EVALUATION OF THE SINGLE AND MULTIPLE-DOSE PHARMACOKINETICS OF EPLERENONE IN SUBJECTS WITH AND WITHOUT RENAL IMPAIRMENT

STUDY INVESTIGATORS AND SITES:

Report No.: NE3-00-02-034

OBJECTIVES:

1. To compare the pharmacokinetic profile of single and multiple oral doses of eplerenone in subjects with varying degrees of renal impairment to that in normal healthy subjects.
2. To determine the safety and tolerability of single and multiple oral doses of eplerenone in patients with varying degrees of renal impairment
3. To measure hemodialysis clearance of the eplerenone
4. To compare plasma concentrations with and without hemodialysis.

FORMULATIONS:

Eplerenone – 100 mg Tablets (lot numbers RCT 11510, RCT 11640 and RCT 11792).

STUDY DESIGN:

This was a stratified, multiple-dose, open-label, parallel groups study in which single and multiple 100 mg eplerenone doses were to be administered to 2 groups of subjects: 23 healthy subjects and 29 subjects with renal impairment. Each normal subject was to correspond to a previously recruited renally impaired subject by sex, age (10 years), and weight (30%). The different groups recruited into the study are:
Group A (normal healthy) consisting of 23 subjects with 24-hour creatinine clearance (CLcr) values >80 mL/min.
The renally impaired patients were to be divided into the following groups:
Group B (Mild): 7 patients with 24-hour CLcr values of 50-80 mL/min
Group C (Moderate): 7 patients with 24-hour CLcr values of 30-49 mL/min
Group D (Severe): 7 patients with 24-hour CLcr values of <30 mL/min, but not on dialysis
Group E (Hemodialysis): 8 patients on hemodialysis with nil or negligible urine output.

All subjects were to received 100 mg eplerenone QD on Days 1 and 4-8. On Days 1 and 8, subjects received eplerenone 100 mg following an overnight fast, while on Days 4-7, subjects received eplerenone 100 mg with a standard low-fat meal.

Table 1: Baseline Demographics of Subjects Enrolled in the Study

	Number (Percent) of Subjects by Subject Group							
	Matched Pair		Matched Pair		Matched Pair		Matched Pair	
	B	A(B)	C	A(C)	D	A(D)	E	A(E)
	N=7	N=6	N=7	N=6	N=7	N=6	N=8	N=5
Age (years)								
Mean ± SD	61 ± 12.4	59 ± 11.0	51 ± 16.0	50 ± 14.7	58 ± 13.7	50 ± 9.8	53 ± 11.1	49 ± 14.0
Range	45 – 76	46 - 72	33 – 72	28 - 63	33 – 73	34 – 60	37 - 71	32 – 66
Ethnicity								
Black	1 (14.3)	2 (33.3)	4 (57.1)	0 (0.0)	2 (28.6)	1 (16.7)	5 (62.5)	0 (0.0)
Caucasian	6 (85.7)	4 (66.7)	3 (42.9)	6 (100.0)	4 (57.1)	5 (83.3)	3 (37.5)	5 (100.0)
Hispanic/Lat	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)
Gender								
Female	2 (28.6)	1 (16.7)	4 (57.1)	3 (50.0)	4 (57.1)	4 (66.7)	1 (12.5)	1 (20.0)
Male	5 (71.4)	5 (83.3)	3 (42.9)	3 (50.0)	3 (42.9)	2 (33.3)	7 (87.5)	4 (80.0)
Height (cm)								
Female Mean ± SD	157 ± 3.6	159 *	166 ± 5.3	168 ± 4.9	167 ± 5.5	158 ± 5.4	165 *	158 *
Male Mean ± SD	177 ± 4.9	177 ± 8.0	173 ± 4.6	175 ± 10.8	174 ± 9.0	177 ± 5.0	173 ± 6.0	176 ± 10.0
Weight (kg)								
Female Mean ± SD	99 ± 13.2	103 *	94 ± 17.7	84 ± 20.6	63 ± 10.9	74 ± 15.2	78 *	79 *
Male Mean ± SD	96 ± 16.2	89 ± 9.4	85 ± 21.6	89 ± 29.3	81 ± 9.6	83 ± 2.1	75 ± 29.2	86 ± 19.4

Group: A(B) = Normal matched to mild impairment, A(C) = Normal matched to moderate, A(D) = Normal matched to severe, A(E) = Normal matched to hemodialysis, B = Mild, C = Moderate, D = Severe, E = Hemodialysis

ASSAY:

Sample Collection

On Day 1, a 7-mL blood sample for analysis of eplerenone, SC-71597, and SC-70303 was collected predose, and at 30 and 45 minutes, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 16, 24, 36, and 48 hours postdose.

On Days 5-7, a 7-mL blood sample was collected 15 minutes predose to measure trough concentrations.

On Day 8, a 7-mL blood sample was collected predose, and at 30 and 45 minutes, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 16, and 24 hours postdose.

On Days 1 and 8, each patient in Group E also provided 7-mL arterial and venous blood samples immediately prior to the start of dialysis, and at the end of each hour of dialysis. Arterial samples were drawn before blood entered the dialyzer and venous samples were drawn after blood exited the dialyzer.

On Days 1-2 and 8-9, serum creatinine samples were drawn predose and at 12 and 24 hours postdose.

Urine was collected for pharmacokinetic analysis and creatinine clearance determination at the following intervals with respect to Day 1 dosing: -24-0 (predose), 0- 6, 6-12, 12-24, and 24-48 hours. The urine collection intervals for Day 8 dosing were identical, except that they ended at 24 hours postdose.

CLcr was determined using the following formula:

$$\text{CLcr (mL/min)} = \frac{\text{Volume of urine (mL)}}{\text{Collection Period (min)}} \times \frac{\text{Urine Creatinine (mg/dL)}}{\text{Serum Creatinine (mg/dL)}} \times \frac{1.73\ m^2}{\text{BSA*}}$$

where BSA = body surface area in m^2; CLrenal/F: Apparent renal clearance of eplerenone, computed as $XU_{(0\text{-}48)}/AUC_{(0\text{-}8)}$ for Day 1 and $XU_{(0\text{-}24)}/AUC_{(0\text{-}24)}$ for Day 8.

For subjects in Group E only, the hemodialysis clearance was calculated as

$$\sum_{i=1}^{n} \frac{C_{\text{dialysate}} * V_{\text{dialysate}}}{\frac{1}{2}(C_{\text{start}} + C_{\text{finish}})\,(\text{duration})}$$

RESULTS:

Effect of Renal Function of Eplerenone Pharmacokinetics

The pharmacokinetic parameters of eplerenone and its metabolites obtained following oral administration of 100-mg tablet of eplerenone given QD for 8 or 9 days in subjects with normal and impaired renal function are listed in the following table.

Table 1: Arithmetic Mean Eplerenone Pharmacokinetic Parameters

Pharmacokinetic Parameter	Subject Group							
	Matched Pair		Matched Pair		Matched Pair		Matched Pair	
	B	A(B)	C	A(C)	D	A(D)	E	A(E)
	N=7	N=6	N=7	N=6	N=7	N=6	N=8	N=5

Single-Dose								
AUC0-lqc (hr*ng/mL)	12006.10	10863.19	12490.27	11587.42	17011.48	11517.79	8009.83	9452.94
AUC0-inf (hr*ng/mL)	11005.07	11121.06	12665.08	11800.57	18282.67	11993.34	8120.48	9585.33
Cmax (ng/mL)	1686.68	1557.48	1687.45	1595.92	2159.56	1729.19	1717.23	1677.95
Tmax (hr)	2.21	1.84	2.41	2.21	2.05	2.13	1.28	2.21
T1/2 (hr)	4.37	4.04	4.83	4.31	6.00	3.93	3.70	2.86
CL/F (L/hr)	10.63	9.89	9.24	9.95	6.24	9.84	13.17	10.74
CL/F/WT (L/hr/70kg)	7.60	7.87	7.50	9.03	6.05	9.94	14.71	9.50
XU0-48 (μg)	1693.43	1546.35	1428.62	3351.36	852.71	1941.93	--	2004.83
Multiple-Dose								
AUC0-24 (hr*ng/mL)	11981.80	11448.79	13110.94	12032.96	16954.81	12588.51	7333.16	9863.02
Cmax (ng/mL)	1668.51	1873.41	1674.78	1659.37	2311.54	1880.16	1709.40	1728.99
Tmax (hr)	2.29	1.58	2.00	1.63	2.04	2.29	1.11	2.20
CL/F (L/hr)	10.09	9.12	9.03	9.44	6.43	9.06	14.25	10.45
CL/F/WT (L/hr/70 kg)	7.21	7.16	7.47	8.49	6.62	8.84	15.80	9.22
XU0-24 (μg)	1877.33	2327.30	1583.33	3071.73	1054.87	1824.02	--	2090.36

Group: A(B) = Normal matched to mild impairment, A(C) = Normal matched to moderate, A(D) = Normal matched to severe, A(E) = Normal matched to hemodialysis, B = Mild, C = Moderate, D = Severe, E = Hemodialysis

Following single dose administration of 100 mg eplerenone, Cmax of eplerenone in mild, and severe impairment subjects was higher by 11% and 25%, respectively, while in moderate impairment and dialysis patients Cmax was similar to normal volunteers. Eplerenone AUC was higher by 54% in severe renal impairment but was similar in other groups (mild, moderate and dialysis patients) compared to normal volunteers. Amount of eplerenone excreted in urine in moderate and severe impairment decreased by 54% and 57%, respectively, while the amount excreted was unchanged in mild renal impairment.

