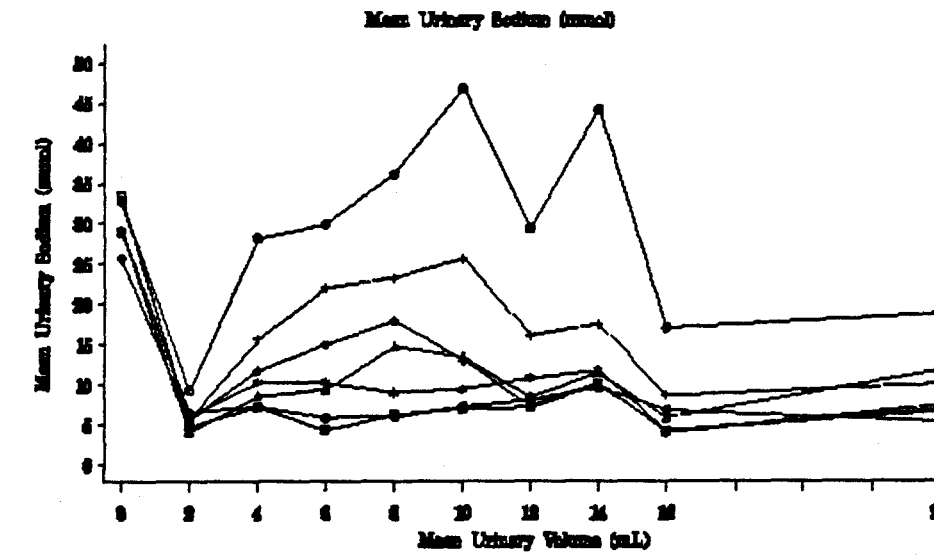
PHARMACODYNAMICS:

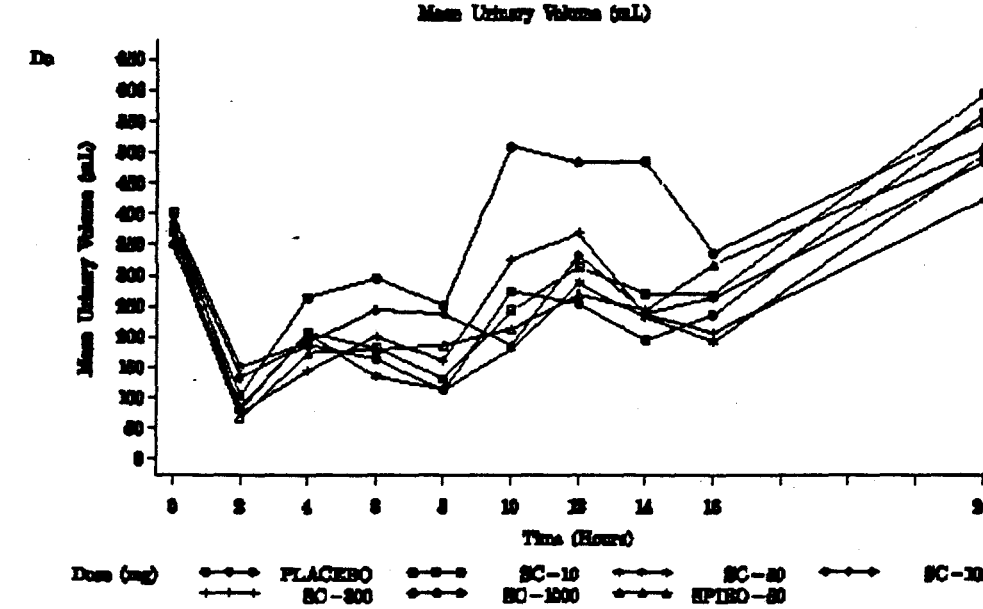
The synthetic mineralocorticoid fludrocortisone administered to healthy subjects decreases urinary sodium excretion and usually increases urinary potassium excretion resulting in a decrease of the urine Na:K ratio. Fludrocortisone mimics the activity of aldosterone. Aldosterone antagonists reverse the fludrocortisone-induced urinary electrolyte changes. Therefore, the antialdosterone activity of eplerenone can be determined by the degree to which it reverses fludrocortisone-induced changes.

A dose related increase in anti-aldosterone activity based upon fludrocortisone-induced changes in urinary sodium and potassium excretion measurements was observed with increasing doses of eplerenone. Urinary sodium excretion and the urine Na/K ratio increased with doses of eplerenone. Urinary log(10 Na/K) was significantly increased 4-8 hours after the 50 and 100 mg doses of eplerenone, 2-14 hours after the 300 mg dose, and 2-24 hours after the 1000 mg dose. Eplerenone appeared to be slightly less potent than spironolactone (relative potency 0.67); however, the confidence interval contained unity (0.45, 1.04).




Mean Urinary Log 10 Na/K
Mean Urinary Log 10 Na/K
Time (Hours)
Dose (mg)
PLACEBO
SC-10
SC-50
SC-100
SC-300
SC-1000
SPIRO-50


Mean Urinary Sodium (mmol)
Mean Urinary Sodium (mmol)
Mean Urinary Volume (mL)


Mean Urinary Volume (mL)
Time (Hours)
Dose (mg)
PLACEBO
SC-10
SC-50
SC-100
SC-300
SC-1000
SPIRO-50

Effect of Single Rising Doses of Eplerenone on ECG Parameters

No subject had a QTc interval greater than 500 msec with eplerenone. Mean change from Baseline between 30 msec and 60 msec in QTc intervals was observed in one subject while on eplerenone 10 mg and one subject while on eplerenone 50 mg group (calculated using Fridericia's correction). No significant changes in any ECG parameters were noted with increasing single oral doses of eplerenone.

Table 4: Mean (±SEM) Change From Baseline in ECG Parameters

Parameter	Placebo	Eplerenone					Spironolactone
		10 mg	50 mg	100 mg	300 mg	1000 mg	50 mg
	N = 8	N = 8	N = 8	N = 8	N = 9	N = 8	N = 8
HR (bpm)	-1.79 ± 2.23	-5.96 ± 0.65[bc]	0.71 ± 1.50	1.33 ± 1.33	-2.04 ± 2.54	0.25 ± 2.35	-6.04 3.50
PR (msec)	-9.46 ± 4.29	-0.4 ± 2.54	4.29 ± 5.30	-4.33 ± 3.14	-1.22 ± 3.79	0.75 ± 2.46	-4.00 ± 5.81
QRS (msec)	4.00 ± 2.05	0.71± 2.14	-0.79 ± 1.62	-0.17 ± 2.02	0.67 ± 0.98	0.08 ± 1.68	3.21 ± 1.91
QT (msec)	-3.96 ± 7.84	9.54 ±3.03 [b]	-2.17 ± 7.36	-14.25 ± 6.57	-3.11 ± 5.22	-7.62 ± 5.94	-6.17 ± 5.27
QTc[c] (msec)	-8.13 ± 2.53 [b]	-3.12 ± 3.74	-0.37 ± 4.34	-10.79 ± 5.24 [b]	-7.07 ± 3.29	-7.13 ± 2.48c	-17.88 ± 6.54 [b]
QTc[d] (msec)	-10.04 ± 2.00[b]	-8.83 ± 4.25	0.88 ± 3.46	-9.08 ± 5.15	-8.63 ± 4.65	-7.04 ± 3.04	-23.71 ± 9.21 [b]
MaxQTc[c](msec)[a]	1.38 ± 3.40	10.63 ± 6.42	6.63 ± 5.89	-2.13 ± 5.54	-0.33 ± 4.11	-0.25 ± 2.93	-12.75 ± 5.96
MaxQTc[d](msec)[a]	2.63 ± 2.04	5.88 ± 5.68	10.00 ± 5.11	0.25 ± 5.68	-0.22 ± 5.84	4.00 ± 4.04	-14.38 ± 9.1[illegible]

a –indicates statistically significant difference in mean change from Baseline across treatments
b- indicates statistically significant change from Baseline, p <0.05
c – calculated using Fridericia's formula
d – calculated using Bazett's formula
Max=mean maximum change from baseline

CONCLUSIONS:

Following single dose administration of 10 mg to 1000 mg eplerenone, eplerenone pharmacokinetics was not dose-proportional. Both Cmax and AUC of eplerenone increased less than dose proportionally with increasing dose. The deviation from dose proportionality was not very marked. The decrease in Cmax especially at the highest dose and the 1 hour increase in Tmax indicate solubility/absorption as the reason for the decreased Cmax and AUC. The apparent oral clearance of eplerenone ranged between 13 L/h and 18 L/h. Mean Tmax and $T_{1/2}$ were 1.3-1.5 hr and 2-5 hr, respectively, in the 10-300 mg dose range; and 2.5 hr and 15.1 hr, respectively, for the 1000 mg dose, the increasing T1/2 with dose is probably an artifact of better characterization of the terminal phase with the highest dose of 1000 mg compared to the lower doses of 10 to 300 mg. Over the entire 24 hours postdose period, total urinary excretion of eplerenone was 0.8%-1.7% of administered dose.

The concentrations of SC-70303, the inactive, open lactone ring form of eplerenone, were about 5% to 7% of eplerenone concentrations. SC-70303 AUC was dose proportional over the range of 10 mg to 1000 mg however, Cmax of SC-70303 increased less than dose proportionally with increasing dose. Mean Tmax and $T_{1/2}$ were 1.0-1.3 hr and 2.7-2.8 hr, respectively, in the 50-300 mg eplerenone dose range; and 2.5 hr and 2.6 hr, respectively, for the 1000 mg dose.

A dose related increase in anti-aldosterone activity based upon fludrocortisone-induced changes in urinary sodium and potassium excretion measurements was observed with increasing doses of eplerenone. Eplerenone appeared to be slightly less potent than spironolactone (relative potency 0.67); however, the confidence interval contained unity (0.45, 1.04).

Except in one subject where QTc change from baseline ranged between 10 msec to 60 msec while on eplerenone 10 mg and one subject while on eplerenone 50 mg group, there were no significant changes in ECG parameters with single rising doses of 10 mg to 1000 mg eplerenone.

EPLERENONE MULTIPLE ORAL DOSE TOLERABILITY AND PHARMACOKINETIC STUDY

STUDY INVESTIGATORS AND SITES:

Protocol No.: EE3-96-02-004

OBJECTIVES:

1. To describe the pharmacokinetic (PK) profile of eplerenone following both single and multiple doses (once a day for 11 days) of eplerenone administered orally at doses of 100, 300, and 1000 mg.
2. To evaluate the renal and hormonal effects of eplerenone after single and multiple doses.
3. To compare the pharmacokinetics, renal, and hormonal effects of eplerenone with 100 mg dose of spironolactone, and of placebo.
4. To measure the antialdosterone activity of eplerenone at steady-state plasma concentrations by assessing its effects on urinary excretion of sodium and potassium following oral administration of the mineralocorticoid, fludrocortisone.

FORMULATIONS:

Eplerenone – 100 mg and 200 mg capsules by Searle (Skokie, IL).
Placebo – matching eplerenone by Searle
Spironolactone – 25 mg tablets by Searle Canada (Oakville, Ontario).
Placebo – matching spironolactone tablets by Searle Canada
Fludrocortisone - Florinef®, ER Squibb; Batch # PL 0034/5027R; expiry date March 1999).

STUDY DESIGN:

This study was a single-center, double-blind, randomized, placebo-controlled, rising oral dose, sequential panel study. A total of 40 male subjects were enrolled into the study: eight in each of the five treatment groups (100, 300, and 1000 mg eplerenone, 100 mg spironolactone, and placebo). On Days 1 and 3-13, each subject received either eplerenone (100 mg, 300 mg, or 1000 mg), 100 mg spironolactone, or placebo. Study medication was administered following an overnight fast on Days 1, 11, and 13. All subjects were male (by design) and ranged in age from 19-64 years with the mean age ranging between 26 and 37 years across treatment groups. Of the 40 enrolled subjects, 38 (95%) were Caucasian, one (2.5%) was Asian, and one (2.5%) was of other race (French/Persian). Mean weight ranged between 73 and 79 Kg.

ASSAY:

Sample Collection

Blood samples for measurement of plasma concentrations of eplerenone closed-ring form (SC-66110) and the open-ring form (SC-70303), spironolactone, and its active metabolites: SC-9376 (canrenone), SC-26519 (7α-thiomethylspironolactone), and SC-26962 (6β-hydroxy-7α-thiomethylspironolactone) were collected at the following times.

Day 1	Prior to dosing and 0.5, 1, 2, 3, 4, 6, 8, 12, and 16 hours after dosing
Day 2	24, 28, 32, and 36 hours after Day 1 dosing
Day 3	Prior to dosing (48 hours after Day 1 dosing)
Days 4-10	Prior to dosing each day
Day 11	Prior to dosing and 0.5, 1, 2, 3, 4, 6, 8, 12, and 16 hours after dosing
Day 12	24 hours after Day 11 dosing

Urine was collected from each subject during the following time intervals:

Day -2 to Day 10	Each 24-hour interval (except as noted otherwise below) including the 24-hour predose collections begun on Day 0 and Day 10
Days 1-2	0-2, 2-4, 4-6, 6-8, 8-12, and 12-24 hours after dosing
Days 11-12	0-2, 2-4, 4-6, 6-8, 8-12, and 12-24 hours after dosing
Days 13-14	-9 to 0 (predose), 0-2, 2-4, 4-6, 6-8, 8-10, 10-12, 12-14, 14-16, and 16-24 hours after dosing

The urine samples collected at the above specified times were analyzed as follows:

Day -1 to Day 11	- Na, K, creatinine, except as noted otherwise below
Days 1-2 and Days 11-12	- Eplerenone and SC-70303, or spironolactone and its metabolites - Renal parameters - Na, K, Mg, Cl, uric acid, creatinine, Na excretion rate, Na:K ratio

- Hormones - aldosterone (predose only
Days 13-14 - - Na, K, Na:K ratio, Na excretion rate

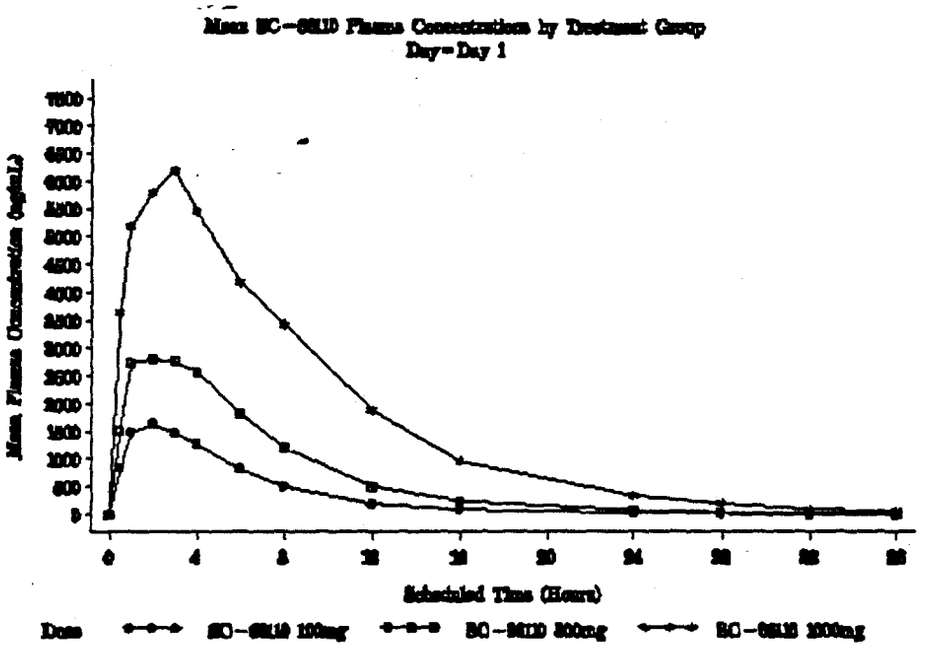
RESULTS

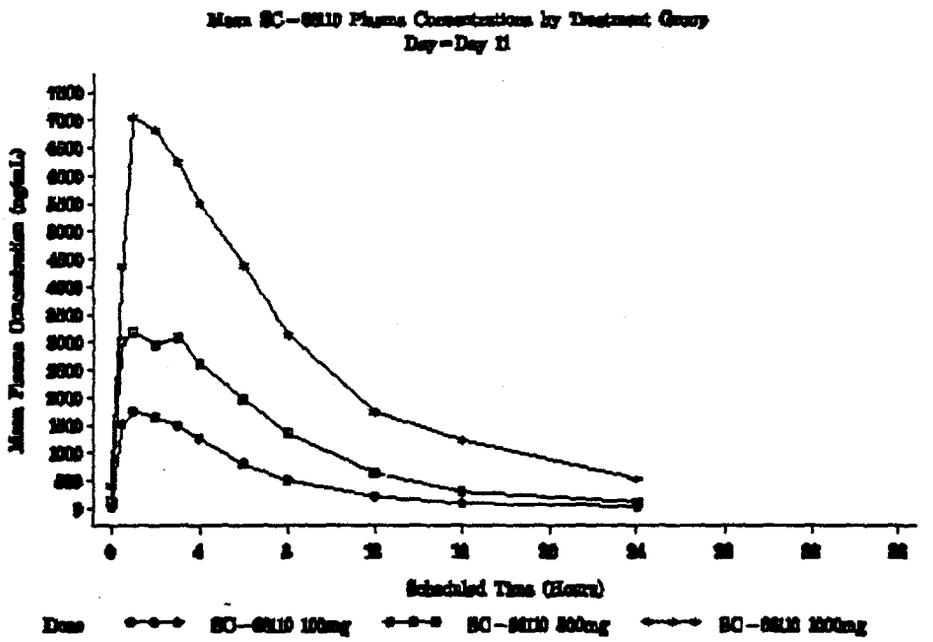
The pharmacokinetic parameters of eplerenone obtained after the first dose and at steady-state following 100, 300 and 1000 mg eplerenone orally in healthy males are listed in the following table.