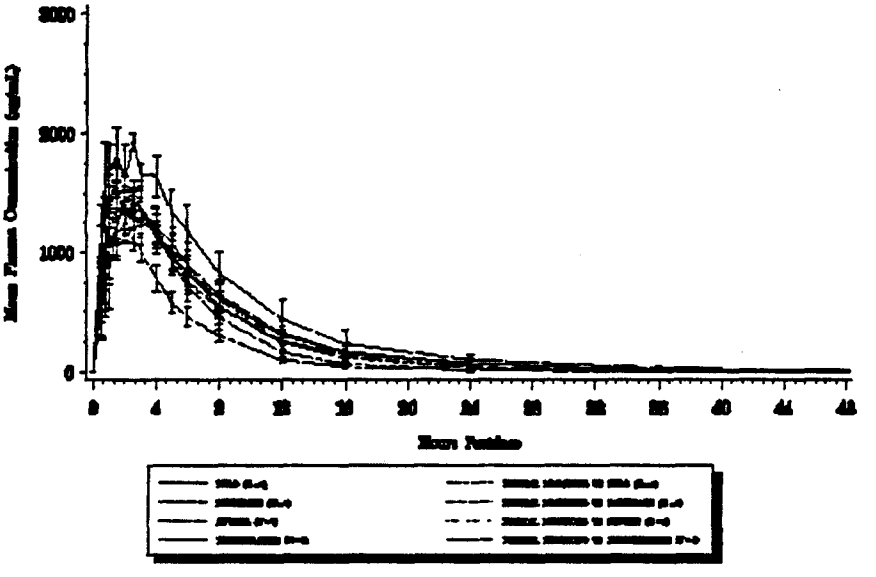
Table 2: Ratios and 90% Confidence Intervals for Single-Dose Eplerenone Pharmacokinetic Parameters

Comparison/ Pharmacokinetic Parameter	Least Squares Means		Ratio of Means	90% CI for	p-Value
	Impaired	Normal	Impaired/Normal	Ratio of Means	
Single-Dose B vs A(B)					
AUC0-lqc (hr*ng/mL)	10958.55	10424.43	1.051	(0.697, 1.587)	0.831
AUC0-inf (hr*ng/mL)	10146.38	10663.81	0.951	(0.632, 1.433)	0.830
Cmax (ng/mL)	1668.32	1507.77	1.106	(0.886, 1.381)	0.430
CL/F (L/hr)	9.86	9.38	1.051	(0.698, 1.582)	0.830
CL/F/WT (L/hr/70 kg)	7.06	7.25	0.974	(0.626, 1.515)	0.916
XU0-48 (μg)	1429.84	1404.48	1.018	(0.558, 1.856)	0.958
Tmax (hr)	2.21	1.84	--	--	0.530
T1/2 (hr)	4.37	4.04	--	--	0.724
Single-Dose C vs A(C)					
AUC0-lqc (hr*ng/mL)	11397.34	10688.90	1.066	(0.695, 1.637)	0.793
AUC0-inf (hr*ng/mL)	11541.17	10846.98	1.064	(0.690, 1.642)	0.802
Cmax (ng/mL)	1636.99	1580.77	1.036	(0.828, 1.295)	0.784
CL/F (L/hr)	8.66	9.22	0.940	(0.609, 1.450)	0.802
CL/F/WT (L/hr/70 kg)	6.84	7.69	0.890	(0.498, 1.590)	0.726
XU0-48 (μg)	1302.19	2833.29	0.460	(0.256, 0.824)	0.037
Tmax (hr)	2.41	2.21	--	--	0.794
T1/2 (hr)	4.83	4.31	--	--	0.724
Single-Dose D vs A(D)					
AUC0-lqc (hr*ng/mL)	15784.18	10751.72	1.468	(0.980, 2.198)	0.116
AUC0-inf (hr*ng/mL)	17008.36	11075.49	1.536	(0.957, 2.465)	0.131

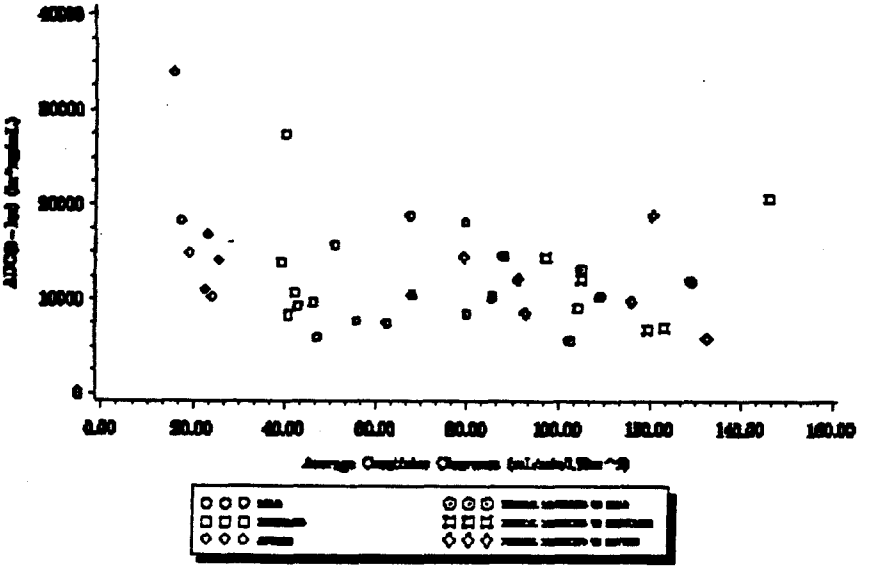
Cmax (ng/mL)	2132.04	1701.65	1.253	(1.043, 1.506)	0.050
CL/F (L/hr)	5.88	9.03	0.651	(0.406, 1.045)	0.131
CL/F/WT (L/hr/70 kg)	5.61	8.52	0.658	(0.365, 1.188)	0.227
XU0-48 (µg)	804.08	1854.83	0.434	(0.292, 0.643)	0.003
Tmax (hr)	2.05	2.13	--	--	0.916
T1/2 (hr)	6.00	3.93	--	--	0.076
Single-Dose E vs A(E)					
AUC0-lqc (hr*ng/mL)	7762.71	9314.80	0.833	(0.655, 1.060)	0.201
AUC0-inf (hr*ng/mL)	7831.25	9442.24	0.829	(0.637, 1.080)	0.227
Cmax (ng/mL)	1681.22	1661.32	1.012	(0.819, 1.250)	0.921
CL/F (L/hr)	12.77	10.59	1.206	(0.926, 1.569)	0.227
CL/F/WT (L/hr/70 kg)	14.00	8.95	1.563	(0.964, 2.535)	0.124
Tmax (hr)	1.28	2.21	--	--	0.031
T1/2 (hr)	3.70	2.86	--	--	0.546

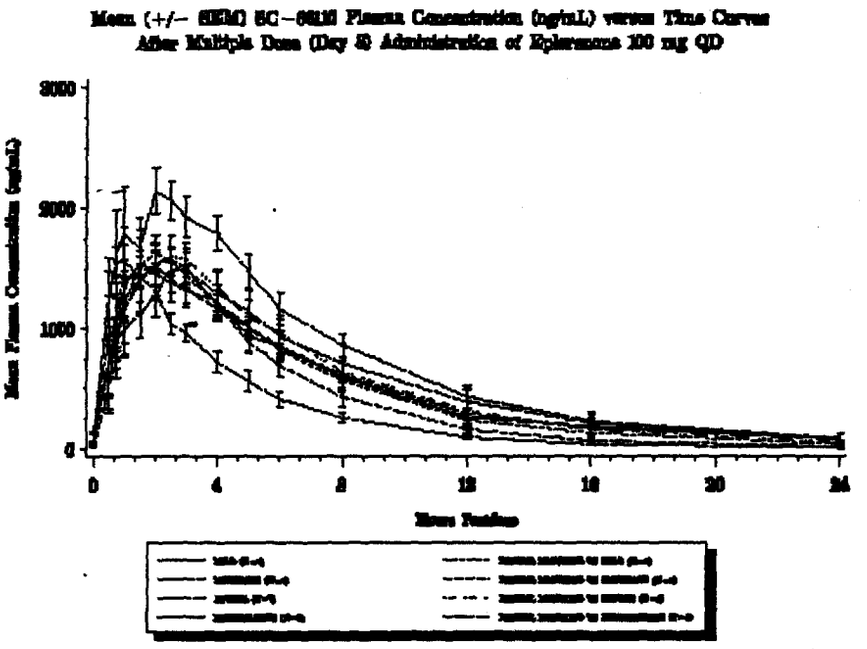
Group: A(B) = Normal matched to mild impairment, A(C) = Normal matched to moderate, A(D) = Normal matched to severe, A(E) = Normal matched to hemodialysis, B = Mild, C = Moderate, D = Severe, E = Hemodialysis

Mean (+/- SEM) SC-6810 Plasma Concentration (ng/mL) versus Time Curves
After Single Dose (Day 1) Administration of Epleronone 100 mg



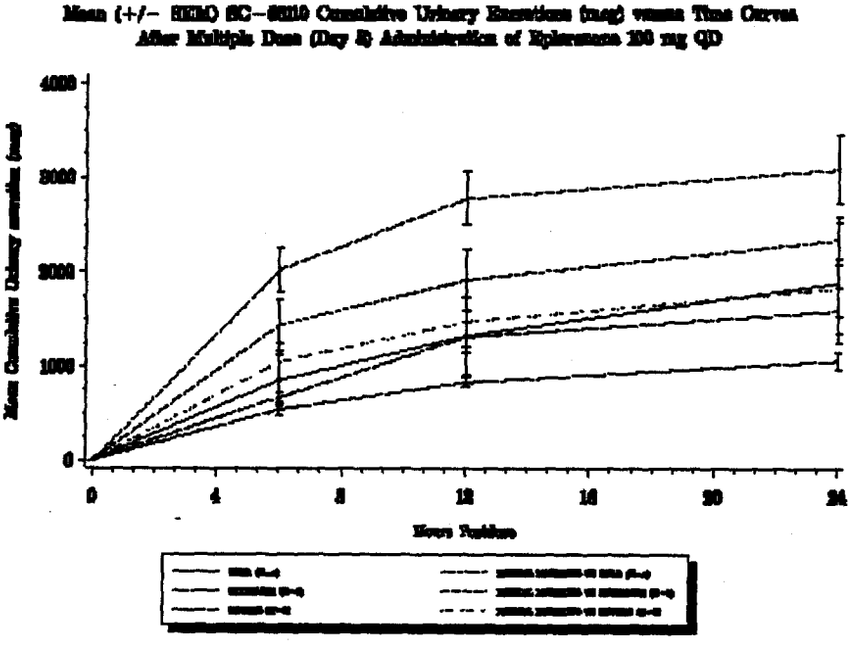
Plot of SC-6810 AUC0-lqd versus Creatinine Clearance by Subject Group
After Single Dose (Day 1) Administration of Epleronone 100 mg



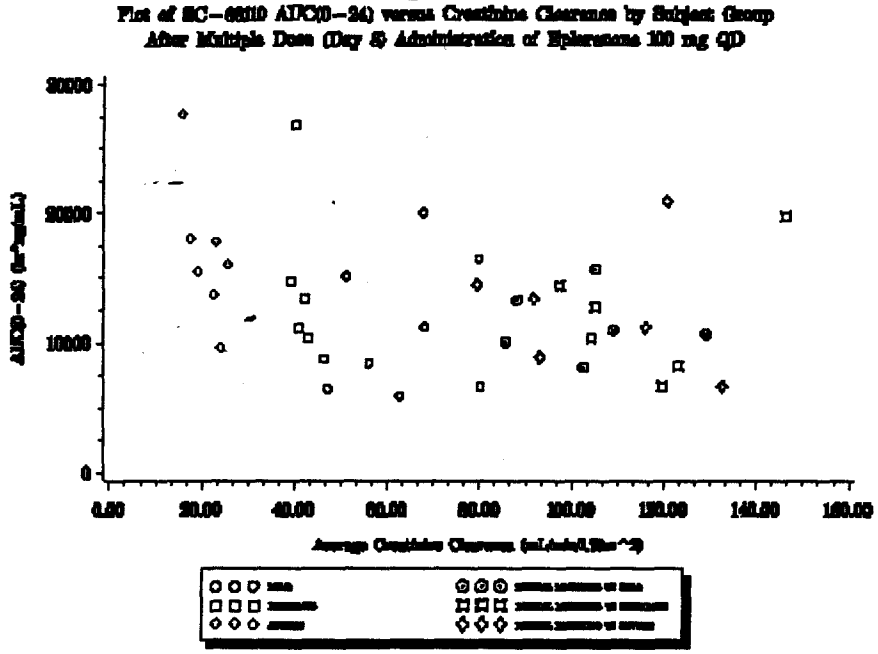


Tmax (hr)	2.04	2.29	--	--	0.687
Multiple-Dose E vs A(E)					
AUC0-24 (hr*ng/mL)	7174.82	9707.27	0.739	(0.593, 0.921)	0.031
Cmax (ng/mL)	1678.00	1724.81	0.973	(0.817, 1.158)	0.782
CL/F (L/hr)	13.94	10.30	1.353	(1.086, 1.685)	0.031
CL/F/WT (L/hr/70 kg)	14.77	8.71	1.695	(1.020, 2.817)	0.090
Tmax (hr)	1.11	2.20	--	--	0.014

Group: A(B) = Normal matched to mild impairment, A(C) = Normal matched to moderate, A(D) = Normal matched to severe, A(E) = Normal matched to hemodialysis, B = Mild, C = Moderate, D = Severe, E = Hemodialysis



The linearity of the relationship between renal function and eplerenone AUC, Cmax, and CL/F was examined using a linear regression model [log(PK parameter) = a + CLcr] for both single-dose and multiple-dose administration. There was no correlation between



single dose and multiple dose pharmacokinetic parameters, Cmax, AUC or CL/F and renal function, except for a linear relationship with respect to single-dose Cmax (p=0.008).