Table 2: Arithmetic Mean (± Std Dev) Eplerenone and SC-70303 Pharmacokinetic Parameters

Eplerenone Dose/ Parameter	Eplerenone		SC-70303	
	Single-Dose	Steady-state	Single-Dose	Steady-state
100 mg				
AUC (ng*hr/mL)	11349 ± 2625	11772 ± 3209	562 ± 197	608 ± 292
Cmax (ng/mL)	1747 ± 212	1904 ± 262	98.9 ± 27.7	118 ± 45.7
Tmax (hr)	1.8 ± 0.70	1.1 ± 0.92	1.7 ± 0.80	0.7 ± 0.26
T1/2 (hr)	3.9 ± 0.75	4.0 ± 0.96	3.5 ± 0.87	3.3 ± 0.67
MRT (hr)b	5.5 ± 0.80	5.0 ± 0.84	5.7 ± 1.17	4.2 ± 0.55
CL/F (L/hr)	9.3 ± 2.32	9.1 ± 2.70	NA	NA
300 mg				
AUC (ng*hr/mL)	23890 ± 7931	26514 ± 10389	1691 ± 579	2017 ± 943
Cmax (ng/mL)	3227 ± 715	3582 ± 977	267 ± 69.4	334 ± 98.1
Tmax (hr)	2.4 ± 1.19	1.8 ± 1.13	1.8 ± 1.19	1.3 ± 0.92
T1/2 hr	4.6 ± 1.59	4.6 ± 0.53	3.0 ± 0.70	3.5 ± 0.97
MRT (hr)	6.1 ± 1.59	5.6 ± 1.19	5.4 ± 1.40	4.9 ± 1.23
CL/F (L/hr)	14.2 ± 6.11	14.0 ± 8.27	NA	NA
1000 mg				
AUC (ng*hr/mL)a	62053 ± 11733	63249 ± 7734	5420 ± 2629	5786 ± 2531
Cmax (ng/mL)	6885 ± 910	7394 ± 1528	717 ± 261	761 ± 270
Tmax(hr)	2.0 ± 1.28	1.4 ± 0.62	1.7 ± 0.96	1.3 ± 0.60
T1/2 (hr)	8.7 ± 4.20	6.2 ± 2.62	3.7 ± 0.62	4.8 ± 1.87
MRT (hr)	8.1 ± 1.26	7.1 ± 0.89	6.7 ± 1.24	6.3 ± 0.85
CL/F (L/hr)	16.6 ± 3.13	16.0 ± 1.91	NA	NA

Mean AUC and Cmax values for eplerenone increased with increasing doses following single and multiple dose administration, but these increases were not dose-proportional. AUC and Cmax at higher doses increased less than dose proportionally with increasing doses of eplerenone. Following once-a-day dosing mean Cmax values were slightly higher at steady-state and Tmax occurred 0.5 hours earlier than those observed after single dose administration. Mean steady state AUC values were slightly higher than the respective single dose values indicating slight accumulation of both eplerenone and SC-70303. Mean $T_{1/2}$ values ranged between 5 and 8 hours and were similar following both single and multiple dose administration. Cmin values on Day 11 were approximately dose-proportionate. Analyses of AUC values suggested a lack of dose proportionality for eplerenone at the doses tested for both single and multiple dose administration.


Mean SC-8810 Plasma Concentrations by Treatment Group
Day=Day 1
Mean Plasma Concentration (ng/mL)
Scheduled Time (Hours)
Dose
SC-8810 100mg
SC-8810 300mg
SC-8810 1000mg


Mean SC-8810 Plasma Concentrations by Treatment Group
Day=Day 11
Mean Plasma Concentration (ng/mL)
Scheduled Time (Hours)
Dose
SC-8810 100mg
SC-8810 300mg
SC-8810 1000mg

The concentrations of SC-70303, the inactive, open lactone ring form of eplerenone, were about 5% to 10% of eplerenone concentrations. The Tmax of SC-70303 occurred around 1 to 2 hours after eplerenone administration. Unlike eplerenone, AUC of SC-70303 did not exhibit any deviation from dose-proportionality.

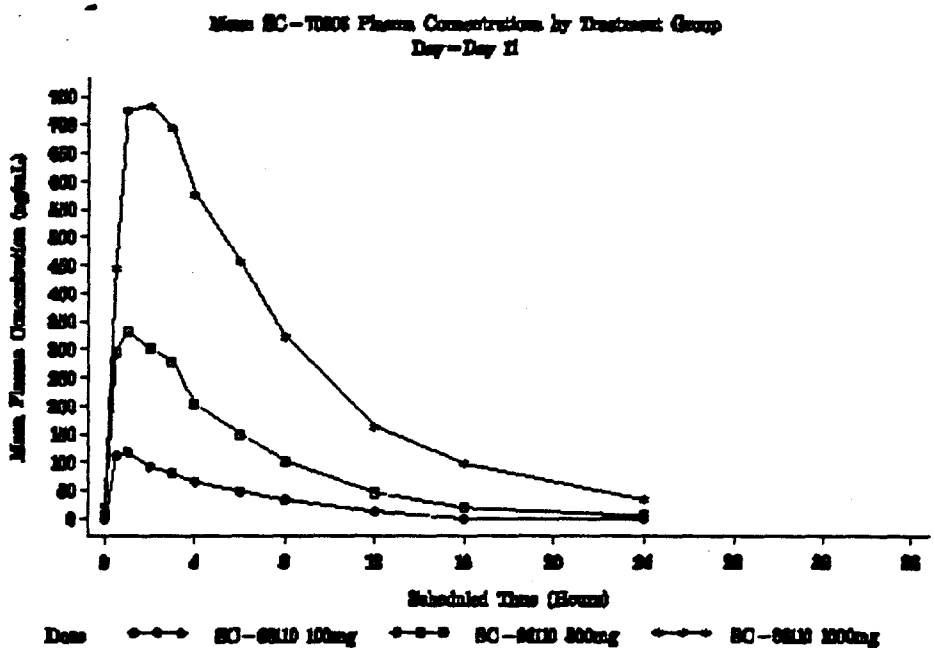


Table 3: Mean (Std Dev) Dose-Adjusted Eplerenone and SC-70303 AUC

Eplerenone Dose	Eplerenone AUC		SC-70303 AUC	
	Single-Dose	Multiple-Dose	Single-Dose	Multiple-Dose
100 mg	113.5 ± 26.25	117.7 ± 32.09	5.6 ± 1.97	6.1 ± 2.92
300 mg	79.6 ± 26.44	88.4 ± 34.63	5.6 ± 1.93	6.7 ± 3.14
1000 mg	62.1 ± 11.73	63.2 ± 7.73	5.4 ± 2.63	5.8 ± 2.53
p-value[b]	0.0007	0.0016	0.8392	0.7099

a) Dose-adjusted AUC is AUC divided by dose (AUC_{0-inf} for SD; AUC_{0-24} for MD)
b) p-value is for group comparison from ANCOVA model (factor: group; covariate: weight) of dose-adjusted AUC. P-value <0.05 suggests lack of dose proportionality.

Ratios of the geometric mean AUC values for multiple (over the dosing interval of 24 hours:single dose (AUCinf) indicate the absence of time-related nonlinearity in eplerenone and SC-70303 pharmacokinetics. There was no evidence for dose-dependent accumulation of eplerenone or SC-70303 following multiple doses.

Table 4: Ratios and 95% Confidence Intervals for Single-Dose versus Multiple-Dose AUC

Eplerenone Dose	Geometric Means	Ratio of Means	95% CI for

	Single-Dose AUC0-inf	Multiple-Dose AUC0-24	(AUC0-24/AUC0-inf)	Ratio of Means
Eplerenone AUCs				
100 mg	11070.24	11392.79	1.03	(0.90, 1.17)
300 mg	22551.11	24164.49	1.07	(0.90, 1.27)
1000 mg	61092.85	62842.40	1.03	(0.93, 1.13)
SC-70303 AUCs				
100 mg	535.05	558.21	1.04	(0.89, 1.22)
300 mg	1598.78	1781.92	1.11	(0.93, 1.34)
1000 mg	5001.43	5407.09	1.08	(1.00, 1.17)

The following table lists the pharmacokinetic paramters of 100 mg single dose and multiple dose spironolactone.

Table 5: Arithmetic Mean (± Std Dev) Pharmacokinetic Parameters for Spironolactone and Its Metabolites

Substance/ Parameter	Spironolactone 100 mg Single-Dose	Multiple-Dose
Spironolactone		
AUC (ng*hr/mL)	190.9 ± –	141.2 ± 63.59
Cmax (ng/mL)	49.0 ± 28.99	67.3 ± 25.61
Tmax (hr)	1.8 ± 1.04	0.9 ± 0.23
T1/2 (hr)	1.1 ± –	2.2 ± –
MRT (hr)	1.8 ± –	1.7 ± 0.43
CL/F (L/hr)	523.9 ± –	847.5 ± 393.05
SC-9376		
AUC (ng*hr/mL)a	1461.5 ± 458.59	1426.1 ± 443.44
Cmax (ng/mL)	94.8 ± 20.66	125.3 ± 34.30
Tmax (hr)	3.4 ± 1.31	3.1 ± 1.35
T1/2 hr	17.0 ± 7.32	11.9 ± 3.42
MRT (hr)	22.0 ± 8.40	8.8 ± 0.94
SC-26519		
AUC (ng*hr/mL)	1792.4 ± 693.81	1956.1 ± 662.19
Cmax (ng/mL)	260.4 ± 52.67	283.3 ± 76.40
Tmax(hr)	2.1 ± 1.13	2.3 ± 0.89
T1/2 (hr)	10.1 ± 7.95	11.6 ± 5.65
MRT (hr)b	10.9 ± 6.47	6.4 ± 1.28
SC-26962		
AUC (ng*hr/mL)	1508.0 ± 748.89	1374.6 ± 494.22
Cmax (ng/mL)	82.5 ± 16.43	111.0 ± 24.42
Tmax(hr)	4.6 ± 3.20	3.4 ± 1.30
T1/2 (hr)	14.4 ± 11.64	13.9 ± 5.93
MRT (hr)	22.2 ± 16.92	8.9 ± 2.22

PHARMACODYNAMICS:

Eplerenone increased mean sodium excretion, starting at 4-6 hours postdose, mean sodium excretion rates were generally increased until 12 hours postdose in the eplerenone 100 and 300 mg treatment groups, and until 24 hours postdose in the 1000 mg and spironolactone groups. Following single dose administration of eplerenone, mean urinary log 10 (Na/K) values were increased compared with placebo for up to 12 hours postdose in the eplerenone 100 mg treatment group, and up to 24 hours postdose in all other active treatment groups (eplerenone and spironolactone).

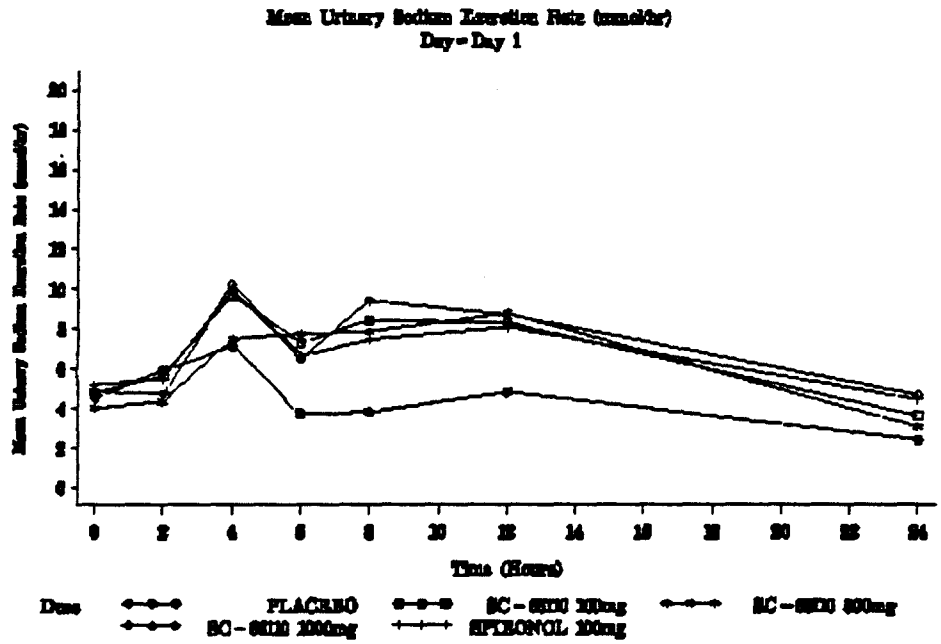
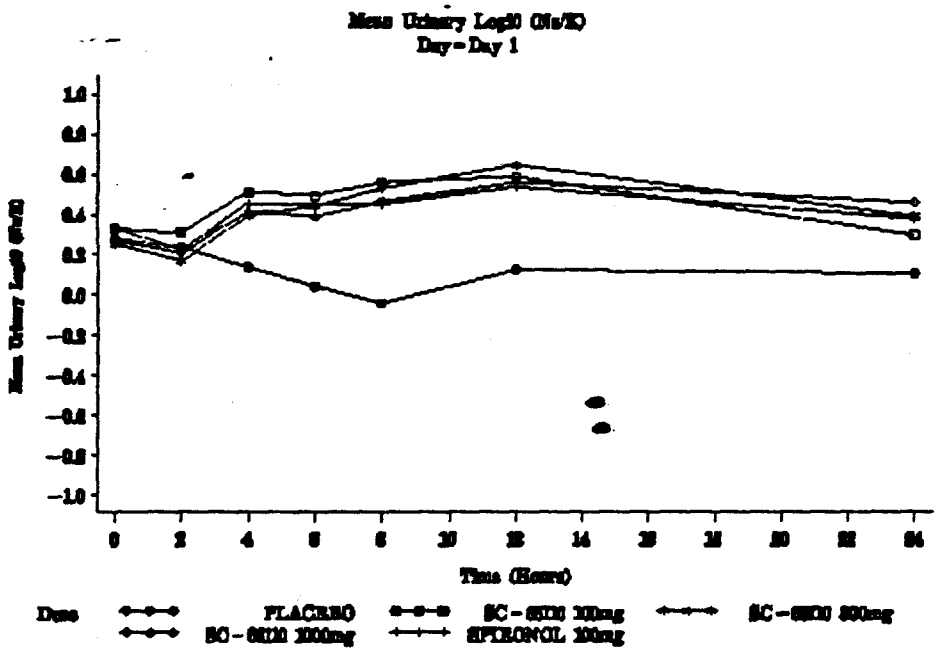


Table 6: Mean Urinary Log10 (Na/K) Following a Single Dose (Day 1)

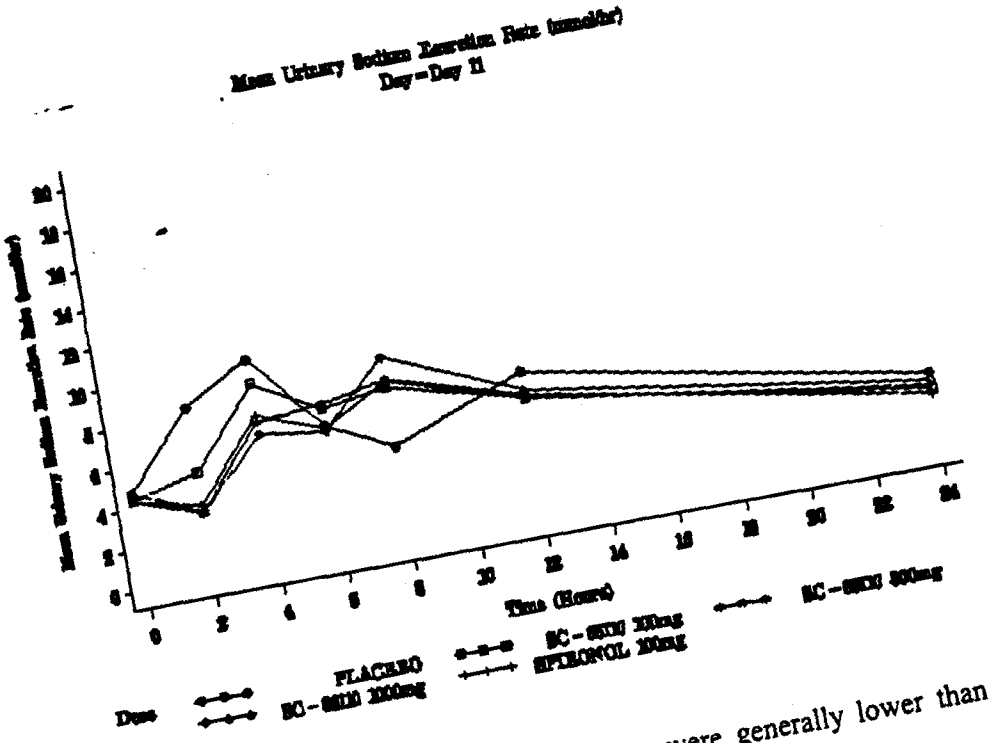
Collection Period (hours postdose)	Treatment				
	Placebo QD	Eplerenone 100 mg QD	Eplerenone 300 mg QD	Eplerenone 1000 mg QD	Spironolactone 100 mg QD
	N=8	N=8	N=8	N=8	N=8
-24 – 0	0.3	0.3	0.3	0.3	0.3
0 – 2	0.2	0.3	0.2	0.2	0.2
2 - 4	0.1	0.5	0.4	0.4	0.5
4 - 6	0.0	0.5	0.4	0.4	0.5
6 - 8	-0.0	0.6	0.5	0.5	0.5
8 – 12	0.1	0.6	0.6	0.6	0.5
12 - 24	0.1	0.3	0.4	0.5	0.4