Table 4: Investigation of a Linear Relationship between Renal Function and Eplerenone Pharmacokinetic Parameters

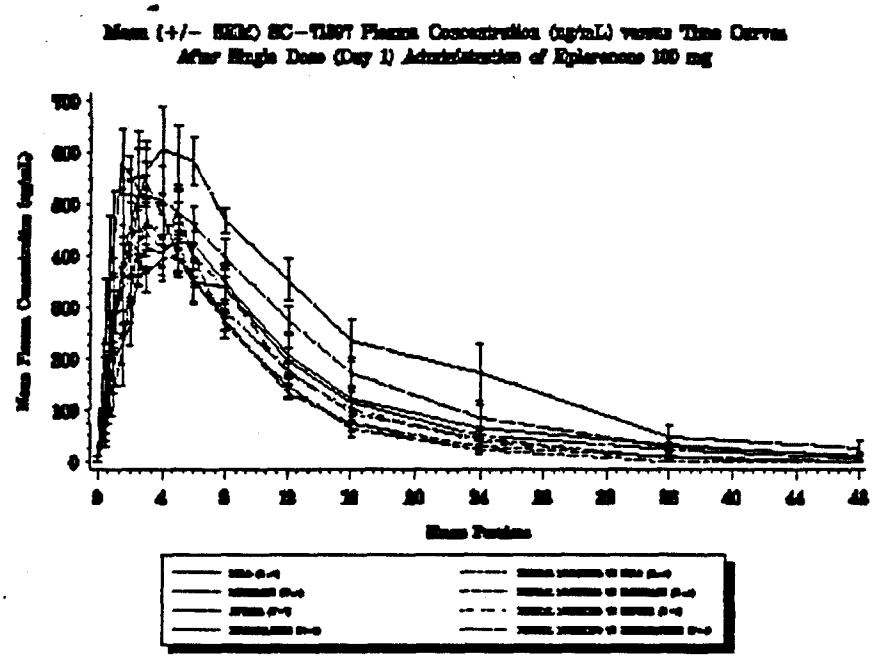
Pharmacokinetic Parameter	90% Confidence		
	Estimate for β	Interval for β	p-Value
Single-Dose			
AUC0-lqc (hr*ng/mL)	-0.0031	(-0.0060, -0.0002)	0.081
AUC0-inf (hr*ng/mL)	-0.0032	(-0.0063, -0.0000)	0.095
Cmax (ng/mL)	-0.0025	(-0.0040, -0.0010)	0.008
CL/F (L/hr)	0.0032	(0.0000, 0.0063)	0.095
Multiple-Dose			
AUC0-24 (hr*ng/mL)	-0.0028	(-0.0056, -0.0001)	0.091
Cmax (ng/mL)	-0.0023	(-0.0043, -0.0002)	0.073
CL/F (L/hr)	0.0028	(0.0001, 0.0056)	0.091

Effect of Renal Function on SC-71597 (Inactive Major Metabolite) Pharmacokinetics

Table 4: Arithmetic Mean SC-71597 Pharmacokinetic Parameters

Pharmacokinetic Parameter	Subject Group							
	Matched Pair		Matched Pair		Matched Pair		Matched Pair	
	B	A(B)	C	A(C)	D	A(D)	E	A(E)
	N=7	N=6	N=7	N=6	N=7	N=6	N=8	N=5
Single-Dose								
AUC0-lqc (hr*ng/mL)	5952.02	4876.88	7110.49	4580.46	10010.75	5397.27	6211.53	4710.36
AUC0-inf (hr*ng/mL)	6511.09	5126.42	7383.69	4801.33	10615.45	5537.36	6432..82	4899.30
Cmax (ng/mL)	476.99	464.24	536.96	501.48	655.32	573.58	629.03	613.65
Tmax (hr)	3.99	3.49	4.66	3.33	4.43	4.16	2.01	4.11
T1/2 (hr)	9.60	5.97	7.60	6.42	9.08	5.40	7.31	4.28
XU0-48 (μg)	15821.45	19563.73	13575.18	28190.59	7515.71	24748.55	--	25008.15

Multiple-Dose								
AUC0-24 (hr*ng/mL)	6490.37	4911.45	7377.30	4785.61	10435.27	6096.00	7409.20	5127.94
Cmax (ng/mL)	540.17	488.18	603.45	501.05	811.47	636.37	740.80	588.00
Tmax (hr)	3.28	3.43	4.00	3.59	4.73	3.67	2.18	3.39
XU (μg)	18763.99	23057.98	13042.18	25474.81	9505.72	24862.34	--	22398.30

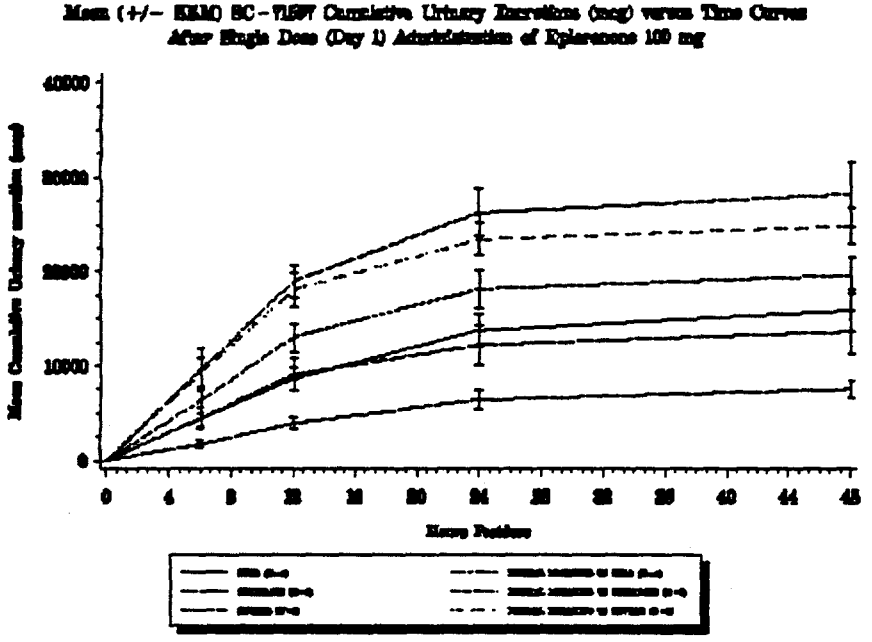


Renal impairment significantly affected SC-715987 pharmacokinetics. Following single dose administration of 100 mg eplerenone, mean Cmax of SC-71597 in mild, moderate, severe impairment and hemodialysis subjects was higher by 11%, 4%, 25% and 1%, respectively, and AUC was higher by 23%, 50%, 88% and 28%, respectively. Amount of eplerenone excreted in urine was lower in mild, moderate and severe renal impairment patients by 11%, 54% and 70%, respectively.

Table 6: Ratios and 90% Confidence Intervals for Single-Dose SC-71597 Pharmacokinetic Parameters

Comparison/ Pharmacokinetic Parameter	Least Squares Means		Ratio of Means	90% CI for	p-Value
	Impaired	Normal	Impaired/Normal	Ratio of Means	
Single-Dose B vs A(B)					
AUC0-lqc (hr*ng/mL)	5694.89	4865.39	1.170	(0.922, 1.486)	0.262
AUC0-inf (hr*ng/mL)	6268.14	5109.45	1.227	(0.973, 1.547)	0.141
Cmax (ng/mL)	472.99	457.61	1.034	(0.877, 1.218)	0.725
XU0-48 (μg)	15060.92	19093.58	0.789	(0.577, 1.077)	0.198
Tmax (hr)	3.99	3.49	--	--	0.492
T1/2 (hr)	9.60	5.97	--	--	0.085
Single-Dose C vs A(C)					
AUC0-lqc (hr*ng/mL)	6899.35	4539.16	1.520	(1.222, 1.891)	0.005
AUC0-inf (hr*ng/mL)	7154.54	4778.90	1.497	(1.213, 1.847)	0.005
Cmax (ng/mL)	529.68	467.71	1.133	(0.809, 1.585)	0.520

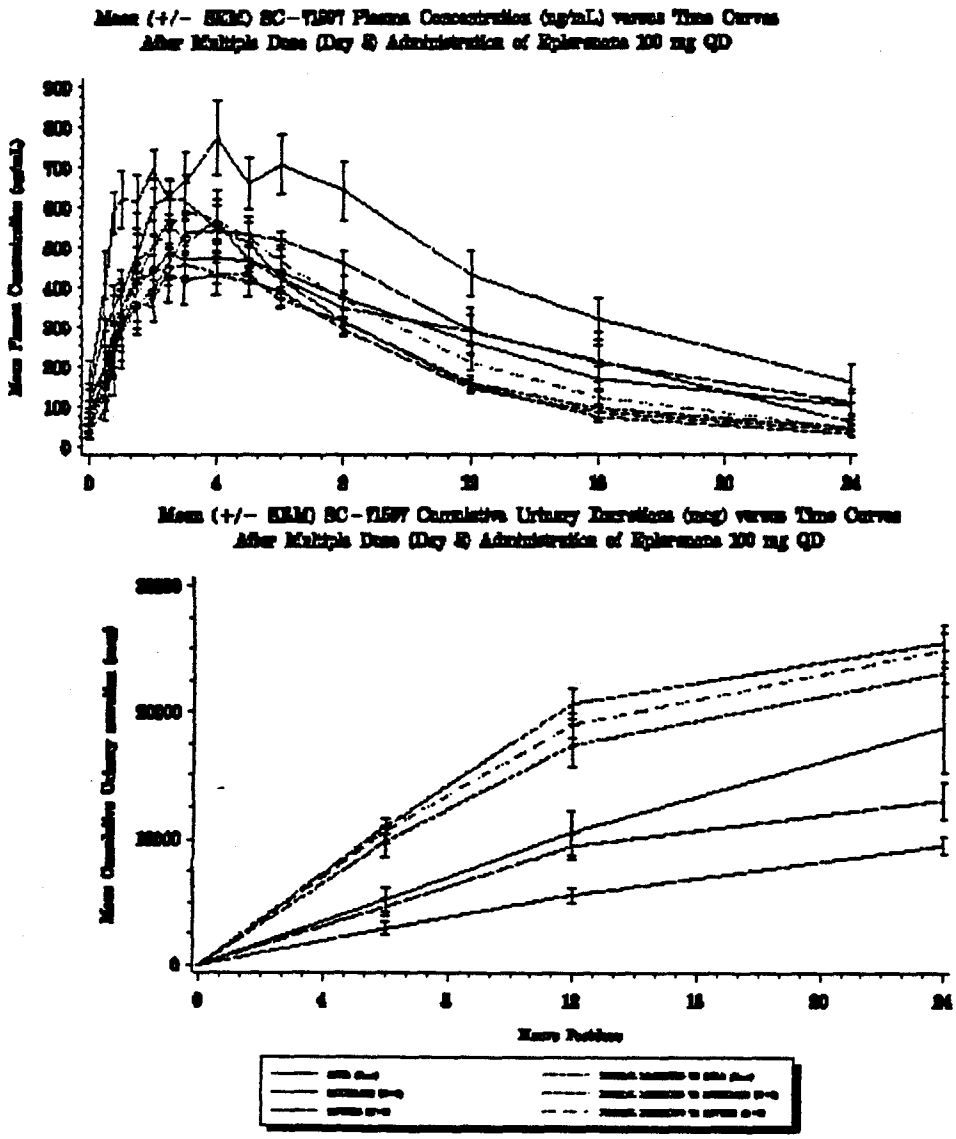
XU0-48 (µg)	12682.43	27365.57	0.463	(0.317, 0.678)	0.005
Tmax (hr)	4.66	3.33	–	–	0.237
T1/2 (hr)	7.60	6.42	–	–	0.477
Single-Dose D vs A(D)					
AUC0-lqc (hr*ng/mL)	9805.21	5369.01	1.826	(1.530, 2.180)	<0.001
AUC0-inf (hr*ng/mL)	10340.39	5509.38	1.877	(1.547, 2.277)	<0.001
Cmax (ng/mL)	638.00	557.40	1.145	(0.893, 1.466)	0.349
XU0-48 (µg)	7225.57	24423.06	0.296	(0.224, 0.391)	<0.001
Tmax (hr)	4.43	4.16	–	–	0.772
T1/2 (hr)	9.08	5.40	–	–	0.027
Single-Dose E vs A(E)					
AUC0-lqc (hr*ng/mL)	5978.86	4651.75	1.285	(0.992, 1.666)	0.110
AUC0-inf (hr*ng/mL)	6213.22	4843.22	1.283	(1.002, 1.642)	0.097
Cmax (ng/mL)	612.77	580.07	1.056	(0.778, 1.435)	0.754
Tmax (hr)	2.01	4.11	–	–	0.009
T1/2 (hr)	7.31	4.28	–	–	0.025



Following multiple dose administration of 100 mg eplerenone, mean Cmax of SC-71597 in mild, moderate, severe impairment and hemodialysis subjects was higher by 9%, 27%, 28% and 26%, respectively, and AUC was higher by 26%, 52%, 69% and 33%, respectively. Amount of eplerenone excreted in urine was lower in mild, moderate and severe renal impairment patients by 28%, 50% and 62%, respectively. The magnitude of alteration in SC-71597 AUC following both single and multiple dose administration of eplerenone indicates that urinary excretion is a major pathway for elimination for SC-71597.

Table 4: Ratios and 90% Confidence Intervals for Multiple-Dose SC-71597 Pharmacokinetic Parameters

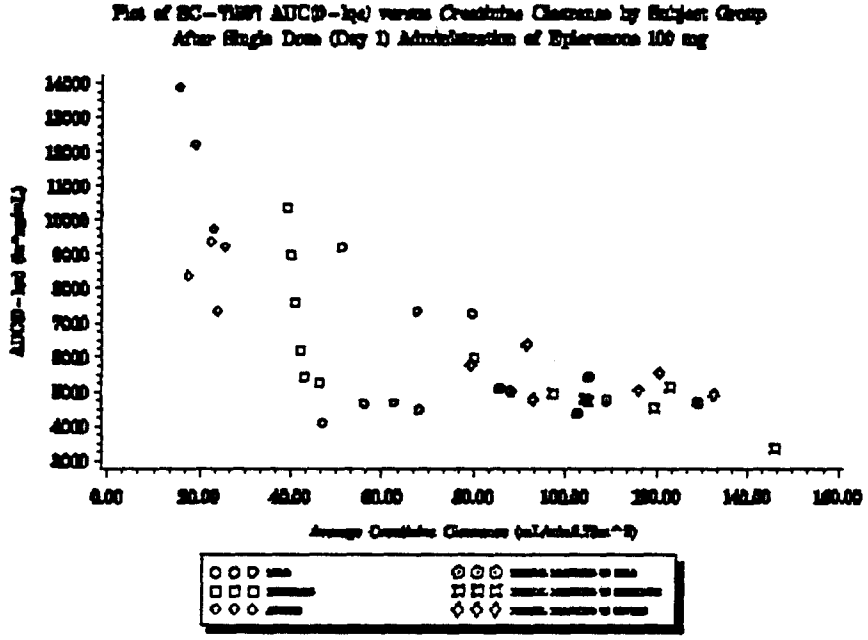
Comparison/ Pharmacokinetic Parameter	Least Squares Means		Ratio of Means	90% CI for	p-Value
	Impaired	Normal	Impaired/Normal	Ratio of Means	
Multiple-Dose B vs A(B)					
AUC0-24 (hr*ng/mL)	6143.68	4884.97	1.258	(0.951, 1.663)	0.169
Cmax (ng/mL)	528.19	483.56	1.092	(0.899, 1.327)	0.432
XU0-24 (µg)	16434.19	22688.59	0.724	(0.453, 1.157)	0.242
Tmax (hr)	3.28	3.43	--	--	0.863
Multiple-Dose C vs A(C)					
AUC0-24 (hr*ng/mL)	7222.03	4738.06	1 524	(1.253, 1.854)	0.003
Cmax (ng/mL)	601.04	472.81	1.271	(0.974, 1.660)	0.135
XU0-24 (µg)	12602.48	25282.24	0.498	(0.398, 0.624)	<0.001
Tmax (hr)	4.00	3.59	--	--	0.578
Multiple-Dose D vs A(D)					
AUC0-24 (hr*ng/mL)	10134.23	6015.08	1.685	(1.350, 2.103)	0.001
Cmax (ng/mL)	787.81	616.16	1.279	(0.980, 1.669)	0.126
XU0-24 (µg)	9358.42	24668.42	0.379	(0.319, 0.451)	<0.001
Tmax (hr)	4.73	3.67	--	--	0.150
Multiple-Dose E vs A(E)					
AUC0-24 (hr*ng/mL)	6754.58	5084.77	1.328	(0.975, 1.810)	0.127
Cmax (ng/mL)	729.08	578.15	1.261	(1.029, 1.545)	0.065
Tmax (hr)	2.18	3.39	--	--	0.086

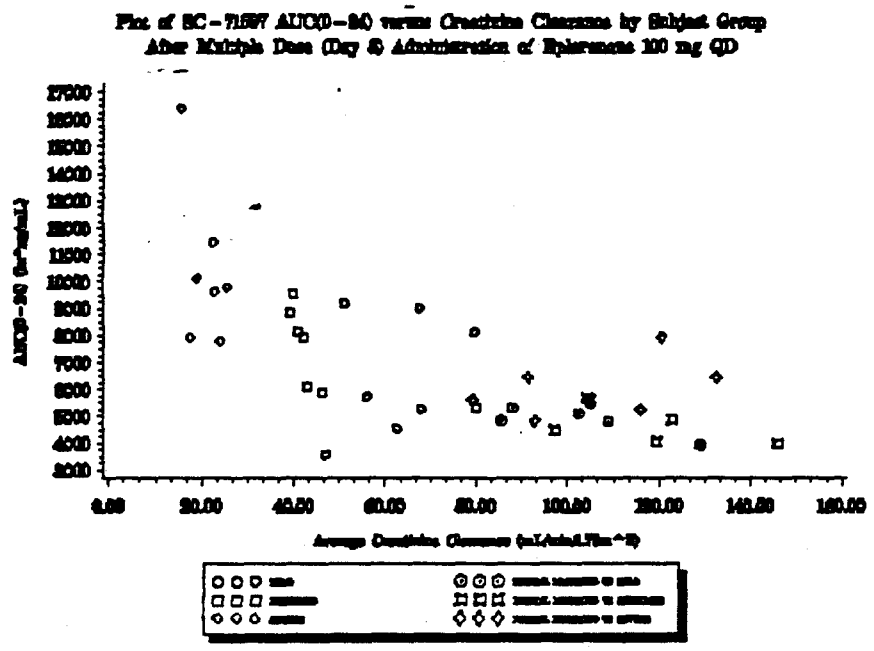


The linearity of the relationship between renal function and SC-71597 AUC and Cmax examined using a linear regression model [log(PK parameter) = a + CLcr] indicated a strong correlation between single dose and multiple dose AUC and creatinine clearance ($p<0.001$). The linear relationship with respect to single- and multiple dose Cmax was not as strong compared to AUC, $p=0.015$ and $p=0.001$, respectively.