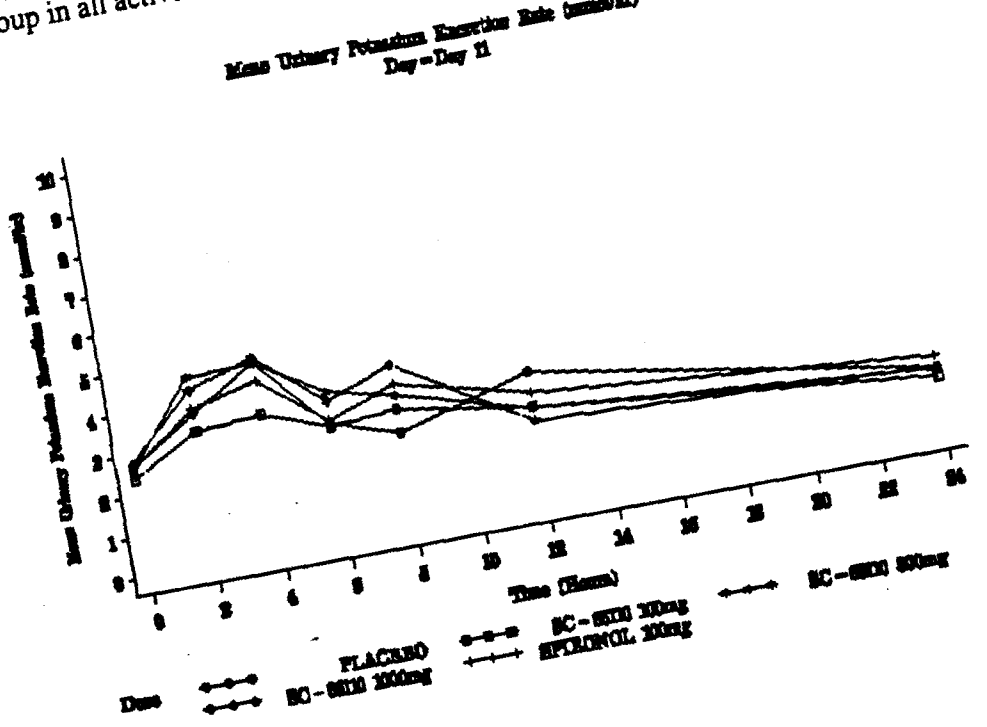
Unlike single dose administration, following multiple dose administration of eplerenone (300 or 1000 mg) or spironolactone, mean urinary log 10 (Na/K) values were significantly reduced compared with placebo from 0-2 or 0-4 hours postdose, but were comparable to the placebo group thereafter. Mean sodium excretion rates were significantly reduced at 0-2 hours after 100 mg eplerenone, and 0-4 hours after 300 or 1000 mg eplerenone, or 100 mg spironolactone. With the latter three treatments, the initial decrease was followed by a significant increase at 6-8 hours postdose.

Table 7: Mean Urinary Log10 (Na/K) Following Multiple Dosing (Day 11)

Collection Period (hours postdose)	Treatment				
	Placebo QD	Eplerenone 100 mg QD	Eplerenone 300 mg QD	Eplerenone 1000 mg QD	Spironolactone 100 mg QD
	N=8	N=8	N=8	N=8	N=8
-24 – 0	0.2	0.3	0.2	0.2	0.2
0 - 2	0.3	0.2	-0.1	-0.2	-0.0
2 - 4	0.3	0.4	0.2	0.1	0.2
4 - 6	0.3	0.4	0.3	0.2	0.3
6 - 8	0.3	0.4	0.4	0.4	0.4
8 – 12	0.3	0.4	0.4	0.5	0.3
12 - 24	0.3	0.3	0.2	0.3	0.2



In addition, mean urinary potassium concentrations were generally lower than in the placebo group in all active treatment groups from 6-12 hours postdose.



Treatment with each dose of eplerenone and with 100 mg spironolactone attenuated the fludrocortisone-induced decrease in urinary log 10 (Na/K) values. Compared to the placebo group, mean urinary log10 (Na/K) values were significantly higher at most time-points from 2-16 hours postdose in the eplerenone 100 and 300 mg treatment groups and the spironolactone group, and from 2-24 hours postdose in the 1000 mg treatment group.

Although eplerenone appeared to be slightly more potent than spironolactone (relative potency 3.73, the confidence interval contained unity (0.12, 20995), indicating no significant difference in potency between eplerenone and spironolactone.

Table 8: Mean Urinary Log10 (Na/K) Following Multiple Dosing (Day 13)

Collection Period (hours postdose)	Treatment				
	Placebo QD	Eplerenone 100 mg QD	Eplerenone 300 mg QD	Eplerenone 1000 mg QD	Spironolactone 100 mg QD
	N=8	N=8	N=8	N=8	N=8
-9 - 0	-0.1	-0.3	-0.3[a]	-0.2	-0.2
0 - 2	-0.5	-0.5	-0.5	-0.5	-0.5
2 - 4	-0.7	-0.2	-0.1	-0.1	-0.3
4 - 6	-0.5	0.0	0.2	0.1	-0.1
6 - 8	-0.7	0.1	0.3	0.3	-0.1
8 - 10	-0.7	-0.1	0.2	0.2	-0.2
10 - 12	-0.3	-0.1	0.4	0.4	0.1
12 - 14	-0.3	-0.0	0.2	0.3	-0.1
14 - 16	-0.4	-0.3	0.1	0.3	-0.2
16 - 24	-0.6	-0.5	-0.3	-0.2	-0.5

Dose-related increases in serum aldosterone concentrations following repeated administration of eplerenone were observed. On Day 11, statistically significant increases compared with placebo were observed for mean aldosterone concentrations in all active treatment groups. Mean aldosterone concentrations in the spironolactone group were significantly higher than in the eplerenone 100 mg treatment group, but significantly lower than in the eplerenone 1000 mg treatment group.

There were a few statistically significant changes in mean serum concentrations of the sex hormone and thyroid hormone parameters measured (LH, FSH, free T4, TSH, testosterone, dihydrotestosterone and estradiol), most of these were transient. Mean estradiol concentrations were increased on Days 3 and 7 in the 1000 mg group, and Day 7 and 11 in the spironolactone group, but decreased on Day 7 in the eplerenone 300 mg group.

CONCLUSIONS:

Plasma concentrations of eplerenone following both single and multiple doses increased less than dose proportionally with increasing doses of eplerenone over the dose range of 100-1000 mg. Plasma concentration of SC-70303, the open-ring form, increased dose-

proportionally. Multiple dose pharmacokinetics of eplerenone were similar to single dose pharmacokinetics indicating absence of time-related nonlinearity in eplerenone pharmacokinetics upon multiple dosing. Accumulation of eplerenone and SC-70303 at steady-state compared to single dose was not significant.

Eplerenone significantly increased urinary log $_{10}$ (Na/K) at doses of 100-1000 mg following single dose administration. In contrast, a sustained increase in log $_{10}$ (Na/K) values was not seen following multiple dose administration of either eplerenone or spironolactone. Eplerenone showed anti-aldosterone activity following the fludrocortisone challenge; the potencies of eplerenone and spironolactone were similar.

COMMENTS:

Details regarding dosing of fludicortosone were not provided in the study.

PHARMACOKINETIC STUDY OF A SINGLE ORAL DOSE OF [^{14}C]SC-66110 (EPLERENONE)

STUDY INVESTIGATORS AND SITES:

Report No.: EE3-96-02-002

OBJECTIVES:

To determine the absorption, distribution, metabolism, and elimination profile of an oral solution of [14C]eplerenone.

FORMULATIONS:

[^{14}C]eplerenone – powder, specific activity 0.75 μCi/mg, Lot # RCT 10035 by Searle

STUDY DESIGN:

This was an open-label, single-dose study in which a solution of 100 mg of [^{14}C]eplerenone (containing approximately 75 μCi per dose) was administered to 8 healthy male Caucasian volunteers, age:18-30 years (mean = 23.0 years) and weight: 66.4-88.9 kg (mean = 74.85 kg) following an overnight fast. Two subjects were administered [^{14}C]eplerenone in the pilot phase. Following the pilot phase 6 additional volunteers were enrolled into the study.

ASSAY:

Sample Collection

A 10 mL blood sample for pharmacokinetic measurement and total radioactivity analysis was to be collected at the following times: 0.5 hours predose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72 and 96 hours postdose. All blood samples collected through 24 hours postdose were also to be used to determine radioactivity distribution calculations for the red blood cells.

During study participation, the urine from each subject was to be collected for the following periods (Day 1 through the morning of Day 8): Predose: -12 to 0 hours and Postdose: 0 to 2 hours, 2 to 4 hours, 4 to 8 hours, 8 to 12 hours, 12 to 24 hours, 24 to 48 hours, 48 to 72 hours, 72 to 96 hours, 96 to 120 hours, 120 to 144 hours, 144 to 168 hours.

Individual fecal samples were to be collected beginning immediately after dosing and continued through 0800 hours on Day 8. In addition, one predose fecal sample was to be collected at home by the subjects and brought to the clinic.

Saliva samples were to be obtained 0.5 hours predose and 0.5, 1, 2, 4, 6, 12, and 24 hours postdose for total radioactivity determination. Also, breath samples were obtained 0.5 hours predose and 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, and 72 hours postdose for total radioactivity determination.

RESULTS:

The pharmacokinetic parameters of total radioactivity in plasma, whole blood and saliva obtained following administration of a single dose of 100-mg [^{14}C]eplerenone administered as an oral solution in 8 healthy males are listed in the following table.

Table 2: Mean (SD) Pharmacokinetic Parameters of Eplerenone from Total Radioactivity

Parameter	Plasma (mean ± SEM)	Whole Blood (mean ± SEM)	Saliva (mean ± SEM)
$AUC_{0\text{-}inf}$ (ng equiv hr/mL)	18400 ± 1200	12800 ± 800	7960 ± 500
Cmax (ng equiv/mL)	2490 ± 110	1770 ± 80	2170 ± 280
Tmax (hr)	1.3 ± 0.2	1.1 ± 0.2	0.6 ± 0.1

Plasma pharmacokinetic parameters of total radioactivity, eplerenone and SC-70303 are summarized in the following table.

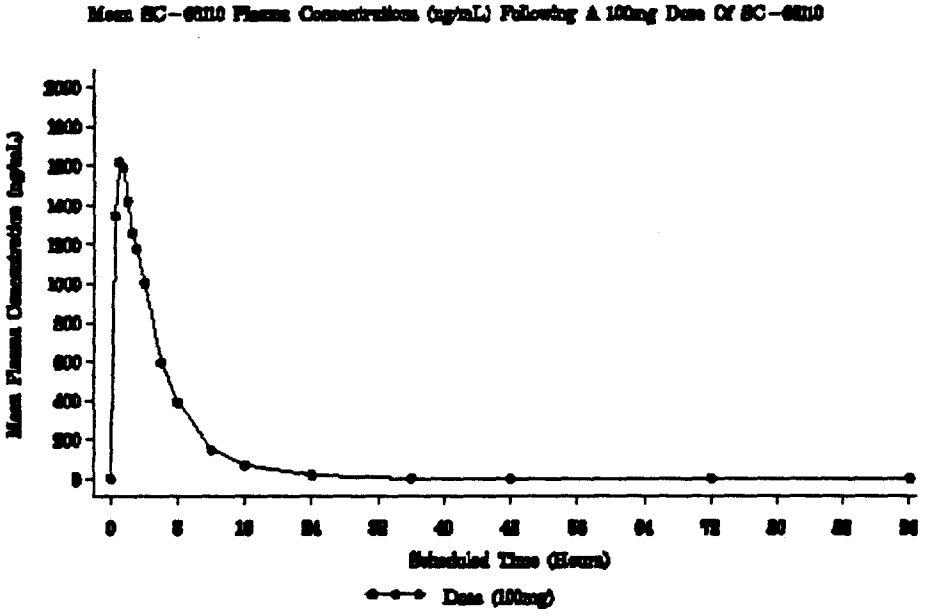
Parameter	Total Radioactivity (mean ± SEM)	EPLERENONE (mean ± SD)	SC-70303 (mean ± SD)
$AUC_{0\text{-}96}$ (nghr/m L)	18400 ± 1200*	9537.2 ± 3201.00	352.2 ± 115.14
Cmax (ng/mL)	2490 ± 110*	1721.3 ± 289.75	82.8 ± 17.18

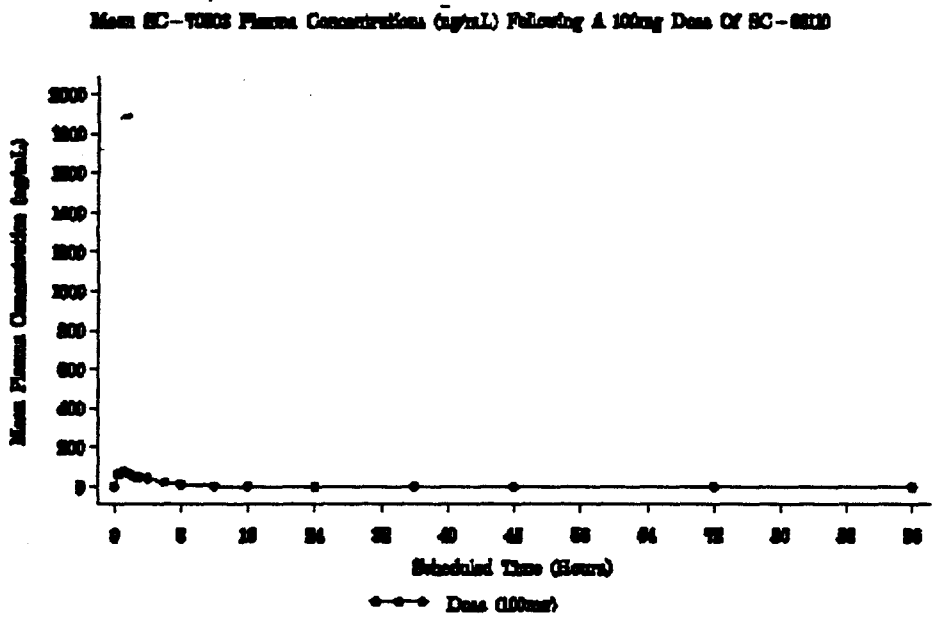
Tmax (hr)	1.3 ± 0.2	1.3 ± 0.75	1.1 ± 0.32
T1/2 (hr)	–	3.8 ± 1.08	3.1 ± 0.80
MRT (hr)	–	4.8 ± 1.05	3.4 ± 0.79
Oral Clearance (L/h)	–	11.4 ± 3.26	306.3 ± 81.60

*ng equivalents in units, rather than ng

Following a single oral dose of [14C]eplerenone, total radioactivity in plasma peaked at 1.3 hours which was similar to the Tmax for eplerenone. Total radioactivity peaked much earlier in saliva, Tmax = 0.6 hours, compared to plasma. Most of the plasma radioactivity is due to intact eplerenone; Cmax of radioactivity was 2490 ng equiv/ml of which 1721 ng/ml was eplerenone and 83 ng/ml was the open-ring form of eplerenone SC-70303. The apparent oral clearance of eplerenone in plasma was 11.4 L/h.

Total radioactivity Cmax in plasma was higher than blood 2490 ng equiv/ml compared to 1770 ng equiv/ml indicating negligible accumulation of eplerenone (the major component) in blood cells.





Metabolic Profiles:

The sponsor has only mentioned 2 analytes in the study report, eplerenone and its open-ring form SC-70303. The majority of acetonitrile-extractable radioactivity in the 1.5 and 4 hours postdose plasma samples was due to eplerenone. The percentages of radioactivity associated with eplerenone were slightly higher after acidification of the samples than those before acidification. This was attributed to cyclization of the open lactone ring of SC-70303 to the closed lactone ring form, eplerenone.

The majority of urinary (0-48 hr) and fecal (0-96 hr) radioactivity was due to metabolites. The percentages of radioactivity associated with eplerenone were substantially higher after acidification of the samples than before acidification.

Excretion

The cumulative mean percent of dose excreted in 0-48 hr urine as eplerenone was 1.65 ± 0.10% and 4.98 ± 0.53% as SC-70303. The mean percentages of dose excreted as total radioactivity in urine and feces were 66.6 ± 1.1% and 32.0 ± 1.3%, respectively. The vast majority of urinary radioactivity was excreted within the first 24 hours. The total recovery of the radioactive dose in urine and feces combined was 98.5 ± 1.1%. The majority of urinary and fecal radioactivity was due to metabolites and less than 15% was due to parent drug, indicating extensive metabolism of eplerenone.

In contrast to plasma concentrations, the percentages of SC-70303 were higher than the percentages of eplerenone in urine. The cumulative mean percent of dose excreted in 0-48 hr urine as eplerenone was 1.65 ± 0.10%. The value for SC-70303 was 4.98 ± 0.53%.

In unacidified feces, the percent of the dose excreted in 0-96 hr feces as eplerenone was 0.807 ± 0.156 and in acidified feces, this value was 2.46 ± 0.29.

No detectable levels of eplerenone were found in the urine after 24 hours postdose. On average, the maximum amount excreted was during the two to four hours postdose collection period. No detectable levels of SC-70303 were found in the urine after 48 hours postdose. On average, the maximum amount excreted was during the four to eight hours postdose collection period.

Plasma Protein Binding

The mean percentage of total radioactivity bound to plasma proteins in the 1.5 hour plasma samples was 49.4%. The mean concentration of total radioactivity in these samples was 2.39 µg/mL. When [^{14}C]eplerenone was spiked into the control plasma, which had been frozen, the percentage of eplerenone bound was 40.4% at a concentration of 14.5 µg/mL.

CONCLUSIONS:

The cumulative mean percent of dose excreted in 0-48 hr urine as eplerenone was only 1.65 ± 0.10% and 4.98 ± 0.53% as SC-70303. The mean percentages of dose excreted as total radioactivity in urine and feces were 66.6% and 32.0%, respectively. The total recovery of the radioactive dose in urine and feces combined was 98.5%. Eplerenone is 40%-50% bound to plasma proteins.

Following a single oral dose of [14C]eplerenone, total radioactivity in plasma peaked at 1.3 hours which was similar to the Tmax for eplerenone. Total radioactivity peaked much earlier in saliva, Tmax = 0.6 hours, compared to plasma. Most of the plasma radioactivity is due to intact eplerenone; Cmax of radioactivity was 2490 ng equiv/ml of which 1721 ng/ml was eplerenone and 83 ng/ml was the open-ring form of eplerenone SC-70303. The apparent oral clearance of eplerenone was 11.4 L/h. The T1/2 of eplerenone in plasma was 3.8 hours. The apparent oral clearance of eplerenone in plasma was 11.4 L/h. Total radioactivity Cmax in plasma was higher than blood 2490 ng equiv/ml compared to 1770 ng equiv/ml indicating negligible accumulation of eplerenone (the major component) in blood cells.

COMMENTS:

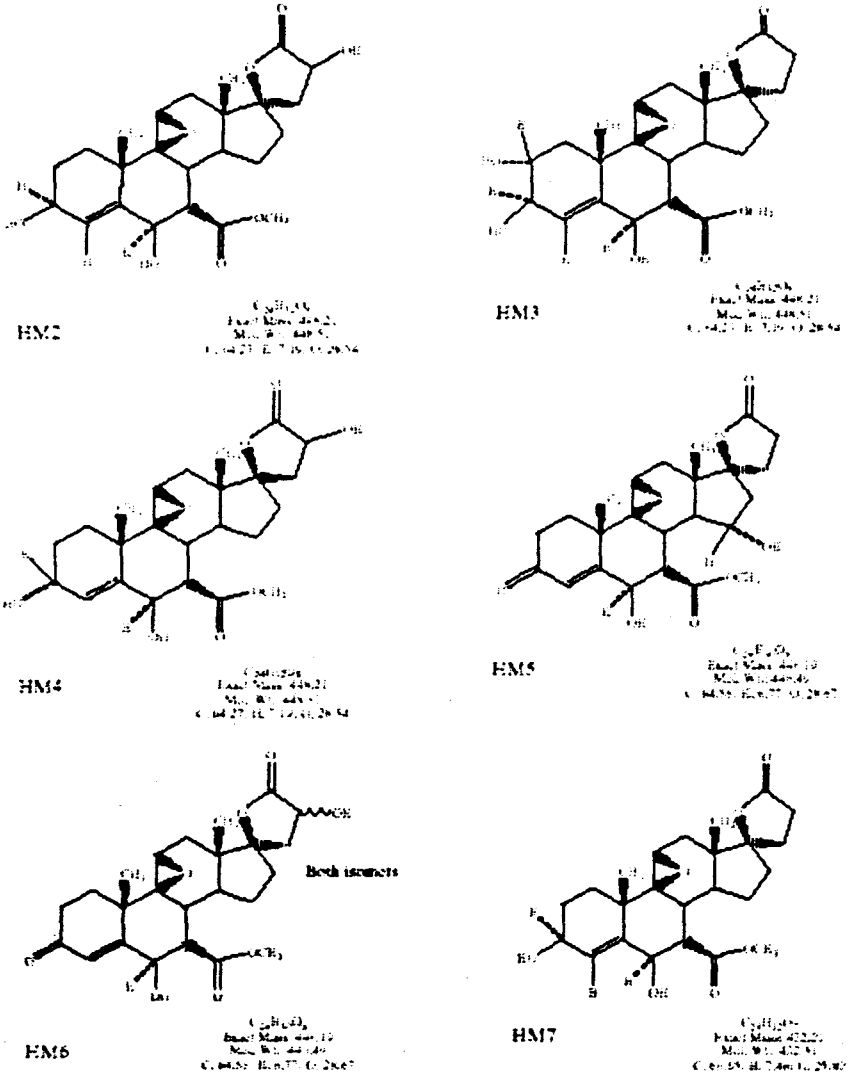
1. The location of [^{14}C] label was not specified in the study report.
2. The sponsor should have identified and measured the concentration of the major metabolites of eplerenone, such as SC-71597.
3. The $T_{1/2}$ of total radioactivity in plasma, blood and saliva was not specified in the study report.

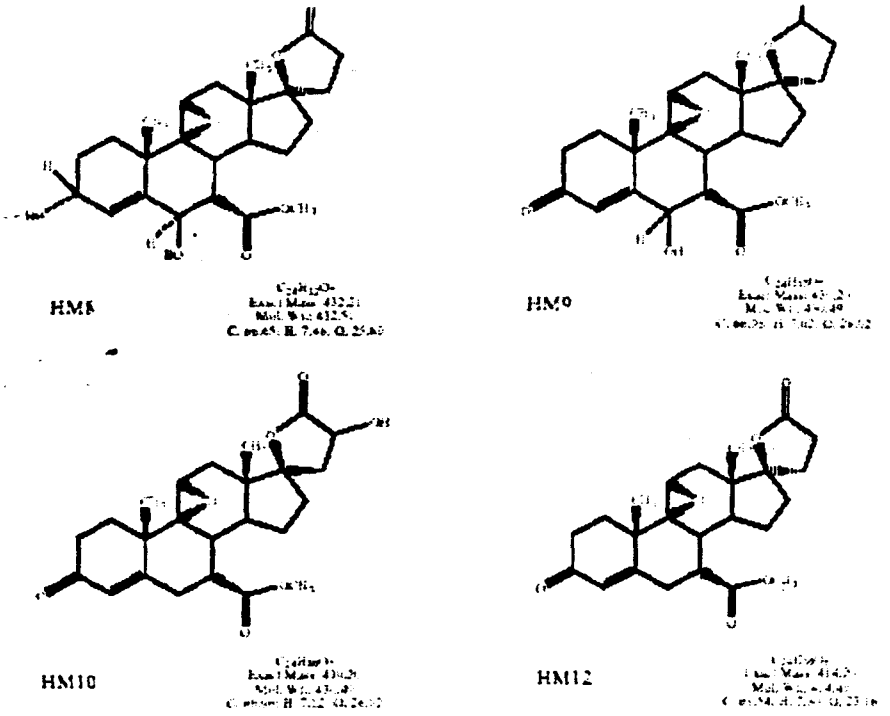
ISOLATION AND IDENTIFICATION OF [^{14}C]EPLERENONE METABOLITES IN HUMANS

After completion of the pharmacokinetics and metabolic balance portion of the [^{14}C]eplerenone study in humans, the remaining urine and fecal samples from selected time points were each pooled and the radioactive metabolite peaks were isolated using a procedure. The chemical structures of the isolated metabolites were identified by) and nuclear magnetic resonance (NMR) spectroscopy.

RESULTS

Figure 1: Chemical structures of eplerenone (HM12) and identified metabolites.





The metabolites identified were 6β-OH; 21-OH; 3β,6β-OH; 3α,6β-OH; 6β,15α-OH; 6β, 21-OH; 2α,3β,6β-OH; 3α,6β,21-OH and 3β,6β,21-OH metabolites. The major metabolic pathways of eplerenone were 6β-hydroxylation, 21-hydroxylation and 3-keto reduction. The 6β-OH metabolite accounted for 32.0% of administered dose with 28.3% in urine and 3.72% in feces (Table 1). The 21-OH metabolite accounted for 7.89% of the dose with 5.01% in urine and 2.88% in feces. The 6β, 21-OH metabolite was 20.5% of the dose with 13.1% in urine and 7.41% in feces. The amounts of metabolites HM1 and HM11 were not sufficient to obtain NMR spectra. Therefore, chemical structures of these metabolites were not elucidated.

Table 1. The Percentages of the [^{14}C]Eplerenone Dose and Its Metabolites Eliminated in Urine and Feces

Revised ID	Original ID(s)		Compound	% Of Dose		
	Feces	Urine		Feces	Urine	Total
HM1	Metabolite #1		not identified	0.976	0	0.976
HM2	Metabolite #2		3β6 β, 21-OH	1.64	0	1.64
HM3	Metabolite #3		2α, 3β, 6β-OH	1.95	0	1.95
HM4	Metabolite #4		3α, 6β, 21-OH	3.42	2.54	5.96
HM5	Metabolite #4A		6β1 5α-OH	1.91	2.54	4.45
HM6	Metabolite #5	Met A	6β2 1-OH	7.41	13.1	20.5
HM7	Metabolite #6		3β6 β-OH	0.938	0	0.938
HM8	Metabolite #7	Met B	3α, 6β-OH	1.02	3.90	4.92
HM9	Metabolite #8	Met C	6β OH	3.72	28.3	32.0
HM10	Metabolite #9A	Met D	21-OH	2.88	5.01	7.89
HM11	Metabolite #10		not identified	2.19	0	2.19
HM12	Metabolite #11B	Met E	Eplerenone	3.20	6.80	10.0
	Total			31.3	62.2	93.4

CONCLUSIONS

Eplerenone is primarily metabolized via 6β-hydroxylation, 21-hydroxylation and 3-keto reduction pathways in the human. In addition, 2α- and 15α- hydroxylation pathways were also observed. The major metabolites in humans were 6β-OH (32.0%), 6β, 21-OH (20.5%), and 21-OH eplerenone(7.9%).

IN VITRO DRUG-DRUG INTERACTION STUDIES WITH SC-66110 (EPLERENONE) AND METOPROLOL

Document #: M20000330

OBJECTIVES:

1. To assess the potential for eplerenone to affect the in vitro clearance of metoprolol.
2. To assess the potential for metoprolol to alter the metabolic formation of SC-71597.

METHODS:

Effect of Eplerenone on the Disappearance of Metoprolol

The metabolism of metoprolol was investigated in human liver microsomes, 1 mg/mL final concentration. A volume of 25 µL microsomes was added to 150 µL 100 mM potassium phosphate buffer pH 7.4. Metoprolol was added in a volume of 4 µL to reach final concentrations of 5 or 10 µg/mL. The enzymatic reactions were initiated by addition of 25 µL of an NADPH regenerating system and the samples were allowed to incubate at 37 °C for 120 minutes. The reactions were quenched by the addition of 2 µL of ethyl acetate. To demonstrate that the disappearance of metoprolol was dependent on the presence of NADPH and therefore a result of P450 metabolism, 6 samples were incubated without the regenerating system.

Effect of Metoprolol on the Formation of SC-71597

Inhibition of SC-71597 formation was estimated by incubating 5 substrate eplerenone (substrate)
concentrations with 6 concentrations of metoprolol (including zero) (TM-411). Human liver microsomes (25 µL) were added to 450 µL of 100 mM potassium phosphate buffer pH 7.4 to achieve a final protein concentration of 0.1 mg/mL. Eplerenone (2 µL in acetonitrile) was added to the appropriate suspensions to achieve the target concentrations of 25.0, 50.0, 100, 200, and 400 µM. Metoprolol was added to appropriate tubes and the suspensions were allowed to equilibrate for approximately 3 minutes. The concentrations used for metoprolol were 0, 25, 50, 100, 250, and 500 µM. The enzymatic reactions were initiated by the addition of NADPH (25.0 mL) so that the final concentration was 1.00 mM. Incubations were quenched after 15 minutes by the addition of the extraction solvent ethyl acetate. The samples were injected onto the [redacted] and peak areas of *m/z* 431→211 product ions of SC-71597 were monitored.

RESULTS:

Evaluation of Metoprolol Disappearance

EPLERENONE PHARMACOKINETIC ASSESSMENT OF MULTIPLE ORAL DOSES OF 100 MG IN HEALTHY AND UNTREATED MILDLY HYPERTENSIVE JAPANESE VOLUNTEERS

STUDY INVESTIGATORS AND SITES:

Protocol No.: NE3-01-02-053

OBJECTIVE:

To investigate the steady state pharmacokinetic profile of eplerenone following once daily oral dosing with 100 mg administered to healthy Japanese volunteers for a period of seven days.

FORMULATIONS:

Eplerenone – 100 mg tablets (batch #: RCT 11671)

STUDY DESIGN:

This was an open-label, parallel, fixed-dose steady-state pharmacokinetic study in 12 healthy or mildly hypertensive Japanese male adults. Only male subjects (mean age = 42 years and mean weight = 69 kg) were enrolled. On Days 1 and 7, eplerenone 100 mg QD was administered following an overnight fast. On Days 2-6, eplerenone 100 mg QD was administered following a two-hour fast with the fast continuing for 30 minutes after dosing.

ASSAY:

[redacted]

Sample Collection:
On Day 1, blood samples were collected at predose (-15 minutes), and 0.5, 1, 2, 3, 4, 6, 8, 12, and 16 hours postdose. Blood was collected predose (-15 minutes) on Days 2 through 6 for trough concentration measurements. On Day 7, blood samples were drawn at predose (-15 minutes), and 0.5,1, 2, 3, 4, 6, 8, 12, 16, 24 and 36 hours postdose.

Urine samples were collected prior to dosing on Day 1 and 0-12 and 12-24 hours after dosing on Day 7. In addition, urine creatinine concentration was determined for each collection interval.

RESULTS

The pharmacokinetic parameters of eplerenone obtained following administration of multiple doses of 100 mg QD eplerenone given orally in hypertensive Japanese males are listed in the following table.

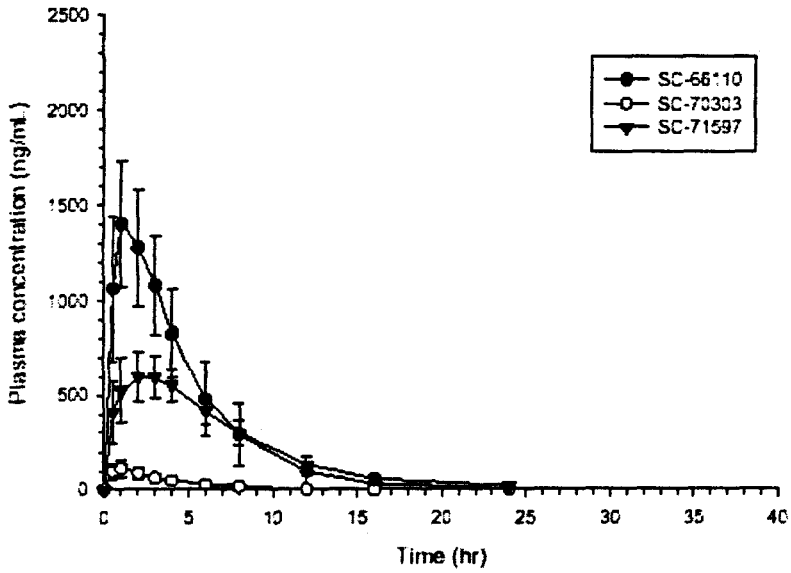
Table 2: Eplerenone Pharmacokinetic Parameters on Days 1 and 7 After 100 mg/Day of Eplerenone

Pharmacokinetic Parameter	Day 1 (N = 12)	Day 7 (N = 12)
AUC (hr*ng/mL)	7631.55 ± 2330.296 (4019.89 - 11715.89)	12303.36 ± 3748.292 (6655.47 - 20039.98)
Cmax (ng/mL)	1458.00 ± 281.316 (1029.38 - 1952.67)	1777.67 ± 343.564 (1218.65 - 2427.42)
Tmax (hr)	1.42 ± 0.791 (1.00 - 3.00)	1.46 ± 0.838 (0.50 - 3.00)
Cmin (ng/mL)	-	58.14 ± 84.661 (0.00 - 310.35)
Kel (1/hr)	0.283 ± 0.0716 (0.188 - 0.380)	0.155 ± 0.0588 (0.077 - 0.305)
T1/2 (hr)	2.62 ± 0.734 (1.82 - 3.70)	5.00 ± 1.740 (2.27 - 9.04)
CL/F (L/hr)	14.34 ± 4.663 (8.54 - 24.88)	8.91 ± 2.985 (4.99 - 15.03)
CL/F/WT (L/hr/70kg)	15.10 ± 5.834 (8.02 - 23.82)	9.39 ± 3.746 (5.13 - 16.52)
CLr (L/hr)	NAP	0.18 ± 0.089 (0.07 - 0.35)
XU(0-24) (mg)	NAP	1.29 ± 1.320 1.30 (0.76 - 4.98)

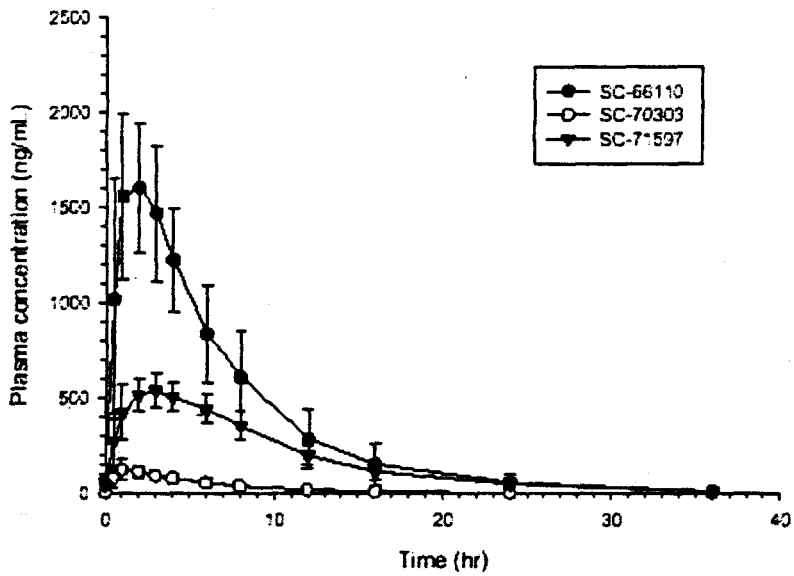
Absorption of eplerenone was rapid, with peak plasma eplerenone concentrations occurring by 1.4 hours after the Ist and 7th dose of eplerenone in Japanese individuals. Concentrations decreased with an average $T_{1/2}$ of 2.6 hours after the first dose, however,

the mean value of $T_{1/2}$ on Day 7 was higher, 5 hours. Average C_{max} values on Days 1 and 7 were 1460 ng/mL and 1780 ng/mL, respectively, indicating slight accumulation. The values of AUC_{0-24} on Day 7 was 1.6 times larger than AUC_{inf} on Day 1 indicating non-linearity in pharmacokinetics upon multiple dosing.