Table 5: Investigation of a Linear Relationship between Renal Function and SC-71597 Pharmacokinetic Parameters

Pharmacokinetic Parameter	Estimate for β	90% Confidence Interval for β	p-Value
Single-Dose			
AUC0-lqc (hr*ng/mL)	-0.0066	(-0.0082, -0.0050)	<0.001
AUC0-inf (hr*ng/mL)	-0.0069	(-0.0084, -0.0054)	<0.001
Cmax (ng/mL)	-0.0028	(-0.0046, -0.0009)	0.015
Multiple-Dose			
AUC0-24 (hr*ng/mL)	-0.0062	(-0.0080, -0.0044)	<0.001
C (ng/mL)	-0.0039	(-0.0057, -0.0020)	0.001

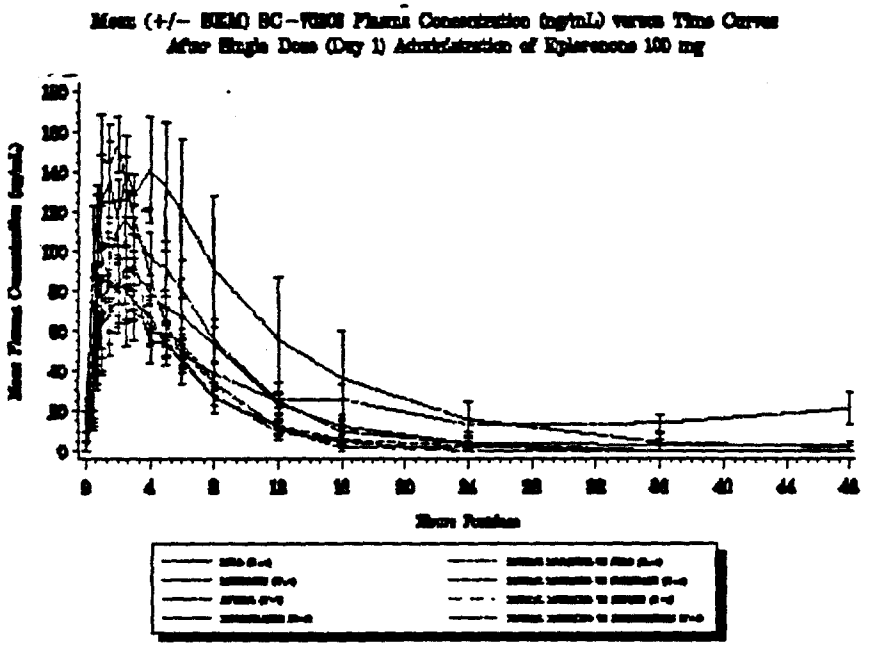




Effect of Renal Function on SC-70303 Pharmacokinetics

Table 6: Arithmetic Mean SC-70303 Pharmacokinetic Parameters

Pharmacokinetic Parameter	Subject Group							
	Matched Pair		Matched Pair		Matched Pair		Matched Pair	
	B	A(B)	C	A(C)	D	A(D)	E	A(E)
	N=7	N=6	N=7	N=6	N=7	N=6	N=8	N=5
Single-Dose								
AUC0-lqc (hr*ng/mL)	875.14	604.08	901.17	576.91	1736.33	523.43	1371.52	523.77
AUC0-inf (hr*ng/mL)	804.85	733.93	1037.73	687.10	1842.93	637.11	1257.03	603.82
Cmax (ng/mL)	113.47	117.90	137.13	109.78	184.79	93.77	178.09	99.92
Tmax (hr)	2.09	1.62	2.87	1.96	2.79	2.54	1.70	2.55
T1/2 (hr)	3.95	4.80	4.53	4.33	5.45	3.72	11.55	3.77
XU0-48 (μg)	7019.68	11619.27	5194.24	7661.91	3872.88	8181.85	–	7434.88
Multiple-Dose								
AUC0-24 (hr*ng/mL)	894.86	654.29	1031.41	713.26	1819.61	640.14	1010.61	568.08
Cmax (ng/mL)	116.72	125.10	133.83	116.52	217.97	101.14	185.43	90.45
Tmax (hr)	1.86	1.75	2.50	1.66	2.79	2.08	1.32	2.10
XU (μg)	10112.11	8770.74	4928.57	5775.69	3004.93	7211.42	–	7495.95

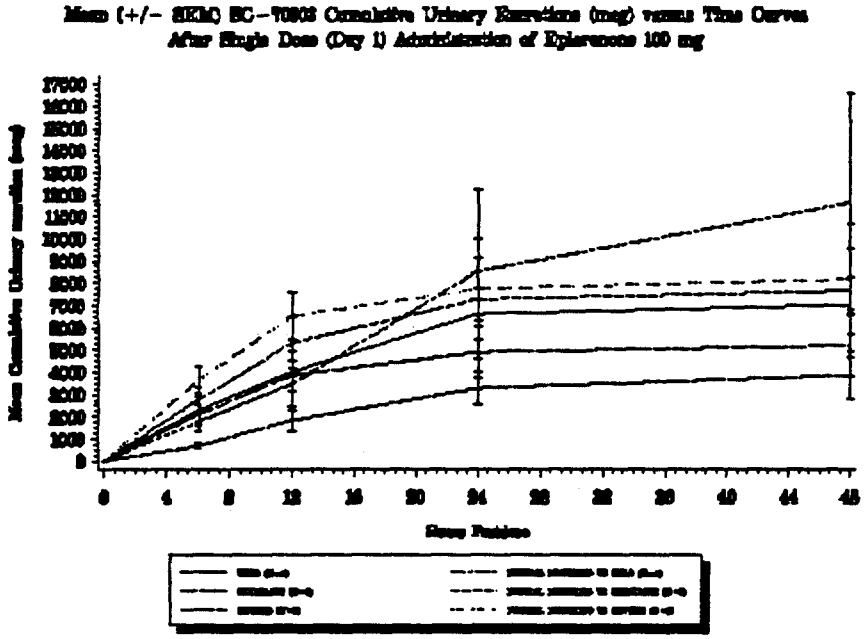


Renal impairment significantly affected both single- and multiple dose pharmacokinetics of SC-70303, open-ring form of eplerenone, pharmacokinetics. Following single dose administration of 100 mg eplerenone, mean SC-70303 Cmax was unaffected in mild renal impairment but was higher by 35%, 90% and 86% in moderate, severe renal impairment and hemodialysis patients, respectively, while, SC-70303 AUC was higher by 31%, 71%, 167%, and 150%, respectively. Mean amount of SC-70303 excreted in the urine in mild, moderate, severe renal impairment patients decreased by 24%, 26% and 60%, respectively.

Table 6: Ratios and 90% Confidence Intervals for Single-Dose SC-70303 Pharmacokinetic Parameters

Comparison/ Pharmacokinetic Parameter	Least Squares Means		Ratio of Means	90% CI for	p-Value
	Impaired	Normal	Impaired/Normal	Ratio of Means	
Single-Dose B vs A(B)					
AUC0-lqc (hr*ng/mL)	739.39	565.50	1.307	(0.748, 2.287)	0.407
AUC0-inf (hr*ng/mL)	733.00	720.38	1.018	(0.687, 1.507)	0.938
Cmax (ng/mL)	106.76	107.30	0.995	(0.653, 1.517)	0.983
XU0-48 (µg)	6411.04	8481.97	0.756	(0.381, 1.501)	0.476
Tmax (hr)	2.09	1.62	–	–	0.351
T1/2 (hr)	3.95	4.80	–	–	0.439
Single-Dose C vs A(C)					
AUC0-lqc (hr*ng/mL)	801.51	459.54	1.744	(0.922, 3.298)	0.145
AUC0-inf (hr*ng/mL)	959.31	561.85	1.707	(0.956, 3.050)	0.126
Cmax (ng/mL)	132.46	98.07	1.351	(0.893, 2.043)	0.219
XU0-48 (µg)	4411.02	5929.78	0.744	(0.345, 1.604)	0.498
Tmax (hr)	2.87	1.96	–	–	0.293
T1/2 (hr)	4.53	4.33	–	–	0.860
Single-Dose D vs A(D)					
AUC0-lqc (hr*ng/mL)	1340.70	501.40	2.674	(1.533, 4.665)	0.009

AUC0-inf (hr*ng/mL)	1445.27	614.38	2.352	(1.294, 4.275)	0.027
Cmax (ng/mL)	173.73	91.60	1.897	(1.382, 2.603)	0.004
XU0-48 (μg)	3131.59	7723.42	0.405	(0.219, 0.751)	0.024
Tmax (hr)	2.79	2.54	--	--	0.805
T1/2 (hr)	5.45	3.72	--	--	0.232
Single-Dose E vs A(E)					
AUC0-lqc (hr*ng/mL)	1279.69	512.84	2.495	(1.740, 3.578)	<0.001
AUC0-inf (hr*ng/mL)	1242.27	589.36	2.108	(1.221, 3.638)	0.049
Cmax (ng/mL)	173.35	93.44	1.855	(1.343, 2.562)	0.006
Tmax (hr)	1.70	2.55	--	--	0.283
T1/2 (hr)	11.55	3.77	--	--	0.046

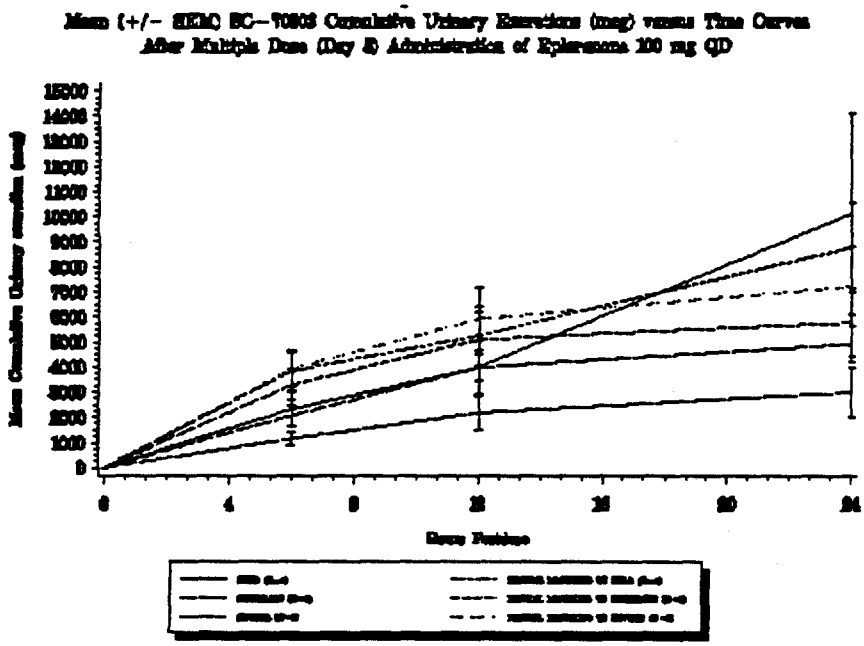


Following multiple dose administration of 100 mg eplerenone, mean SC-70303 Cmax was similar in mild renal impairment but was higher by 20%, 105% and 103% in moderate, severe renal impairment and hemodialysis patients, respectively, while, SC-70303 AUC was higher by 19%, 31%, 162%, and 74%, respectively. Mean amount of SC-70303 excreted in the urine in mild, moderate, severe renal impairment patients decreased by 19%, 10% and 63%, respectively. The increasing magnitude of effect on SC-70303 AUC with increasing severity of renal impairment suggests that renal elimination is a major pathway of SC-70303 elimination.

Table 7: Ratios and 90% Confidence Intervals for Multiple-Dose SC-70303 Pharmacokinetic Parameters

Comparison/ Pharmacokinetic Parameter	Least Squares Means		Ratio of Means	90% CI for	p-Value
	Impaired	Normal	Impaired/Normal	Ratio of Means	
Multiple-Dose B vs A(B)					
AUC0-24 (hr*ng/mL)	751.68	633.79	1.186	(0.702, 2.004)	0.571
Cmax (ng/mL)	111.00	120.40	0.922	(0.659, 1.290)	0.672

XU0-24 (μg)	6489.64	8043.51	0.807	(0.360, 1.808)	0.642
Tmax (hr)	1.86	1.75	--	--	0.849
Multiple-Dose C vs A(C)					
AUC0-24 (hr*ng/mL)	846.18	648.35	1.305	(0.717, 2.375)	0.441
Cmax (ng/mL)	128.83	108.02	1.193	(0.833, 1.709)	0.398
XU0-24 (μg)	4664.22	5193.48	0.898	(0.596, 1.354)	0.647
Tmax (hr)	2.50	1.66	--	--	0.308
Multiple-Dose D vs A(D)					
AUC0-24 (hr*ng/mL)	1611.73	614.58	2.622	(1.752, 3.925)	0.001
Cmax (ng/mL)	204.80	99.68	2.055	(1.536, 2.748)	<0.001
XU0-24 (μg)	2333.69	6262.88	0.373	(0.186, 0.748)	0.027
Tmax (hr)	2.79	2.08	--	--	0.158
Multiple-Dose E vs A(E)					
AUC0-24 (hr*ng/mL)	979.24	562.45	1.741	(1.358, 2.233)	0.002
Cmax (ng/mL)	181.93	89.71	2.028	(1.676, 2.454)	<0.001
Tmax (hr)	1.32	2.10	--	--	0.079

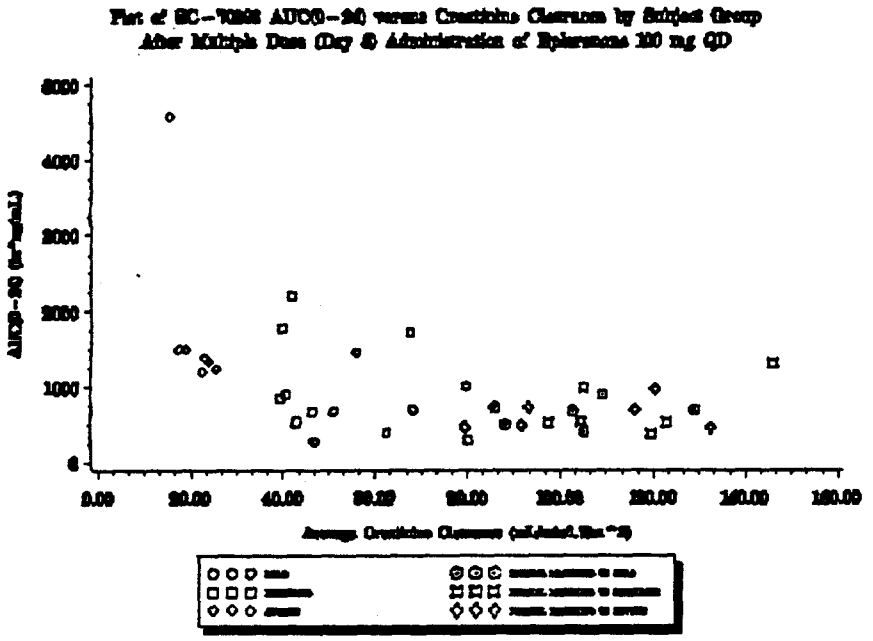


The linearity of the relationship between renal function and SC-70303 AUC and C_{max} examined using a linear regression model [log(PK parameter) = α + CLcr] for both single-dose and multiple-dose administration indicated strong relationship between SC-70303 Cmax and AUC with creatinine clearance ($p<0.003$).

Table 7: Investigation of a Linear Relationship between Renal Function and SC-70303 Pharmacokinetic Parameters

Pharmacokinetic Parameter	90% Confidence		
	Estimate for β	Interval for β	p-Value
Single-Dose			
AUC0-lqc (hr*ng/mL)	-0.0087	(-0.0129, -0.0046)	0.001

AUC0-inf (hr*ng/mL)	-0.0075	(-0.0112, -0.0038)	0.002
Cmax (ng/mL)	-0.0052	(-0.0080, -0.0025)	0.003
Multiple-Dose			
AUC0-24 (hr*ng/mL)	-0.0075	(-0.0113, -0.0037)	0.002
Cmax (ng/mL)	-0.0050	(-0.0075, -0.0024)	0.002



Effect of Renal Impairment on Similarity of Multiple Dose and Single Dose Kinetics of Eplereone, SC-71597 and SC-70303 Pharmacokinetics

Comparison of steady-state AUC to single dose AUC_{inf} for eplerenone, SC-71597 and SC-70303 for determination of linear pharmacokinetics indicated that renal impairment did not affect the time-related linearity of pharmacokinetics to any large degree for the analytes tested, except for SC-70303 in hemodialysis patients, where steady-state AUC was only 60% of single dose AUC.

Table 8: Investigation of Linear Pharmacokinetics

Analyte Subject Group	Least Squares Means		Ratio AUC0-24/AUC0-inf	95% CI for Ratio of AUC
	Single-Dose AUC0-inf	Multiple-Dose AUC0-24		
Eplerenone				
Normal	10511.39	11016.07	1.05	(1.00, 1.10)
Mild Impairment	10146.38	9846.86	0.97	(0.85, 1.11)
Moderate Impairment	11541.17	11970.48	1.04	(0.87, 1.23)
Severe Impairment	17008.36	16692.39	0.98	(0.87, 1.11)
Hemodialysis	7831.25	7380.70	0.94	(0.83, 1.07)
SC-71597				
Normal	5061.54	5161.36	1.02	(0.96, 1.08)
Mild Impairment	6268.14	6722.40	1.07	(0.98, 1.17)
Moderate Impairment	7154.54	7222.03	1.01	(0.89, 1.15)
Severe Impairment	10340.39	10134.23	0.98	(0.87, 1.10)

Hemodialysis	3774.73	6754.58	1.17	(0.87, 1.57)
SC-70303				
Normal	625.48	629.53	1.01	(0.87, 1.18)
Mild Impairment	733.00	672.83	0.92	(0.75, 1.12)
Moderate Impairment	959.31	846.18	0.88	(0.65, 1.20)
Severe Impairment	1445.27	1611.73	1.12	(0.85, 1.47)
Hemodialysis	1242.27	745.55	0.60	(0.14, 2.63)

CONCLUSIONS:

Following single and multiple dose administration of 100 mg eplerenone, the greatest effect on eplerenone was observed in severe renal impairment patients where single and multiple dose Cmax of eplerenone was higher by 25% and 38%, respectively, and AUC was higher by 54% and 38%, respectively. Single dose amount of eplerenone excreted in urine in moderate and severe impairment decreased by 54% and 57%, respectively. Multiple dose amount of eplerenone excreted in urine in mild, moderate and severe impairment decreased by 39%, 50% and 37%, respectively. Apparent oral clearance of eplerenone adjusted for 70 kg body weight in moderate and severe renal impairment decreased by 10% and 21%, respectively, while it increased by 70% in hemodialysis patients. However, only 9.6% of administered dose was removed by dialysis. The trend of lowered eplerenone CL/F up to 21% with increasing severity of renal impairment is unexpected since 2% of administered eplerenone dose is excreted unchanged in urine indicating that the renal excretion is not the primary pathway for eplerenone metabolism.

Renal impairment significantly affected SC-71598 (major inactive metabolite) pharmacokinetics. Following single dose administration of 100 mg eplerenone, mean Cmax of SC-71597 in mild and severe impairment was higher by 11% and 25%, respectively, and following multiple dose administration mean Cmax of SC-71597 was higher by 9%, 27%, 28% and 26%, respectively, while, single dose AUC was higher by 23%, 50%, 88% and 28%, respectively, and multiple-dose AUC was higher by 26%, 52%, 69% and 33%, respectively. Amount of eplerenone excreted in urine was lower in mild, moderate and severe renal impairment patients by 11%, 54% and 70%, respectively, after single dose and was lower by 28%, 50% and 62%, respectively, following multiple-dose administration. The magnitude of alteration in SC-71597 AUC following both single and multiple dose administration of eplerenone indicates that urinary excretion is a major pathway for elimination for SC-71597. Following both single- and multiple-dose administration there was a strong correlation between single dose and multiple dose AUC and creatinine clearance ($p<0.001$).

Renal impairment significantly affected both single- and multiple dose pharmacokinetics of SC-70303, open-ring form of eplerenone, pharmacokinetics. Following single dose administration of 100 mg eplerenone, mean SC-70303 Cmax was higher by 35%, 90% and 86% in moderate, severe renal impairment and hemodialysis patients, respectively, while, SC-70303 AUC was higher by 31%, 71%, 167%, and 150%, respectively. Mean amount of SC-70303 excreted in the urine in mild, moderate, severe renal impairment patients decreased by 24%, 26% and 60%, respectively. Following multiple dose

administration of 100 mg eplerenone, mean SC-70303 Cmax was higher by 20%, 105% and 103% in moderate, severe renal impairment and hemodialysis patients, respectively, while, SC-70303 AUC was higher by 19%, 31%, 162%, and 74%, respectively. Mean amount of SC-70303 excreted in the urine in mild, moderate, severe renal impairment patients decreased by 19%, 10% and 63%, respectively. The increasing magnitude of effect on SC-70303 AUC with increasing severity of renal impairment suggests that renal elimination is a major pathway of SC-70303 elimination. Following both single- and multiple-dose administration there was a strong relationship between SC-70303 Cmax and AUC with creatinine clearance ($p<0.003$).

Comparison of steady-state AUC to single dose AUC_{inf} for eplerenone, SC-71597 and SC-70303 for determination of linear pharmacokinetics indicated that renal impairment did not affect the linearity of pharmacokinetics to any large degree for the analytes tested, except for SC-70303 in hemodialysis patients, where steady-state AUC was only 60% of single dose AUC.

COMMENTS:

1. The C_{max} and AUC of eplerenone were substantially higher in severe renal impairment subjects compared to normal subjects. This information is recommended to be included in the label.
2. Based on the dose-response relationship, the higher eplerenone concentrations in severe renal impairment patients is not expected to result in significant additional blood pressure lowering, therefore from a blood pressure lowering perspective no dose adjustment is necessary. However, there might be a concern with hyperkalemia at higher eplerenone concentrations especially in renal impairment patients, the medical officer is requested to assess the impact the higher eplerenone concentrations on hyperkalemia potential.
3. At higher doses of eplerenone a significant increase in C_{max} and AUC could potentially lead to hypotension in severe renal impairment subjects. Therefore, the sponsor is encouraged to recommend that patients with severe renal impairment start therapy on the lowest dose of eplerenone with gradual upward titration of dose.
4. The metabolite concentrations were significantly higher in severe renal impairment subjects compared to normal subjects. These metabolites are not active and are not expected to contribute to an increase in pharmacodynamic effect.