Mean Eplerenone, SC-70303, and SC-71597 Plasma Concentrations After Eplerenone 100 mg on Day 1

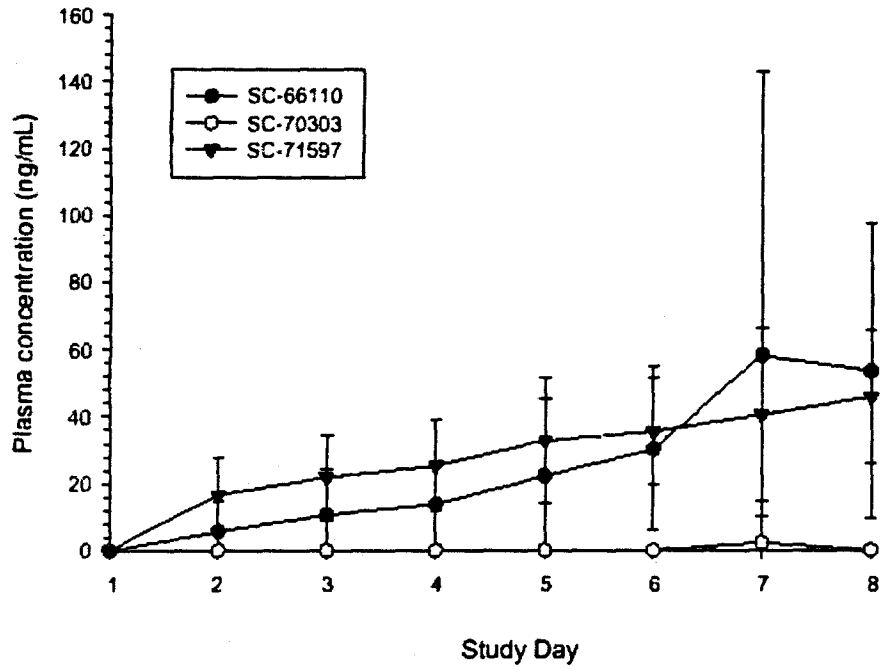


Mean Eplerenone, SC-70303, and SC-71597 Plasma Concentrations After Eplerenone 100 mg on Day 7



After the first administration of eplerenone on Day 1, the peak of plasma concentrations of SC-70303, the lactone ring opened form of SC-66110, were observed at about 1 hour postdose, which is similar to eplerenone. Concentrations decreased with an average $T_{1/2}$ of 3 hours, which is also similar to eplerenone. Average C_{max} values on Days 1 and 7 were 119 ng/mL and 137 ng/mL respectively, indicating that the values were less than 1/10 of the C_{max} of eplerenone. The value of AUC_{0-24} on Day 7 was 1.5 times larger than the AUC_{inf} on Day 1.

Mean Eplerenone, SC-70303 and SC-71597 Trough Plasma Concentrations on Days 2-8



The pharmacokinetic parameters of SC-70303, the open ring form of the lactone, are summarized in the following table.

SC-70303 Pharmacokinetic Parameters on Days 1 and 7 After 100 mg/Day of Eplerenone

Pharmacokinetic Parameter	Day 1 (N = 12)	Day 7 (N = 12)
AUC (hr*ng/mL)	509.49 ± 171.222 (279.32 – 846.47)	765.87 ± 305.785 (401.06 – 1320.92)
Cmax (ng/mL)	119.38 ± 38.104 (79.55 – 208.11)	137.26 ± 43.763 (83.33 – 228.94)
Tmax (hr)	0.92 ± 0.419 (0 50 - 2.00)	1.13 ± 0.569 (0.50 - 2.00)

Cmin (ng/mL)	-	2.28 ± 7.884 (0.00 – 27.31)
Kel (1/hr)	0.268 ± 0.0682 (0.154 - 0.351)	0.194 ± 0.0622 (0.100 - 0.291)
T(1/2) (hr)	2.78 ± 0.827 (1.98 – 4.51)	4.01 ± 1.525 (2.38 – 6.93)
XU(0-24) (mg)	-	4.03± 2.384 4.04(1.92 – 8.66)

SC-71597 is the 6 -hydroxy metabolite of eplerenone. The pharmacokinetic parameters of SC-71597 are summarized in the following Table.

Table 3: SC-71597 Pharmacokinetic Parameters on Days 1 and 7 after 100 mg/Day of Eplerenone

Pharmacokinetic Parameter	Day 1 (N = 12)	Day 7 (N = 12)
AUC (hr*ng/mL)	5399.09 ± 871.523 (4387.87 – 7267.81)	5844.05 ± 764.513 (4475.09 – 6939.56)
Cmax (ng/mL)	641.49 ± 111.211 (370.93 – 805.10)	570.03 ± 88.189 (466.03 – 745.55)
Tmax (hr)	2.33 ± 0.890 (1.00 – 4.02)	2.50 ± 1.382 (1.00 - 6.00)
Cmin (ng/mL)	-	40.59 ± 25.761 (0.00 – 103.97)
Kel (1/hr)	0.181 ± 0.0400 (0.141 - 0.263)	0.120 ± 0.0299 (0.091 - 0.192)
T1/2 (hr)	3.97 ± 0.708 (2.63 – 4.93)	6.07 ± 1.216 (3.60 – 7.63)
XU(0-24) (mg)	-	13.91 ± 3.743 (8.74 – 19.56)

After the first administration of eplerenone on Day 1, the peak plasma concentrations of SC-71597 were observed at about 2.0 to 2.5 hours after dosing which occurred later than the peak of eplerenone. Concentrations decreased with an average $T_{1/2}$ of 4 hours, which is similar to eplerenone. However, upon multiple dosing average $T_{1/2}$ increased to 6 hours on Day 7. Six hours after dosing on Day 1, the plasma concentration profiles of SC-71597 overlapped the profiles of eplerenone. On Day 7, the peak plasma concentrations occurred at about 2.5 hours. Average C_{max} values on Days 1 and 7 were 641 ng/mL and 570 ng/mL respectively, indicating that the values were less than 1/2–1/3 of the C_{max} of eplerenone. The values for AUC_{inf} on Day 1 were similar to AUC_{0-24} on Day 7 indicating linear kinetics upon multiple dosing. The amount of SC-71597 excreted into urine was 13.9 mg, accounting for approximately 15% of dose.

Comparison of Eplerenone Pharmacokinetics in Japanese and Caucasians

AUC and Cmax of eplerenone and SC-70303 obtained in the present study were compared to a multiple dose study in Caucasians where eplerenone 100 mg QD was administered for 11 days to Caucasians.

Ratios and 90% Confidence Intervals for Eplerenone and SC-70303 Pharmacokinetic Parameters for Japanese Compared With Caucasians

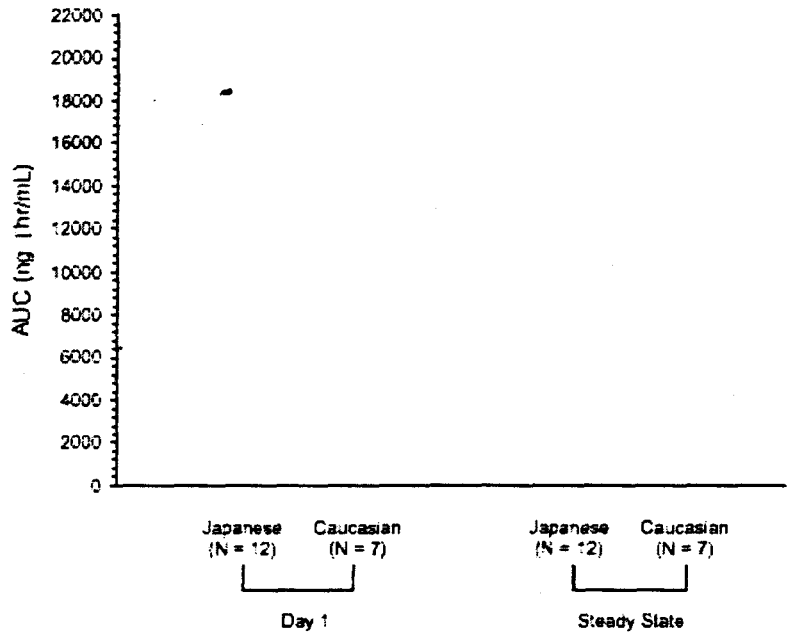
Parameter	Least Squares Means		Ratio Japanese/ Caucasian	90% Confidence Interval	p-value
	Japanese	Caucasian			
	N = 12	N = 7			
EPLERENONE					
Day 1					
AUC (hr*ng/mL)	7302.29	11566.22	0.63	(0.50 - 0.80)	0.0035
Cmax (ng/mL)	1433.61	1764.89	0.81	(0.71 – 0.93)	0.0198
Steady State					
AUC (hr*ng/mL)	11766.66	11566.53	1.02	(0.79 – 1.32)	0.9088
Cmax (ng/mL)	1746.46	1921.98	0.91	(0.78 – 1.05)	0.2779
SC-70303					
Day 1					
AUC (hr*ng/mL)	485.38	524.94	0.92	(0.70 – 1.22)	0.6272
Cmax (ng/mL)	114.71	90.23	1.27	(1.02 – 1.58)	0.0705
Steady State					
AUC (hr*ng/mL)	712.93	543.69	1.31	(0.93 – 1.86)	0.1924
Cmax (ng/mL)	131.61	110.37	1.19	(0.91 – 1.56)	0.2673

Day 7 for Japanese in Study NE3-01-02-053 and Day 11 for Caucasian subjects in Study EE3-96-02-004.

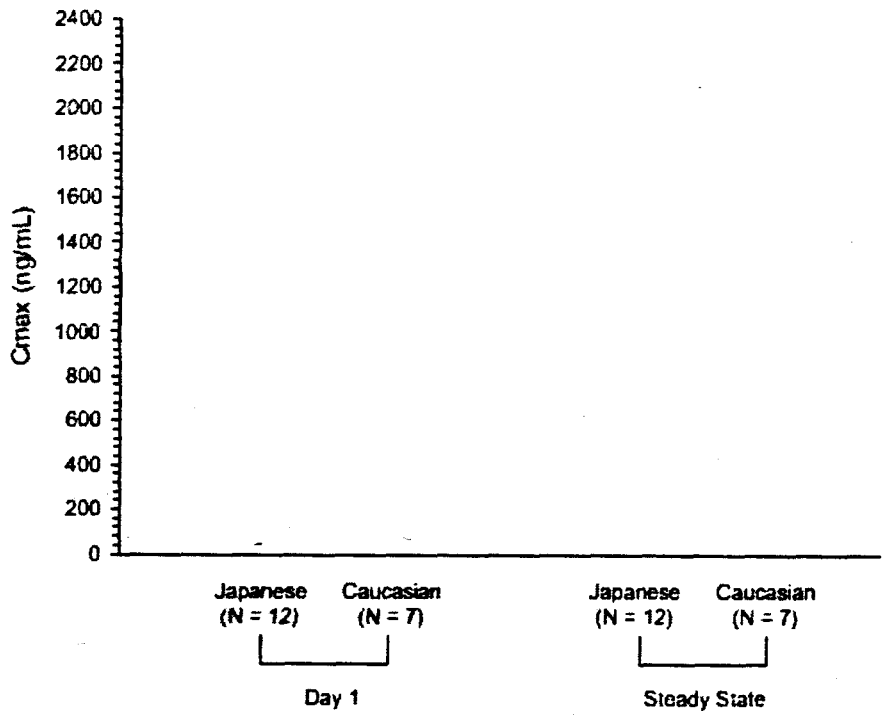
On Day 1, the 90% confidence intervals of the ratios of means of eplerenone AUCinf and C_{max} in the present Japanese study and those in Caucasians were 0.50-0.80 and 0.71-0.93, Respectively, indicating lower concentrations in Japanese subjects compared to Caucasians. The differences of both parameters between Japanese and Caucasians on Day 1 were statistically significant. In contrast at steady state, the 90% confidence intervals of the ratios of means of eplerenone AUC_{0-24} and C_{max} were 0.79-1.32 and 0.78-1.05, respectively, and these differences were not statistically significant. In scatterplots of eplerenone AUC_{inf} and C_{max} approximately half of the Day 1 values in Japanese overlapped with the values in Caucasians while half of the Japanese had lower exposures than Caucasians. Scatterplots of eplerenone AUC and C_{max} at steady state show overlap of the Japanese and Caucasian values. Steady state pharmacokinetics of eplerenone was probably attained around Days 4-7. There were no statistically significant differences in AUC and C_{max} of SC-70303 between Japanese and Caucasians.

Scatterplot of Individual Eplerenone AUC for Japanese and Caucasians

Following a Single Dose and at Steady State



Scatterplot of Individual Eplerenone C_{max} for Japanese and Caucasians Following a Single Dose and at Steady State



The CL/F at steady state of 8.91 L/h in the present study was smaller than the CL/F of 16.1 L/h at steady state obtained in another multiple dose study in Japanese healthy volunteers, where 400 mg was administered once daily. It is not clear if the increased CL/F value in the other study is related to the higher dose studied.

The fraction of eplerenone dose excreted in urine as intact drug was approximately 2% of the dose. The fraction of metabolite SC-71597 excreted into urine was 15% of the dose.

Day 7 AUC was 1.6 times larger than that on Day 1. Moreover, the mean value of $T_{1/2}$ on Day 7 was larger than that on Day 1. These apparent differences are likely an artifact due to Day 1 concentrations being below the limit of quantitation of the assay (ng/mL) at 16 hours (four subjects) and 24 hours (eight subjects). While, on Day 7 only 1 subject had concentrations below ng/mL at 24 hours. This probably resulted in underestimation of $T_{1/2}$ and AUC_{inf} for Day 1.

Comparison of steady state pharmacokinetics is more appropriate than comparison of Day 1 pharmacokinetics because of concentrations lower than the limit of quantitation in the terminal phase on Day 1. AUC and C_{max} of eplerenone and SC-70303 at steady state in the present Japanese study were similar to those in Caucasians following multiple dosing at 100 mg in another study (Final report for eplerenone multiple oral dose tolerability and pharmacokinetic study, Protocol No. EE3-96-02-004). Similar values of T_{max} (1.1-1.5 hours) and $T_{1/2}$ (4-5 hours) of eplerenone suggest comparable absorption and elimination among Japanese and Caucasians.

CONCLUSIONS:

AUC and C_{max} of eplerenone and SC-70303 at steady state in the present Japanese study were similar to those in Caucasians following multiple dosing at 100 mg in another study (Final report for eplerenone multiple oral dose tolerability and pharmacokinetic study. Protocol No. EE3-96-02-004). Similar values of T_{max} (1.1-1.5 hours) and $T_{1/2}$ (4-5 hours) of eplerenone suggest comparable absorption and elimination among Japanese and Caucasians.

THE STUDY EFFECT OF AGE AND GENDER ON THE PHARMACOKINETIC PROFILE OF EPLERENONE IN HEALTHY SUBJECTS

STUDY INVESTIGATORS AND SITES:

Report No.: NE3-99-02-028

OBJECTIVES:

1. To examine the single- and multiple-dose pharmacokinetics of eplerenone in healthy young subjects as compared to healthy elderly subjects, as well as pharmacokinetic differences in their gender, following single and multiple (steady-state) doses.
2. To compare the safety and tolerability of single and multiple doses of eplerenone in healthy young versus healthy elderly subjects, as well as pharmacokinetic differences in their gender, following single and multiple (steady-state) oral doses.

FORMULATIONS:

Eplerenone – 100 mg tablets (Lot #: 11039) by Searle

STUDY DESIGN:

This was an open-label, multiple-dose, parallel design study conducted in 48 healthy adult subjects, according to the following distribution:
12 healthy young males (18-45 years of age)
12 healthy young females (18-45 years of age)
12 healthy elderly males (65 years of age or older)
12 healthy elderly females (65 years of age or older)

All subjects received a single eplerenone 100 mg dose on Day 1, followed by a eplerenone 100 mg QD for 12 days (Days 3 through 14). Eplerenone doses were administered on Days 1, 7 and 14 following an overnight fast, while, dosing on Days 3-6 and 8-13 were administered at least 1 hour following a meal.