THE EFFECT OF RACE ON THE PHARMACOKINETIC PROFILE OF EPLERENONE IN HEALTHY, ELDERLY SUBJECTS

STUDY INVESTIGATORS AND SITES:

Report No.: NE3-00-02-046

OBJECTIVES:

1. To compare the eplerenone pharmacokinetic profile in healthy, elderly Black subjects versus healthy, elderly Caucasian subjects after a single eplerenone dose and at steady-state.
2. To determine the safety and tolerability of eplerenone (100 mg QD) in healthy, elderly Black subjects and in healthy, elderly Caucasian subjects after a single dose and at steady-state.

FORMULATIONS:

Eplerenone – 100 mg tablets (Lot #: RCT 11561) by Searle

STUDY DESIGN:

This was a double-blind, randomized, multiple-dose, parallel groups study conducted in a total of 49 subjects (24 Blacks and 25 Caucasians) randomized to placebo or eplerenone treatment (four placebo patients per race group). One patient dropped out of the study. At least half of the subjects in each group were to be at least 65 years old. The following table lists the baseline demographics of the subjects enrolled into the study.

Baseline Demographics of Randomized Subjects

	CAUCASIANS		BLACKS	
	Eplerenone	Placebo	Eplerenone	Placebo
	N=21	N=4	N=20	N=4
Age (years)				
Mean ± SD	67.1 ± 5.30	64.8 ± 5.56	65.7 ± 6.0	63.0 ± 10.5
Range	55 - 76	59 - 70	55 - 77	55 - 77
Gender				
Female	12 (57.1%)	1 (25.0%)	10 (50.0%)	2 (50.0%)
Male	9 (42.9%)	3 (75.0%)	10 (50.0%)	2 (50.0%)
Height (cm)				
Female Mean ± SD	164.2 ± 6.32	155.0 ±	162.5 ± 4.23	172.9 ± 0.21
Male Mean ± SD	173.0 ± 4.90	178.0 ± 12.17	175.8 ± 7.96	172.1 ± 2.69
Weight (kg)				

Female Mean ± SD	74.7 ± 9.39	62.8 ±	74.4 ± 5.76	81.7 ± 19.73
Male Mean ± SD	78.8 ± 7.13	78.9 ± 3.59	76.3 ± 13.99	70.3 ± 6.72

Each subject was randomized to a treatment group and received either placebo or eplerenone 100 mg QD on Days 1 and 4-10. On Day 1 and Day 10, a single dose of eplerenone or placebo was administered in the morning following an overnight fast, while on Days 4-9, eplerenone or placebo was administered each morning with food. Standard low-fat meals were served every day.

ASSAY:

Sample Collection

On Days 1 and 10, (7-mL) blood samples were collected for analysis of eplerenone, SC-70303, and SC-71597 concentrations 30 minutes predose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, and 48 hours postdose. On Days 7-9, (7-mL) blood samples were drawn for analysis of eplerenone, SC-70303, and SC-71597 trough concentrations 30 minutes predose.

Urine was to be collected for pharmacokinetic analysis and creatinine clearance determination during the following intervals with respect to Day 1 and Day 10 dosing: -24-0 (predose), 0-6, 6-12, 12-24, and 24-48 hours.

RESULTS:

The pharmacokinetic parameters of eplerenone, SC-70303 (open-ring form of eplerenone) and SC-71597 (major inactive metabolite) following administration of single and multiple oral doses of 100 mg eplerenone in healthy elderly Caucasian and Black are listed in the following table.

Table 1: Mean Eplerenone, SC-70303, and SC-71597 Pharmacokinetic Parameters

Pharmacokinetic	EPLERENONE	SC-70303	SC-71597

Parameter	Black	Caucasian	Black	Caucasian	Black	Caucasian
Single-Dose:						
AUC(0-lqc) (hr*ng/mL)	11373.67	13275.18	718.12	801.08	6268.19	6185.99
AUC(0-inf) (hr*ng/mL)	11745.95	13439.87	911.41	894.84	6410.08	6621.89
Cmax (ng/mL)	1738.78	1966.88	130.35	152.07	600.85	613.52
CL/F (L/hr)	10.10	8.77	--	--	--	--
CL/F/WT (L/hr/70kg)	9.69	8.19	--	--	--	--
Tmax (hr)	1.80	1.62	1.83	1.50	2.73	2.83
T1/2 (hr)	4.32	4.08	5.33	5.32	5.27	5.60
XU(0-48) (µg)	1128.35	1684.70	5224.25	6392.13	17880.23	24914.08
Multiple-Dose:						
AUC(0-24) (hr*ng/mL)	11283.30	14925.14	1512.18	1532.33	5062.28	6100.50
Cmin (ng/mL)	119.79	137.75	28.62	20.47	96.54	79.74
Cmax (ng/mL)	1718.49	1981.91	217.95	214.18	514.42	534.08
CL/F (L/hr)	11.71	8.07	--	--	--	--
CL/F/WT (L/hr/70kg)	11.16	7.67	--	--	--	--
Tmax (hr)	1.88	1.95	1.88	1.95	3.23	3.47
T1/2 (hr)	5.03	5.96	3.93	5.26	6.86	7.77
XU(0-48) (µg)	1319.93	1784.43	6484.23	6616.60	20184.95	26125.47

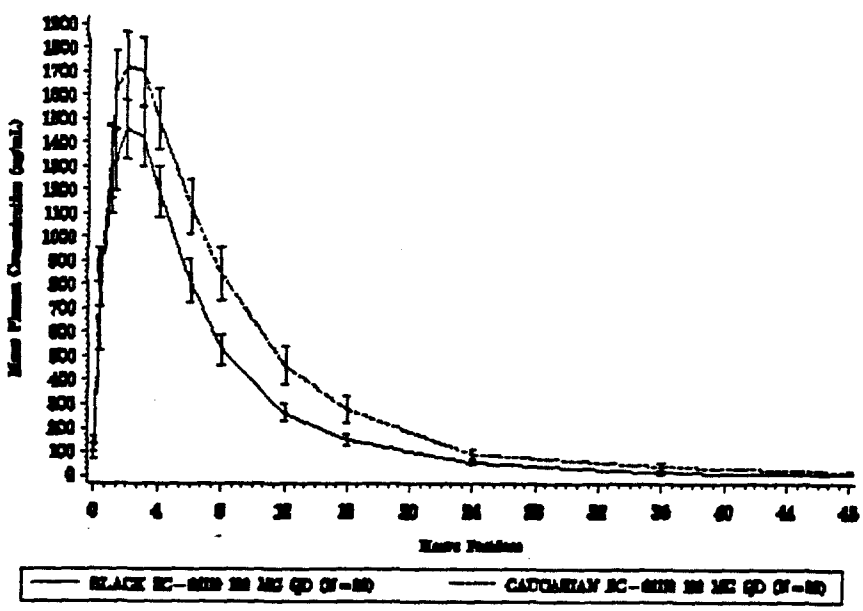
Following single and multiple dose administration of 100 mg eplerenone, mean Cmax in elderly black subjects was lower by 11% and 19%, respectively, and mean eplerenone AUC were lower by 14% and 26%, respectively, compared to elderly Caucasian subjects. Apparent oral clearance of eplerenone adjusted for 70-kg body weight following single and multiple dosing was higher by 14% and 36%, respectively, in elderly black subjects. The higher CL/F of eplerenone in black subjects could be attributed to either increased metabolism or lower bioavailability. The lower mean amount of unchanged eplerenone excreted in urine following single and multiple dosing, 39% and 40%, respectively, in elderly black subjects compared to Caucasian subjects, could be attributed to lower bioavailability or increased metabolism in black subjects.

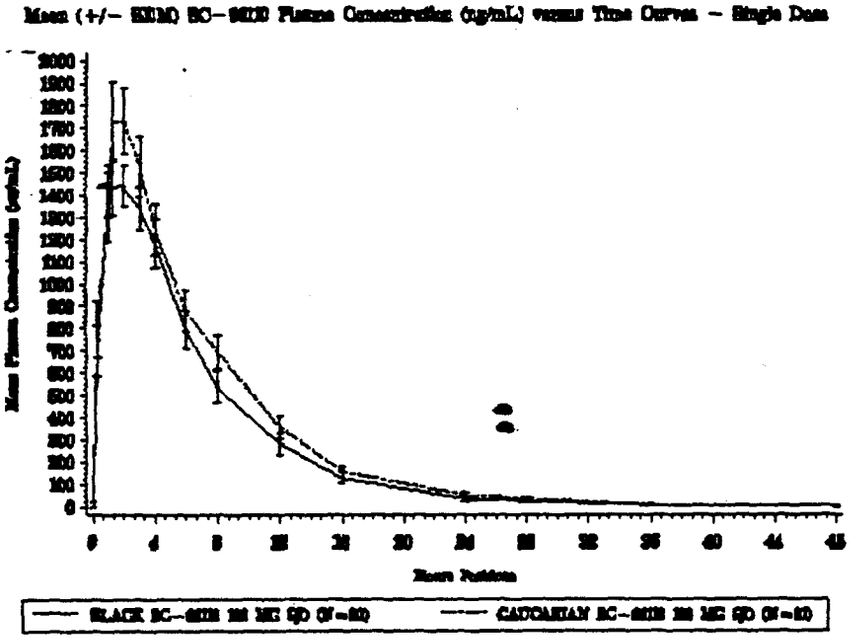
Table 4: Ratios and 90% Confidence Intervals for the Effect of Race on Eplerenone, SC-70303, and SC-71597 Pharmacokinetic Parameters

Pharmacokinetic Parameter	Least Squares Means		Ratio of Means (Test/Ref)	90% CI for Ratio of Means	p-Value
	Blacks	Caucasians			
	Eplerenone 100 mg QD (Test)	Eplerenone 100 mg QD (Reference)			
Eplerenone Single-Dose					
AUC(0-lqc) (hr*ng/mL)	10513.79	12190.45	0.862	(0.689, 1.079)	0.273
AUC(0-inf) (hr*ng/mL)	10851.55	12345.83	0.879	(0.699, 1.105)	0.348
Cmax (ng/mL)	1666.94	1868.73	0.892	(0.755, 1.054)	0.256
CL/F (L/hr)	9.22	8.10	1.138	(0.905, 1.430)	0.348
CL/F/WT (L/hr/70 kg)	8.95	7.53	1.141	(0.907, 1.436)	0.338
Tmax (hr)	1.80	1.62	--	--	0.530
T1/2 (hr)	4.37	4.04	--	--	0.514
XU(0-48) (µg)	964.72	1576.52	0.612	(0.450, 0.832)	0.010
Eplerenone Multiple-Dose					
AUC(0-24) (hr*ng/mL)	10056.14	13599.26	0.739	(0.561, 0.975)	0.073
Cmin (ng/mL)	73.44	82.07	0.895	(0.485, 1.651)	0.761
Cmax (ng/mL)	1547.23	1919.68	0.806	(0.641, 1.014)	0.122
CL/F (L/hr)	9.94	7.35	1.352	(1.026, 1.782)	0.073
CL/F/WT (L/hr/70 kg)	9.31	6.86	1.357	(1.030, 1.786)	0.070
Tmax (hr)	1.87	1.95	--	--	0.800