Table 1: Baseline Demographics and Characteristics

	Eplerenone 100 mg			
	Young		Elderly	
	Female	Male	Female	Male
	N = 12	N = 12	N = 12	N = 12
Age (yr)				
Mean ± SD	37.2 ± 5.49	33.8 ± 6.68	67.3 ± 3.5	71.8 ± 2.3
Range	25 - 45	22 - 41	65 - 76	68 - 75
Race/Ethnic Origin (N,%)				

Asian	1 (8.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Black	1 (8.3%)	2 (16.7%)	2 (16.7%)	2 (16.7%)
Caucasian	0 (0.0%)	4 (33.3%)	4 (33.3%)	3 (25.0%)
Hispanic/Latin American	9 (75.0%)	5 (41.7%)	6 (50.0%)	7 (58.3%)
Other	1 (8.3%)	1 (8.3%)	0 (0.0%)	0 (0.0%)
Gender				
Female	12 (100.0%)	NA	12 (100.0%)	NA
Male	NA	12 (100.0%)	NA	12 (100.0%)
Weight (kg) (Mean ± SD)	64.9 ± 6.81	77.3 ± 6.55	67.3 ± 5.09	78.8 ± 8.90
Height (cm) (Mean ± SD)	160.9 ± 5.46	173.8 ± 7.32	158.2 ± 4.98	169.6 ± 8.91

ASSAY:

[redacted]

Sample Collection

Blood samples for eplerenone and SC-70303 pharmacokinetic analyses were drawn on Days 1 and 14 for all subjects at the following time points: predose (-30 minutes) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36 and 48 hours postdose. Blood samples were also drawn on Day 7 at the same time-points through 24 hours postdose.

Urine samples were collected and pooled at -12 to 0 hours on Day 0, 0-24 hours postdose on Day 7, and 0-24 and 24-48 hours postdose on Days 1 and 14.

RESULTS

*On Day 7, eplerenone plasma concentrations for Subject 0110 (a young male) were substantially lower than those on Days 1 and 14. Corresponding plasma concentrations for SC-70303 were all below the limit of quantification. This was attributed to possible dosing error for this subject on Day 7.

Effect of Age on Eplerenone and SC-70303 Pharmacokinetics

The pharmacokinetic parameters of eplerenone and SC-70303 (open-ring form of eplerenone) following administration of single and multiple oral doses of 100 mg eplerenone in healthy young and elderly males and females are listed in the following table.

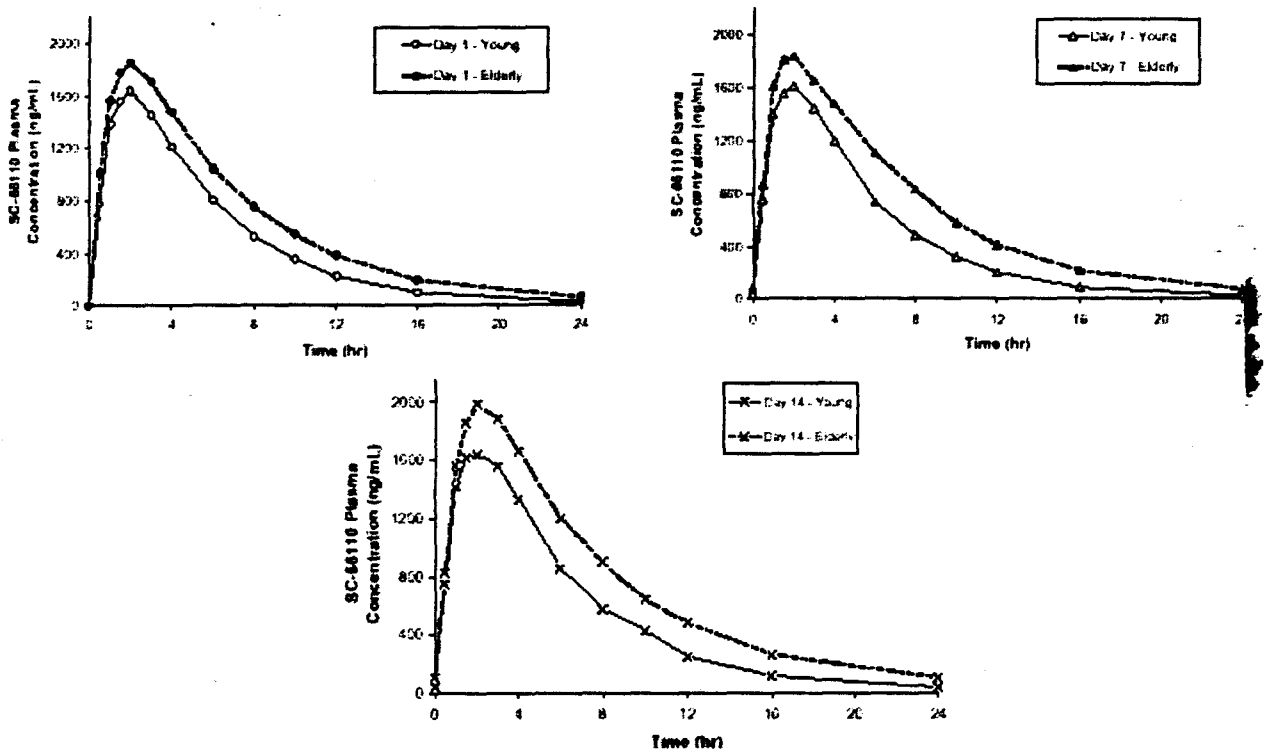
Table 2: Ratios and 90% Confidence Intervals for Eplerenone and SC-70303 Pharmacokinetic Parameters by Age Group (Excluding Subject 0110 for Eplerenone Data on Day 7)

Pharmacokinetic Parameter	Least Squares Means		Ratio Elderly/Young	90% CI for Ratio	P-Value
	Elderly	Young			
	N = 24	N = 24			
EPLERENONE					
Single Dose (Day 1)					
AUC(0-lqc) (hr*ng/mL)	14253.51	10478.36	1.360	(1.1392, 1.6241)	0.006
AUC(0-∞) (hr*ng/mL)	14391.16	10577.05	1.361	(1.1406, 1.6229)	0.005
Cmax (ng/mL)	1965.04	1729.49	1.136	(1.0331, 1.2495)	0.029
CL/F (L/hr)	6.95	9.45	0.735	(0.6161, 0.8766)	0.005
CL/F/WT (L/hr/70 kg)	6.80	9.26	0.735	(0.6160, 0.8763)	0.005
XU(0-48) (μg)	1584.05	1332.72	1.189	(0.9152, 1.5434)	0.273
Multiple Dose (Day 7)					
AUC(0-24) (hr*ng/mL)	14521.66	10314.25	1.408	(1.1827, 1.6760)	0.002
Cmax (ng/mL)	2033.69	1785.55	1.139	(1.0058, 1.2896)	0.085
CL/F (L/hr)	6.89	9.70	0.710	(0.5966, 0.8455)	0.002
CL/F/WT (L/hr/70 kg)	6.76	9.52	0.710	(0.5965, 0.8449)	0.002
XU(0-24) (μg)	1533.29	1594.37	0.962	(0.7464, 1.2390)	0.797
Multiple Dose (Day 14)					
AUC(0-24) (hr*ng/mL)	16114.15	11082.35	1.454	(1.2141, 1.7412)	0.001
Cmax (ng/mL)	2181.81	1794.57	1.216	(1.0886, 1.3578)	0.005
CL/F (L/hr)	6.21	9.02	0.688	(0.5742, 0.8235)	0.001
CL/F/WT (L/hr/70 kg)	6.09	8.86	0.687	(0.5743, 0.8228)	0.001
XU(0-24) (μg)	1623.43	1483.43	1.094	(0.8346, 1.4349)	0.579
SC-70303					
Single Dose (Day 1)					
AUC(0-lqc) (hr*ng/mL)	611.16	405.25	1.508	(1.2693, 1.7917)	<0.001
AUC(0-∞) (hr*ng/mL)	675.14	446.18	1.513	(1.2772, 1.7926)	<0.001
Cmax (ng/mL)	99.15	85.42	1.161	(1.0390, 1.2965)	0.029
XU(0-48) (μg)	5604.89	4838.76	1.158	(0.9203, 1.4579)	0.289
Multiple Dose (Day 7)					
AUC(0-24) (hr*ng/mL)	673.63	402.84	1.672	(1.4076, 1.9864)	<0.001
Cmax (ng/mL)	102.73	82.59	1.244	(1.1004, 1.4058)	0.005
XU(0-24) (μg)	6106.83	4542.93	1.344	(0.9888, 1.8274)	0.113
Multiple Dose (Day 14)					
AUC(0-24) (hr*ng/mL)	781.22	465.88	1.677	(1.4357, 1.9585)	<0.001
Cmax (ng/mL)	113.20	88.03	1.286	(1.1671, 1.4166)	<0.001
XU(0-24) (μg)	5664.55	5696.51	0.994	(0.8051, 1.2280)	0.964

Following a single oral 100 mg dose of eplerenone, mean eplerenone Cmax and AUC in the elderly were higher, 14% and 36%, respectively, compared to young subjects. Mean eplerenone apparent oral clearance adjusted for 70-kg body weight was lower by 27% in the elderly compared to young subjects. A similar difference in pharmacokinetic parameters were observed following multiple dosing too. Following multiple oral doses of 100 mg eplerenone, mean Day 7 eplerenone Cmax and AUC in the elderly were higher by 14% and 40%, respectively, and Day 14 eplerenone Cmax and AUC in the elderly

were higher–by 22% and 45%, respectively, compared to young subjects. Mean eplerenone apparent oral clearance adjusted for 70-kg body weight on Day 7 and Day 14 were lower by 29% and 31%, respectively, in the elderly compared to young subjects. The reduction in apparent oral clearance in the elderly is probably not due to reduced bioavailability, since the amount of eplerenone excreted in urine in elderly subjects over 48 hours following single dose and over a dosing interval, 24 hours, following multiple dosing were not statistically significantly different compared to young subjects.

Mean Eplerenone Plasma Concentrations by Age Group, 0-24 Hours (Including Day 7 Eplerenone Data for Subject 0110)



Mean Day 1, Day 7 and Day 14 SC-70303, open-ring form of eplerenone, Cmax in the elderly were higher by 16%, 24% and 29%, respectively, and mean SC-70303 AUC were higher by 51%, 67% and 68%, respectively, compared to young subjects. The increase in SC-70303 concentrations in the elderly is probably a consequence of higher eplerenone concentrations in the elderly, as evidenced by the increase in amount of SC-70303 recovered in the urine 16% and 34% on Day 1 and Day 7, respectively. The amounts of SC-70303 recovered in the urine from both elderly and young subjects on Day 14 were identical.

Table 3: Eplerenone and SC-70303 AUC Values Within Age Group (Excluding Subject 0110 on Day 7)

	AUC Geometric Means						Ratio Test/Ref	95% CI for Ratio of Means
	Test	Reference	Test		Reference			
			N	LS Mean	N	Mean		
EPLERENONE								
AUC								
Young	Day 7	Day 1	23	10364.4	23	10338.6	1.00	(0.92, 1.09)
	Day 14	Day 1	23	11118.0	23	10338.6	1.08	(0.96, 1.21)
	Day 14	Day 7	23	11118.0	23	10364.4	1.07	(1.02, 1.13)
Elderly	Day 7	Day 1	24	14467.4	24	14428.7	1.00	(0.94, 1.07)
	Day 14	Day 1	24	16066.5	24	14428.7	1.11	(1.05, 1.18)
	Day 14	Day 7	24	16066.5	24	14467.4	1.11	(1.05, 1.18)
SC-70303								
AUC								
Young	Day 7	Day 1	23	407.58	23	447.15	0.93	(0.85, 1.01)
	Day 14	Day 1	24	468.73	24	447.15	1.05	(0.95, 1.15)
	Day 14	Day 7	23	468.73	23	407.58	1.15	(1.08, 1.22)
Elderly	Day 7	Day 1	24	666.45	24	673.68	0.99	(0.92, 1.06)
	Day 14	Day 1	24	776.48	24	673.68	1.15	(1.08, 1.23)
	Day 14	Day 7	24	776.48	24	666.45	1.17	(1.10, 1.24)

Mean accumulation at steady-state, Day 14 compared to Day 1 were not very different between young (8%) and elderly (11%) subjects. Mean steady-state accumulation of SC-70303, Day 14 compared to Day 1, was 5% in young subjects and 17% in elderly subjects. These differences are expected to be clinically significant.

Effect of Gender on Eplerenone and SC-70303 Pharmacokinetics

Following single and multiple oral doses of eplerenone, mean eplerenone plasma pharmacokinetic parameters were not significantly different between female and males except for amount of eplerenone excreted unchanged in urine. Following single and multiple dosing, Cmax in females was 5%-7% higher compared to males while AUC was similar between sexes. Apparent oral clearance adjusted for 70-kg body weight was similar between females and males. Oral bioavailability seemed to be higher in females as evidenced by Day 1, Day 7 and Day 14 mean urinary recoveries of eplerenone which were higher by 34%, 20% and 4%, respectively, in females compared to males.

Table 5: Ratio and 90% Confidence Interval for Eplerenone and SC-70303 Pharmacokinetic Parameters by Gender (Excluding Subject 0110 Day 7 Data for SC-66110)

Pharmacokinetic Parameter	Least Squares Means		Ratio Female/Male	90% CI for Ratio	P-Value
	Female	Male			
	N = 24	N = 24			
EPLERENONE					
Single Dose (Day 1)					
AUC(0-lqc) (hr*ng/mL)	12087.99	12355.52	0.978	(0.7729, 1.2382)	0.877
AUC(0-∞) (hr*ng/mL)	12191.52	12485.40	0.976	(0.7724, 1.2342)	0.865
Cmax (ng/mL)	1884.80	1803.12	1.045	(0.9212, 1.1860)	0.559

CL/F (L/hr)	8.20	8.01	1.024	(0.8101, 1.2945)	0.865
CL/F/WT (L/hr/70 kg)	8.02	7.85	1.023	(0.8091, 1.2926)	0.873
XU(0-48) (μg)	1682.39	1254.81	1.341	(0.9474, 1.8973)	0.163
Multiple Dose (Day 7)					
AUC(0-24) (hr*ng/mL)	12506.60	11976.07	1.044	(0.8302, 1.3134)	0.752
Cmax (ng/mL)	2005.26	1810.87	1.107	(0.9403, 1.3040)	0.300
CL/F (L/hr)	8.00	8.35	0.958	(0.7613, 1.2044)	0.752
CL/F/WT (L/hr/70 kg)	7.84	8.20	0.956	(0.7604, 1.2023)	0.744
XU(0-24) (μg)	1717.74	1423.17	1.207	(0.8647, 1.6845)	0.348
Multiple Dose (Day 14)					
AUC(0-24) (hr*ng/mL)	13400.88	13326.18	1.006	(0.7932, 1.2748)	0.969
Cmax (ng/mL)	2003.46	1954.33	1.025	(0.8851, 1.1872)	0.778
CL/F (L/hr)	7.46	7.50	0.994	(0.7844, 1.2606)	0.969
CL/F/WT (L/hr/70 kg)	7.32	7.37	0.993	(0.7838, 1.2579)	0.960
XU(0-24) (μg)	1585.74	1518.68	1.044	(0.7284, 1.4967)	0.841
SC-70303					
Single Dose (Day 1)					
AUC(0-lqc) (hr*ng/mL)	479.26	516.77	0.927	(0.7375, 1.1661)	0.583
AUC(0-∞) (hr*ng/mL)	529.83	568.56	0.932	(0.7439, 1.1673)	0.601
Cmax (ng/mL)	91.28	92.79	0.984	(0.8491, 1.1396)	0.852
XU(0-48) (μg)	5680.43	4774.41	1.190	(0.8763, 1.6152)	0.345
Multiple Dose (Day 7)					
AUC(0-24) (hr*ng/mL)	527.29	514.64	1.025	(0.8168, 1.2851)	0.858
Cmax (ng/mL)	96.84	87.62	1.105	(0.9407, 1.2984)	0.302
XU(0-24) (μg)	5766.22	4811.29	1.198	(0.7968, 1.8025)	0.460
Multiple Dose (Day 14)					
AUC(0-24) (hr*ng/mL)	594.56	612.14	0.971	(0.7901, 1.1938)	0.814
Cmax (ng/mL)	102.70	97.02	1.059	(0.9306, 1.2040)	0.462
XU(0-24) (μg)	5559.41	5804.25	0.958	(0.7235, 1.2680)	0.798

Following single and multiple oral doses of eplerenone, mean SC-70303 plasma pharmacokinetic parameters were not significantly different between female and males except for amount of eplerenone excreted unchanged in urine. Following single and multiple dosing, Cmax in females was 2%-10% higher compared to males while AUC was about 7% lower in females following a single dose but was similar at steady-state. Day 1 and Day 7 mean urinary recoveries of SC-70303 were higher by 19% and 20%, respectively, in females compared to males. Day 14 mean urinary recovery was similar in females and males.

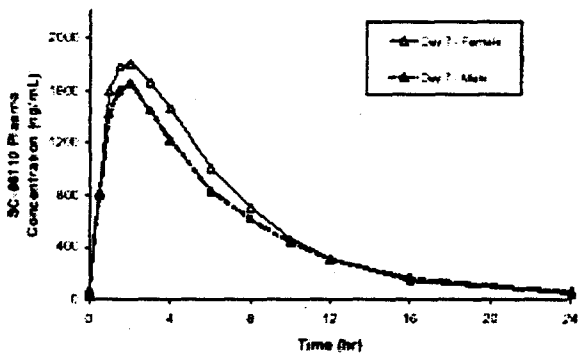
Table 5: Eplerenone and SC-70303 AUC Values Within Gender (Excluding Subject 0110 on Day 7)

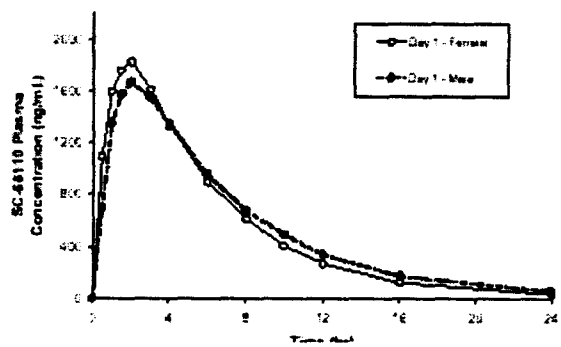
	Test	Reference	AUC Geometric Means		Ratio Test/Ref	95% CI for Ratio of Means
			Test	Reference		
			N = 24	N = 24		
Eplerenone AUC						
Female	Day 7	Day 1	12743.7	12001.3	1.06	(0.99, 1.13)
	Day 14	Day 1	13601.7	12001.3	1.13	(1.04, 1.24)

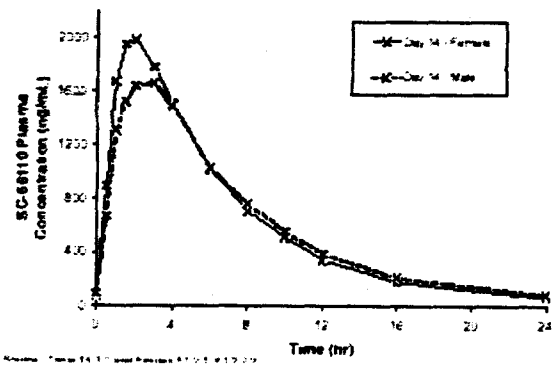
	Day 14	Day 7	13601.7	12743.7	1.07	(1.01, 1.12)
Male	Day 7	Day 1	11831.3	12529.6	0.94	(0.88, 1.01)
	Day 14	Day 1	13228.2	12529.6	1.06	(0.96, 1.16)
	Day 14	Day 7	13228.2	11831.3	1.12	(1.05, 1.19)
SC-70303 AUC						
Female	Day 7	Day 1	556.40	536.81	1.04	(0.96, 1.12)
	Day 14	Day 1	616.85	536.81	1.15	(1.05, 1.26)
	Day 14	Day 7	616.85	556.40	1.11	(1.06, 1.16)
Male	Day 7	Day 1	492.05	561.16	0.88	(0.83, 0.94)
	Day 14	Day 1	590.02	561.16	1.05	(0.98, 1.12)
	Day 14	Day 7	590.02	492.05	1.21	(1.13, 1.29)

Following multiple dosing, mean accumulation in females for both eplerenone and SC-70303 was higher compared to males. Mean steady-state eplerenone accumulation (Day 14 to Day 1), was 13% in females while males exhibited a mean accumulation of 6%. Mean SC-70303 accumulation was 15% in females and 5% in males.

Mean Eplerenone Plasma Concentrations by Gender, 0-24 Hours (Including Day 7 Eplerenone Data for Subject 0110)







Analysis of pharmacokinetic parameters by gender and age group for the single and multiple dose data indicated that mean eplerenone Cmax in elderly male subjects on Day 1, Day 7 and Day 14 were higher by 15%, 8% and 16%, respectively, and AUC on Day 1, Day 7 and Day 14 were higher by 34%, 36% and 46%, respectively, compared to young male subjects. Mean eplerenone apparent oral clearance adjusted for 70-kg body weight in elderly male subjects on Day 1, Day 7 and Day 14 were lower by 25%, 26% and 32%, respectively, compared to young male subjects. Mean amount of eplerenone excreted in urine (XU) in elderly male subjects over 48 hours following single dose was higher by 7% while on Day 7 XU_{0-24} was lower in elderly male subjects by 24% compared to young male subjects. Day 14 XU_{0-24} was similar between young and elderly male subjects.

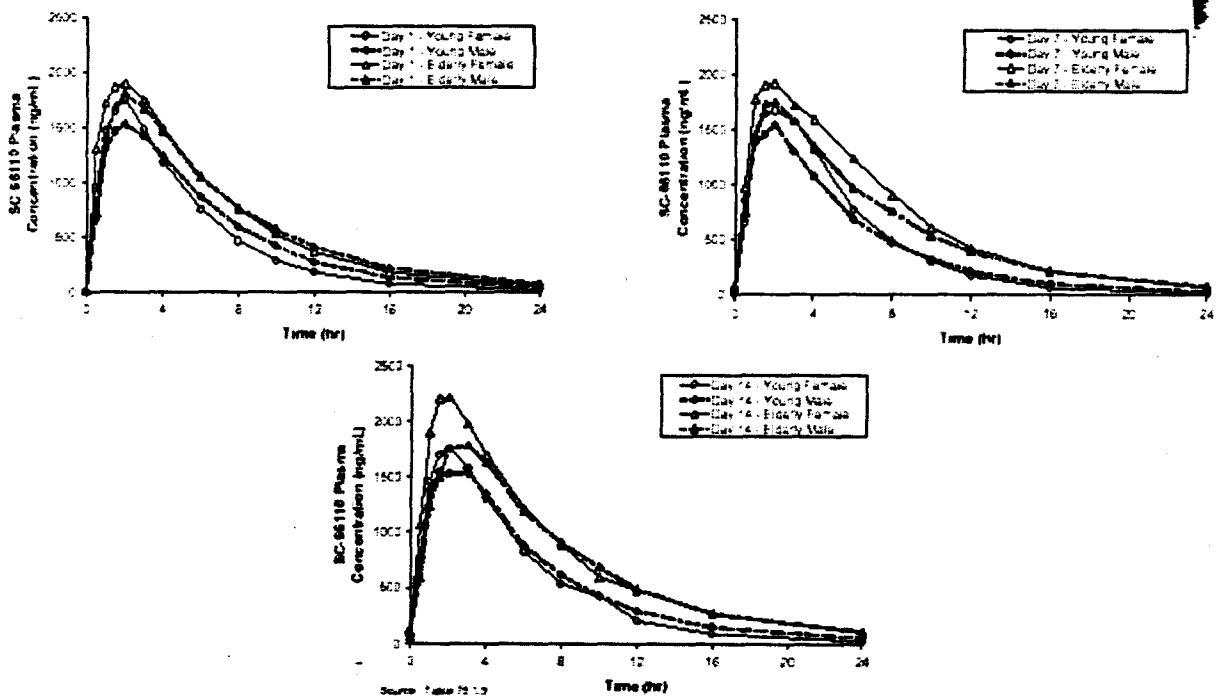
Table 6: Ratio and 90% Confidence Interval for Eplerenone Pharmacokinetic Parameters by Gender and Age Group (Excluding Subject 0110 Day 7 Data)

Pharmacokinetic Parameter	Least Squares Means		Ratio Elderly/Young	90% CI for Ratio	p-value
	Elderly	Young			
	N = 12	N = 12			
MALES					
Single Dose (Day 1)					
AUC(0-lqc) (hr*ng/mL)	14521.71	10862.16	1.337	(1.0322, 1.7315)	0.067
AUC(0-∞) (hr*ng/mL)	14662.33	10971.35	1.336	(1.0336, 1.7278)	0.066
Cmax (ng/mL)	1904.95	1663.12	1.145	(0.9925, 1.3218)	0.118
CL/F (L/hr)	6.82	9.11	0.748	(0.5787, 0.9674)	0.066
CL/F/WT (L/hr/70 kg)	6.15	8.20	0.751	(0.5802, 0.9710)	0.069
XU(0-48) (µg)	1329.76	1235.36	1.076	(0.7274, 1.5927)	0.750
Multiple Dose (Day 7)					
AUC(0-24) (hr*ng/mL)	13706.74	10076.74	1.360	(1.0187, 1.8162)	0.081
Cmax (ng/mL)	1859.71	1719.65	1.081	(0.9082, 1.2876)	0.448
CL/F (L/hr)	7.30	9.92	0.735	(0.5505, 0.9816)	0.081
CL/F/WT (L/hr/70 kg)	6.59	8.94	0.737	(0.5518, 0.9850)	0.085
XU(0-24) (µg)	1254.88	1639.26	0.766	(0.5041, 1.1624)	0.283
Multiple Dose (Day 14)					
AUC(0-24) (hr*ng/mL)	15873.31	10842.65	1.464	(1.0943, 1.9584)	0.035
Cmax (ng/mL)	2009.22	1735.73	1.158	(0.9673, 1.3852)	0.175
CL/F (L/hr)	6.30	9.22	0.683	(0.5106, 0.9137)	0.035
CL/F/WT (L/hr/70 kg)	5.69	8.31	0.685	(0.5122, 0.9162)	0.036
XU(0-24) (µg)	1478.75	1503.64	0.983	(0.6600, 1.4652)	0.943
FEMALES					
Single Dose (Day 1)					
AUC(0-lqc) (hr*ng/mL)	14006.22	10096.60	1.387	(1.0609, 1.8138)	0.048
AUC(0-∞) (hr*ng/mL)	14142.75	10184.12	1.389	(1.0633, 1.8136)	0.046
Cmax (ng/mL)	2029.00	1796.76	1.129	(0.9827, 1.2975)	0.147
CL/F (L/hr)	7.07	9.82	0.720	(0.5513, 0.9404)	0.046
CL/F/WT (L/hr/70 kg)	7.52	10.45	0.719	(0.5510, 0.9384)	0.045
XU(0-48) (µg)	1853.13	1464.00	1.266	(0.8888, 1.8025)	0.264
Multiple Dose (Day 7)					
AUC(0-24) (hr*ng/mL)	15424.17	10529.12	1.465	(1.1687, 1.8360)	0.008
Cmax (ng/mL)	2227.26	1853.29	1.202	(0.9922, 1.4556)	0.114
CL/F (L/hr)	6.48	9.50	0.683	(0.5446, 0.8555)	0.008
CL/F/WT (L/hr/70 kg)	6.89	10.11	0.682	(0.5443, 0.8537)	0.008
XU(0-24) (µg)	1867.78	1571.32	1.189	(0.8727, 1.6190)	0.347
Multiple Dose (Day 14)					

AUC(0-24) (hr*ng/mL)	16365.26	11304.78	1.448	(1.1334, 1.8488)	0.017
Cmax (ng/mL)	2378.73	1847.98	1.287	(1.1167, 1.4836)	0.006
CL/F (L/hr)	6.11	8.85	0.691	(0.5408, 0.8822)	0.017
CL/F/WT (L/hr/70 kg)	6.50	9.42	0.690	(0.5407, 0.8799)	0.016
XU(0-24) (μg)	1782.75	1463.08	1.218	(0.8147, 1.8223)	0.408

Analysis of pharmacokinetic parameters by gender and age group for the single and multiple dose data indicated that mean eplerenone Cmax in elderly female subjects on Day 1, Day 7 and Day 14 were higher by 13%, 20% and 29%, respectively, and AUC on Day 1, Day 7 and Day 14 were higher by 39%, 47% and 45%, respectively, compared to young female subjects. The differences in Cmax are similar to those observed between elderly and young male subjects, however, the differences in AUC between elderly female and young female subjects is slightly more pronounced compared to their male counterparts. Mean eplerenone apparent oral clearance adjusted for 70-kg body weight in elderly female subjects on Day 1, Day 7 and Day 14 were lower by 28%, 32% and 31%, respectively, compared to young female subjects. Mean amount of eplerenone excreted in urine (XU) in elderly female subjects over 48 hours following single dose was higher by 27% and Day 7 and Day 14 XU_{0-24} were higher in elderly female subjects by 27% and 22%, respectively, compared to young female subjects.

Mean Eplerenone Plasma Concentrations Stratified by Age Group and Gender, 0-24 Hours (Including Day 7 Eplerenone Data for Subject 0110)



Analysis of pharmacokinetic parameters by age group and gender for the single and multiple dose data indicated that mean eplerenone Cmax in young female and male subjects on Day 1, Day 7 and Day 14 were similar. Mean AUC in young female subjects on Day 1, Day 7 and Day 14 were lower by 13%, 8% and 3%, respectively, compared to

young male subjects. Mean eplerenone apparent oral clearance adjusted for 70-kg body weight in young female subjects on Day 1 and Day 7 were higher by 15% and 9%, respectively, while on Day 14 they were similar compared to young male subjects. Mean amount of eplerenone excreted in urine (XU) in young female subjects over 48 hours following single dose was higher by 20% and Day 7 and Day 14 XU_{0-24} were similar compared to young male subjects.

Table 7: Ratio and 90% Confidence Interval for Eplerenone Pharmacokinetic Parameters by Age Group and Gender (Excluding Subject 0110 Day 7 Data)

Pharmacokinetic Parameter	Least Squares Means		Ratio Female/Male	90% CI for Ratio	p-value
	Female	Male			
	N = 12	N = 12			
YOUNG					
Single Dose (Day 1)					
AUC(0-lqc) (hr*ng/mL)	9733.72	11219.04	0.868	(0.5944, 1.2556)	0.516
AUC(0-∞) (hr*ng/mL)	9824.63	11327.97	0.867	(0.6001, 1.2532)	0.513
Cmax (ng/mL)	1727.81	1738.61	0.994	(0.8199, 1.2044)	0.956
CL/F (L/hr)	10.18	8.83	1.153	(0.7978, 1.6661)	0.513
CL/F/WT (L/hr/70 kg)	10.10	8.77	1.153	(0.7972, 1.6661)	0.515
XU(0-48) (µg)	1457.36	1210.22	1.204	(0.6434, 2.2536)	0.615
Multiple Dose (Day 7)					
AUC(0-24) (hr*ng/mL)	9948.35	10838.09	0.918	(0.6452, 1.3057)	0.680
Cmax (ng/mL)	1780.55	1809.63	0.984	(0.7794, 1.2420)	0.906
CL/F (L/hr)	10.05	9.23	1.089	(0.7658, 1.5497)	0.680
CL/F/WT (L/hr/70 kg)	10.03	9.21	1.089	(0.7663, 1.5475)	0.680
XU(0-24) (µg)	1546.16	1660.91	0.931	(0.5652, 1.5332)	0.807
Multiple Dose (Day 14)					
AUC(0-24) (hr*ng/mL)	10988.84	11260.69	0.976	(0.6658, 1.4301)	0.913
Cmax (ng/mL)	1777.88	1838.88	0.967	(0.7651, 1.2216)	0.806
CL/F (L/hr)	9.10	8.88	1.025	(0.6992, 1.5017)	0.913
CL/F/WT (L/hr/70 kg)	9.08	8.87	1.024	(0.7000, 1.4988)	0.914
XU(0-24) (µg)	1478.04	1497.88	0.987	(0.5649, 1.7233)	0.968
ELDERLY					
Single Dose (Day 1)					
AUC(0-lqc) (hr*ng/mL)	14840.11	13764.43	1.078	(0.7802, 1.4898)	0.693
AUC(0-∞) (hr*ng/mL)	14958.78	13917.34	1.075	(0.7794, 1.4821)	0.703
Cmax (ng/mL)	2043.52	1881.50	1.086	(0.9085, 1.2983)	0.435
CL/F (L/hr)	6.69	7.19	0.930	(0.6747, 1.2829)	0.703
CL/F/WT (L/hr/70 kg)	6.44	6.95	0.928	(0.6729, 1.2789)	0.692
XU(0-48) (µg)	1938.77	1303.34	1.488	(1.0129, 2.1844)	0.090
Multiple Dose (Day 7)					
AUC(0-24) (hr*ng/mL)	15592.26	13423.68	1.162	(0.8415, 1.6031)	0.433
Cmax (ng/mL)	2244.09	1833.42	1.224	(0.9595, 1.5613)	0.168
CL/F (L/hr)	6.41	7.45	0.861	(0.6237, 1.1882)	0.433
CL/F/WT (L/hr/70 kg)	6.18	7.20	0.858	(0.6217, 1.1852)	0.425
XU(0-24) (µg)	1896.18	1241.18	1.528	(0.9595, 2.4323)	0.132
Multiple Dose (Day 14)					
AUC(0-24) (hr*ng/mL)	16296.86	15839.31	1.029	(0.7441, 1.4224)	0.881
Cmax (ng/mL)	2251.63	2082.58	1.081	(0.8848, 1.3210)	0.510
CL/F (L/hr)	6.14	6.31	0.972	(0.7029, 1.3437)	0.881
CL/F/WT (L/hr/70 kg)	5.92	6.10	0.969	(0.7012, 1.3394)	0.869
XU(0-24) (µg)	1705.61	1535.88	1.111	(0.6692, 1.8427)	0.725

Analysis of pharmacokinetic parameters by age group and gender for the single and multiple dose data indicated that mean eplerenone Cmax in elderly female subjects in Day 1, Day 7 and Day 14 were slightly higher by 9%, 22% and 8%, respectively, compared to elderly male subjects. Contrary to the comparison between young male and female subjects, mean eplerenone AUC in elderly female subjects in Day 1 and Day 7 were slightly higher by 8% and 16%, respectively, while Day 14 values were similar to elderly male subjects. Mean eplerenone apparent oral clearance adjusted for 70-kg body weight in elderly female subjects were similar (decrease of <14%) on Day 1, Day 7 and Day 14 to elderly male subjects. Mean amount of eplerenone excreted in urine (XU) in elderly female subjects on Day 1, Day 7 and Day 14 were 49%, 53% and 11% higher, respectively, compared to elderly male subjects.

Table 8: Eplerenone and SC-70303 AUC Values Within Age Group and Gender (Excluding Subject 0110 on Day 7)

	Test	Reference	AUC Geometric LSM		Ratio Test/Ref	95% CI for Ratio of Means
			Test	Reference		
			N = 12	N = 12		
Eplerenone AUC						
Young Female	Day 7	Day 1	10630.2	10171.2	1.05	(0.93, 1.18)
	Day 14	Day 1	11360.8	10171.2	1.12	(0.95, 1.31)
	Day 14	Day 7	11360.8	10630.2	1.07	(0.98, 1.17)
Young Male	Day 7	Day 1	10082.0	10524.4	0.96	(0.84, 1.09)
	Day 14	Day 1	10859.1	10524.4	1.03	(0.85, 1.25)
	Day 14	Day 7	10859.1	10082.0	1.08	(0.99, 1.17)
Elderly Female	Day 7	Day 1	15277.5	14160.8	1.08	(1.00, 1.17)
	Day 14	Day 1	16284.6	14160.8	1.15	(1.04, 1.27)
	Day 14	Day 7	16284.6	15277.5	1.07	(0.99, 1.14)
Elderly Male	Day 7	Day 1	13700.2	14701.6	0.93	(0.85, 1.02)
	Day 14	Day 1	15851.3	14701.6	1.08	(0.99, 1.17)
	Day 14	Day 7	15851.3	13700.2	1.16	(1.04, 1.28)
SC-70303 AUC						
Young Female	Day 7	Day 1	435.22	436.70	1.00	(0.87, 1.15)
	Day 14	Day 1	476.33	436.70	1.09	(0.93, 1.28)
	Day 14	Day 7	476.33	435.22	1.09	(1.03, 1.16)
Young Male	Day 7	Day 1	379.43	457.85	0.86	(0.78, 0.94)
	Day 14	Day 1	461.25	457.85	1.01	(0.89, 1.13)
	Day 14	Day 7	461.25	379.43	1.21	(1.09, 1.34)
Elderly Female	Day 7	Day 1	711.32	659.86	1.08	(0.98, 1.18)
	Day 14	Day 1	798.83	659.86	1.21	(1.09, 1.34)
	Day 14	Day 7	798.83	711.32	1.12	(1.04, 1.21)
Elderly Male	Day 7	Day 1	624.42	687.78	0.91	(0.82, 1.00)
	Day 14	Day 1	754.75	687.78	1.10	(1.02, 1.18)
	Day 14	Day 7	754.75	624.42	1.21	(1.09, 1.34)

Mean accumulation of eplerenone (Day 14 to Day 1) in young males was lower (3%) compared to young female subjects (12%). Mean accumulation in elderly males was

lower (8%) compared to elderly females (15%). The difference in accumulation between gender is not expected to be clinically significant.

Mean accumulation of SC-70303 (Day 14 to Day 1) in young females was higher (9%) compared to no accumulation in young male subjects. Mean accumulation in elderly subjects was higher compared to younger subjects. Mean accumulation in elderly females was higher (21%) compared to elderly males (10%).

CONCLUSIONS:

Following a single oral 100 mg dose of eplerenone, mean eplerenone Cmax and AUC in the elderly were higher, 14% and 36%, respectively, compared to young subjects. Mean eplerenone apparent oral clearance adjusted for 70-kg body weight was lower by 27% in the elderly compared to young subjects. A similar difference in pharmacokinetic parameters were observed following multiple dosing too. Mean accumulation at steady-state, Day 14 compared to Day 1 were not very different between young (8%) and elderly (11%) subjects. Following single and multiple oral doses of eplerenone, mean eplerenone plasma pharmacokinetic parameters were not significantly different between female and males except for amount of eplerenone excreted unchanged in urine: Day 1, Day 7 and Day 14 mean urinary recoveries of eplerenone were higher by 34%, 20% and 4%, respectively, in females compared to males. Mean steady-state eplerenone accumulation (Day 14 to Day 1), was 13% in females while males exhibited a mean accumulation of 6%.

The above differences in eplerenone pharmacokinetic parameters between young and elderly subjects or the differences in accumulation between sexes are not expected to be clinically relevant.

EPLERENONE SINGLE AND MULTIPLE DOSE PHARMACOKINETIC EVALUATION IN SUBJECTS WITH AND WITHOUT HEPATIC IMPAIRMENT

STUDY INVESTIGATORS AND SITES: Three Investigators, one in the U.S. and two in Spain

Report No.: NE3-96-02-012

OBJECTIVES:

1. To determine the effect of hepatic impairment on the pharmacokinetic profile of eplerenone after single and multiple oral doses of eplerenone.
2. To determine the safety and tolerability of single and multiple oral doses of eplerenone in hepatically impaired subjects relative to healthy subjects.
3. To evaluate the hormonal effects of single and multiple doses of eplerenone in hepatically impaired subjects relative to healthy subjects.

FORMULATIONS:

Eplerenone –100 mg capsules (Lot numbers RCT 10486 and RCT 10348) by Searle.

STUDY DESIGN:

This was an open-label, multiple-dose study conducted in 16 normal (6 F/11 M, age range: 32-64 years) healthy subjects and 16 subjects (6 F/12 M, age range: 40-64 years) with moderate hepatic impairment. The degree of the subject's impairment was Class B (with ascites), based on the Child-Pugh Classification System The hepatically impaired individuals were matched with normal healthy volunteers based on sex, age, weight, and smoking status. All study participants received a single 400 mg dose of eplerenone on the morning of Day 1, no drug on Day 2, and a 400 mg dose of eplerenone on the morning of Days 3-7.

ASSAY:

Sample Collection

Blood samples for measuring plasma concentrations of eplerenone and SC-70303 were drawn on Days 1 and 7 for all subjects at the following time-points: predose and at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, and 48 hours postdose. In addition trough (predose) blood samples were drawn on Days 4 through 8.

Urine samples were collected and pooled on Days 1 and 7 during the following time periods: -24 to 0 hours predose and 0-2, 2-4, 4-8, 8-12, 12-24, and 24-48 hours postdose.

RESULTS:

Eplerenone is primarily metabolized hepatically by CYP 3A4. This study assessed the impact of moderate hepatic impairment on the pharmacokinetics of eplerenone and its open-ring form SC-70303.

The pharmacokinetic parameters of eplerenone and its metabolites obtained following oral administration of 400-mg capsule of eplerenone once daily for 14 days in subjects with hepatic impairment and in normal volunteers are listed in the following table.

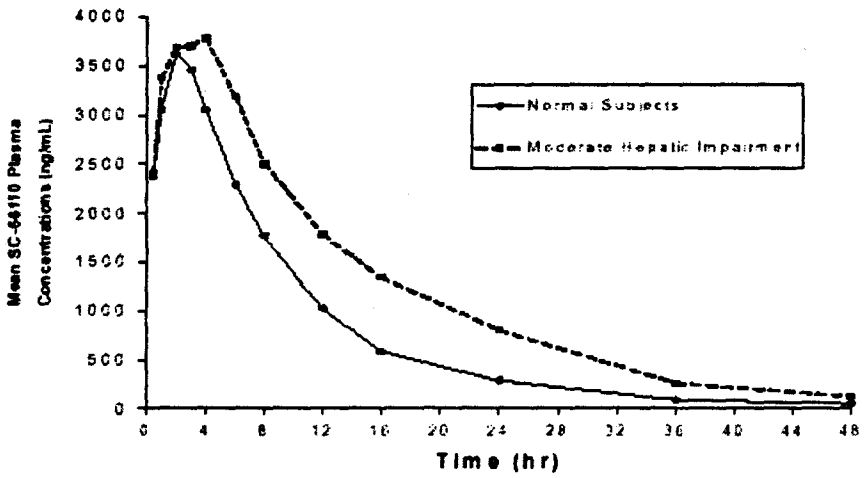
Table 1: Single and Multiple-Dose Eplerenone and SC-70303 Pharmacokinetic Parameters

Parameter	EPLERENONE				SC-70303			
	Single-Dose		Multiple-Dose		Single-Dose		Multiple-Dose	
	Normal	Impaired	Normal	Impaired	Normal	Impaired	Normal	Impaired
AUC (hr*ng/mL)								
n	16	17	17	16	16	16	17	17
Mean	31015.37	51438.98	33784.48	48821.25	2468.49	5753.17	2787.50	6119.46
%CV	(38.73)	(46.50)	(46.94)	(32.87)	(46.03)	(47.60)	(56.70)	(64.47)
Cmax (ng/mL)								
n	17	18	17	18	17	18	17	18
Mean	3840.23	3787.53	3883.18	4168.10	357.53	473.47	369.43	505.52
%CV	(28.30)	(35.69)	(33.17)	(26.95)	(33.31)	(44.49)	(36.83)	(52.10)
Tmax (hr)								
n	17	18	17	18	17	18	17	18
Mean	2.03	2.56	2.12	2.81	2.21	4.22	1.82	3.56
%CV	(49.64)	(42.38)	(49.05)	(50.83)	(62.62)	(51.09)	(54.79)	(43.38)
T1/2 (hr)								
n	16	17	17	18	16	16	17	18
Mean	6.31	6.78	7.61	8.07	4.42	5.85	5.25	7.31
%CV	(37.20)	(25.49)	(26.67)	(26.58)	(63.03)	(29.39)	(48.02)	(26.18)
CL/F (L/hr)								
n	16	17	17	16	NA	NA	NA	NA
Mean	15.21	10.51	13.82	8.96				
%CV	(46.33)	(81.02)	(36.01)	(29.33)				

CL/F/WT (L/hr/70 kg)								
n	16	17	17	16	NA	NA	NA	NA
Mean	14.09	10.35	12.87	9.37				
%CV	(45.15)	(69.50)	(35.79)	(36.54)				
XU0-48 (µg)								
n	16	14	16	10	16	16	16	13
Mean	8.78	10.27	9.12	16.92	23.03	56.15	23.37	65.39
%CV	(64.97)	(75.25)	(86.79)	(71.42)	(43.25)	(63.52)	(44.56)	(50.33)

Administration of a single 400 mg dose of eplerenone to moderate hepatic impairment subjects resulted in a 47% increase in eplerenone AUC, while Cmax of eplerenone decreased by 10%. Apparent oral clearance of eplerenone adjusted for 70-kg body weight decreased by 32% in moderate hepatic impairment subjects compared to normal subjects. Mean amount of eplerenone excreted unchanged in urine decreased by 8% in moderate hepatic impairment subjects. Mean $T_{1/2}$ was practically unchanged in hepatic impairment subjects compared to normal subjects.

Mean Eplerenone Plasma Concentrations Following Multiple Dose (Day 7) Administration



The effect of hepatic impairment on eplerenone pharmacokinetic parameters was similar following both single and multiple oral dosing of eplerenone. Following multiple oral doses of 400 mg eplerenone, mean steady-state eplerenone AUC increased by 42% in moderate hepatic impairment subjects and mean Cmax increased by 4%. Apparent oral clearance of eplerenone adjusted for 70-kg body weight decreased by 29% in moderate hepatic impairment subjects compared to normal subjects. Unlike single dose eplerenone pharmacokinetics, mean amount of eplerenone excreted unchanged in urine increased by 87% in moderate hepatic impairment subjects compared to normal subjects, which indicates a substantial increase in bioavailability. Mean $T_{1/2}$ was increased by 0.5 hours in hepatic impairment subjects compared to normal subjects. Following both single and

multiple dosing, Tmax in hepatic impairment subjects increased by 0.5-0.7 hours compared to normal subjects.

Following both single and multiple dosing, SC-70303, open-ring form of eplerenone, Tmax increased by about 2 hours in subjects with moderate hepatic impairment compared to normal subjects. Mean SC-70303 AUC was higher by 115% and 101%, and Cmax was higher by 17% and 22%, after single and multiple dosing, respectively in subjects with hepatic impairment compared to normal subjects. The amount of SC-70303 excreted in urine in hepatic impairment subjects was higher by 112% and 168% following single and multiple dosing, respectively.

Table 3: Ratio and 90% Confidence Interval for Eplerenone and SC-70303 Pharmacokinetic Parameters

Parameter	Least Squares Means		Ratio of Means Impaired/Normal	95% CI for Ratio of Means	p-Value
	Moderate Impairment	Normal			
Eplerenone Single-Dose					
AUC (0-∞) (hr*ng/mL)	42887.6	29244.8	1.467	(1.038, 2.073)	0.031 *
AUC (0-lqc) (hr*ng/mL)	42119.4	30438.8	1.384	(0.986, 1.942)	0.060
CL/F (L/hr)	9.3	13.7	0.682	(0.483, 0.964)	0.031 *
CL/F/WT (L/hr/70 kg)	9.1	13.3	0.687	(0.486, 0.972)	0.035 *
Cmax (ng/mL)	3484.4	3862.2	0.902	(0.732, 1.112)	0.323
Tmax (hr)	2.6	2.1	--	--	0.154
T1/2 (hr)	6.6	6.3	--	--	0.709
XU (0-48) (mg)	7.1	7.6	0.926	(0.483, 1.777)	0.811
Eplerenone Multiple-Dose					
AUC (0-24) (hr*ng/mL)	42451.0	29983.4	1.416	(1.121, 1.789)	0.005 **
CL/F (L/hr)	9.4	13.3	0.706	(0.559, 0.892)	0.005 **
CL/F/WT (L/hr/70 kg)	9.3	13.1	0.713	(0.562, 0.904)	0.007 **
Cmax (ng/mL)	3834.1	3700.9	1.036	(0.866, 1.239)	0.690
Tmax (hr)	2.8	2.1	--	--	0.135
T1/2 (hr)	8.1	7.6	--	--	0.567
XU (0-48) (mg)	13.3	7.1	1.871	(0.910, 3.845)	0.087
SC-70303 Single-Dose					
AUC (0-∞) (hr*ng/mL)	4884.9	2277.4	2.145	(1.567, 2.936)	<0.001 ***
AUC (0-lqc) (hr*ng/mL)	5057.8	2360.2	2.143	(1.513, 3.034)	<0.001 ***
Cmax (ng/mL)	416.1	356.7	1.166	(0.944, 1.441)	0.148
Tmax (hr)	4.2	2.1	--	--	0.003 **
T1/2 (hr)	5.6	4.3	--	--	0.151
XU (0-48) (mg)	44.7	21.1	2.122	(1.339, 3.363)	0.002 **
SC-70303 Multiple-Dose					
AUC (0-24) (hr*ng/mL)	4877.1	2433.0	2.005	(1.460, 2.753)	<0.001 ***
Cmax (ng/mL)	428.1	350.0	1.223	(0.949, 1.577)	0.116
Tmax (hr)	3.5	1.8	--	--	<0.001 ***
T1/2 (hr)	7.1	5.2	--	--	0.016 *
XU (0-48) (mg)	57.7	21.5	2.679	(1.744, 4.114)	<0.001 ***

Comparison of steady-state AUC over a dosing interval to Day 1 AUC indicated that the pharmacokinetics of eplerenone and SC-70303 were linear in moderate hepatic impairment although the AUC values were higher than those in normal subjects.

Table 5: Time-Related Linearity Upon Multiple Dosing

Parameter	Least Squares Means		Ratio of Means $AUC_{0-24}/AUC_{0-\infty}$	95% CI for Ratio of Means
	Single-Dose $AUC_{0-\infty}$	Multiple-Dose AUC_{0-24}		
Eplerenone				
Moderate Hepatic Impairment	49815.47	47239.78	0.95	(0.84, 1.07)
Normal	28713.97	29318.67	1.02	(0.93, 1.12)
SC-70303				
Moderate Hepatic Impairment	5351.13	4970.80	0.93	(0.77, 1.12)
Normal	2261.35	2317.09	1.02	(0.91, 1.15)

CONCLUSIONS

Eplerenone metabolism was affected by moderate hepatic impairment as evidenced by the higher AUC (42%-47%) in subjects with hepatic impairment compared to normal subjects following both single and multiple oral dosing of 400 mg eplerenone. Mean Cmax of eplerenone was not affected by moderate hepatic impairment. Mean amount of eplerenone excreted unchanged in urine was not affected following a single dose but increased by 87% following multiple dosing in moderate hepatic impairment subjects compared to normal subjects, which indicates a substantial increase in bioavailability due to a decrease in metabolism. SC-70303, open-ring form of eplerenone, concentrations were affected to a larger extent compared to eplerenone. SC-70303 AUC increased by 115% and 101% following single and multiple oral dosing. The amount of SC-70303 excreted in urine in hepatic impairment subjects was higher by 112% and 168% following single and multiple dosing, respectively.

COMMENTS:

1. The effect of moderate hepatic impairment on eplerenone AUC should be specified in the label.
2. Based on the dose-response of eplerenone, the increased eplerenone concentrations (approximately 50% higher) in moderate hepatic impairment patients is not expected to result in significant additional lowering of blood pressure. No dosing adjustment is warranted in moderate hepatic impairment patients from a blood pressure lowering perspective. The medical officer is requested to assess the impact of higher eplerenone concentrations on hyperkalemia.

3. Use of eplerenone in severe hepatic impairment patients should be contraindicated since the effect of severe hepatic impairment on eplerenone pharmacokinetics was not studied.