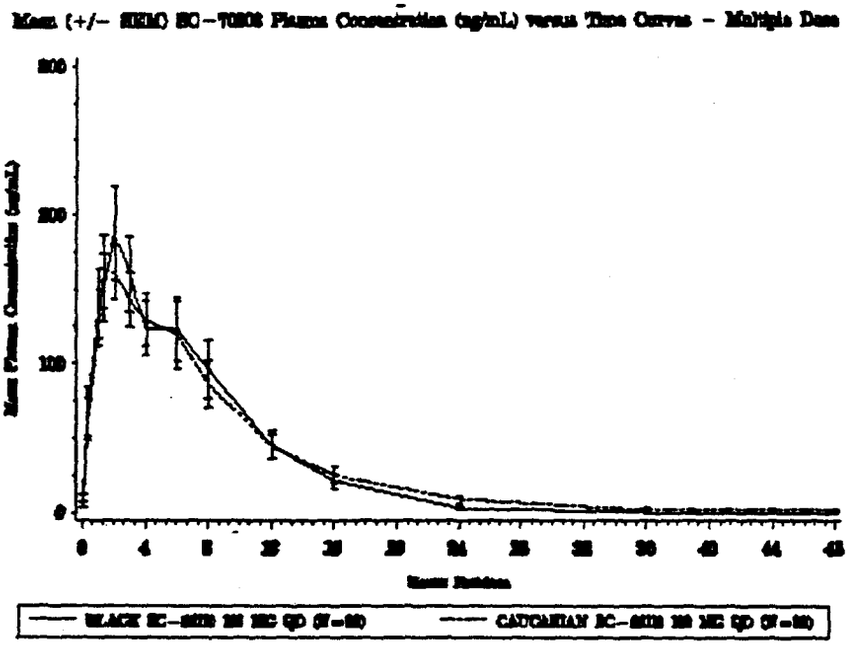
T1/2 (hr)	5.03	5.96	--	--	0.230
XU(0-48) (μg)	921.74	1544.50	0.597	(0.388, 0.918)	0.051
SC-70303 Single-Dose					
AUC(0-lqc) (hr*ng/mL)	638.28	707.21	0.903	(0.685, 1.189)	0.534
AUC(0-inf) (hr*ng/mL)	834.01	798.66	1.044	(0.800, 1.363)	0.785
Cmax (ng/mL)	123.24	141.17	0.873	(0.724, 1.053)	0.228
Tmax (hr)	1.82	1.50	--	--	0.265
T1/2 (hr)	5.26	5.37	--	--	0.953
XU(0-48) (μg)	4206.52	5931.26	0.709	(0.527, 0.954)	0.058
SC-70303 Multiple-Dose					
AUC(0-24) (hr*ng/mL)	1092.40	1316.55	0.830	(0.531, 1.296)	0.484
Cmin (ng/mL)	24.55	16.05	1.529	(0.877, 2.666)	0.191
Cmax (ng/mL)	175.20	196.35	0.892	(0.632, 1.260)	0.581
Tmax (hr)	1.88	1.94	--	--	0.877
T1/2 (hr)	3.93	5.26	--	--	0.035
XU(0-48) (μg)	4890.45	6165.12	0.793	(0.553, 1.138)	0.285
SC-71597 Single-Dose					
AUC(0-lqc) (hr*ng/mL)	5955.10	5907.34	1.008	(0.854, 1.190)	0.935
AUC(0-inf) (hr*ng/mL)	6201.63	6362.95	0.975	(0.832, 1.142)	0.785
Cmax (ng/mL)	574.96	588.69	0.977	(0.852, 1.120)	0.773
Tmax (hr)	2.73	2.83	--	--	0.824
T1/2 (hr)	5.33	5.56	--	--	0.698
XU(0-48) (μg)	16935.14	23762.89	0.713	(0.594, 0.855)	0.003
SC-71597 Multiple-Dose					
AUC(0-24) (hr*ng/mL)	4740.64	5841.89	0.811	(0.676, 0.974)	0.061
Cmin (ng/mL)	77.46	63.89	1.212	(0.816, 1.801)	0.416
Cmax (ng/mL)	484.07	523.41	0.925	(0.802, 1.067)	0.361
Tmax (hr)	3.25	3.45	--	--	0.690
T1/2 (hr)	6.86	7.77	--	--	0.276
XU(0-48) (μg)	18070.46	23869.67	0.757	(0.583, 0.983)	0.081

Mean (+/- SEM) SC-60010 Plasma Concentration (ng/mL) versus Time Curves - Multiple Dose

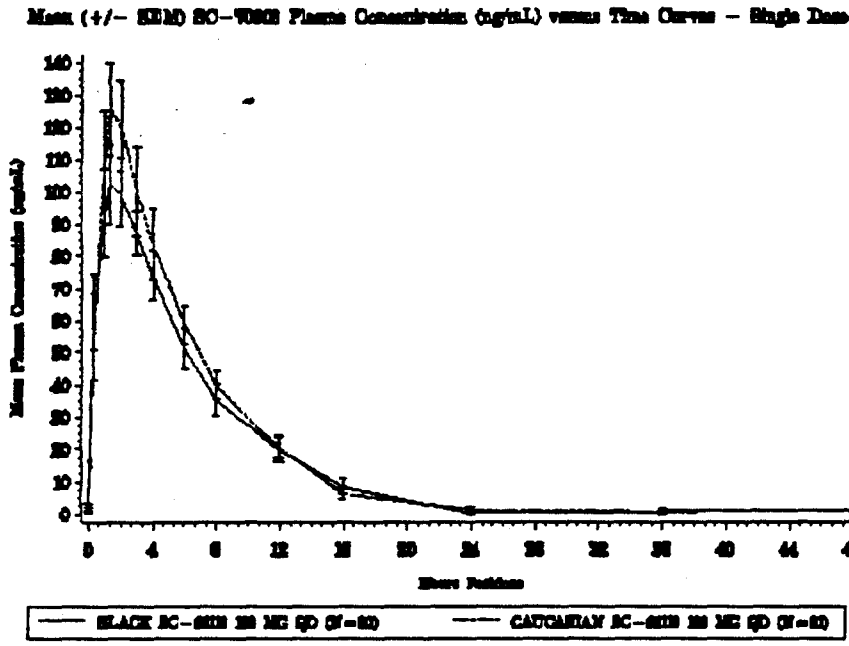




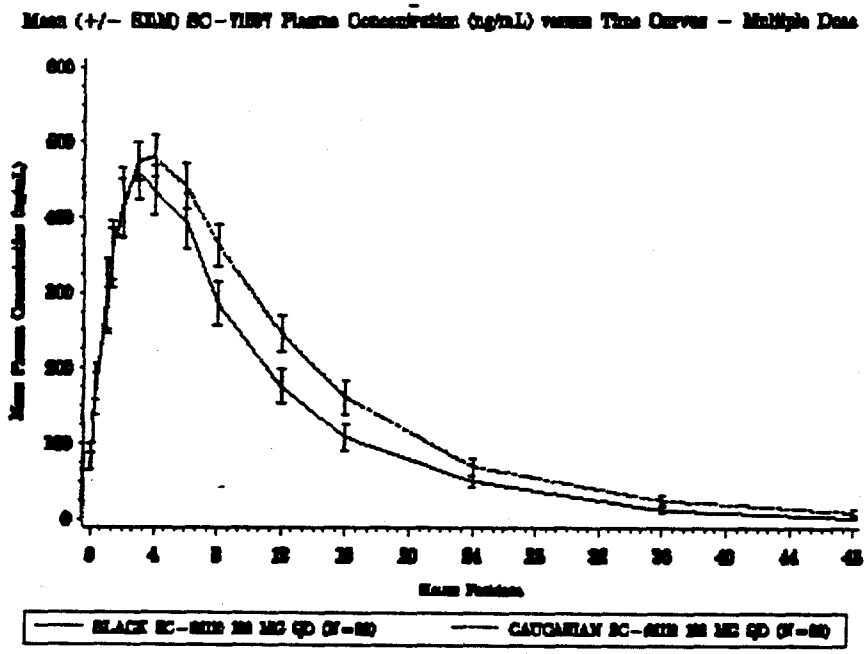
Following single and multiple dose administration of 100 mg eplerenone, mean SC-70303 Cmax in elderly black subjects was lower by 13% and 11%, respectively, and mean SC-70303 AUC were lower by 10% and 17%, respectively, compared to elderly Caucasian subjects. Following multiple dosing, SC-70303 T1/2 was lower in black subjects by 1.3 hours compared to Caucasian subjects. Mean amount of SC-70303



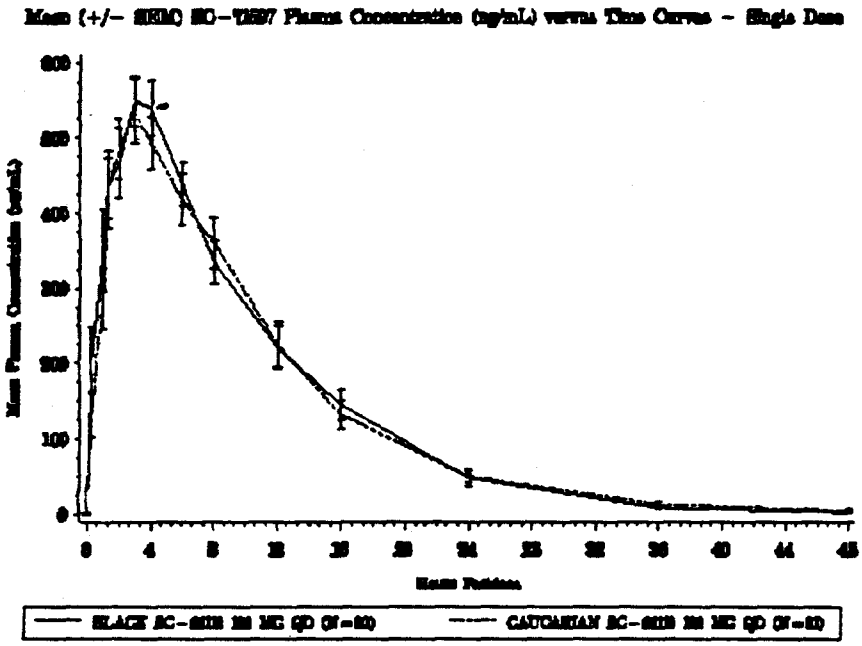
excreted in urine following single and multiple dosing was lower by 30% and 20%, respectively, in elderly black subjects compared to Caucasian subjects.



Following single and multiple dose administration of 100 mg eplerenone, mean SC-71597 Cmax and single dose AUC in elderly black subjects were similar to Caucasians Multiple dose SC-71597 AUC was lower by 19% in elderly blacks compared to elderly Caucasian subjects. Following multiple dosing, SC-71597 T1/2 was lower in black subjects by 1 hour compared to Caucasian subjects. Mean amount of SC-70303 excreted



in urine following single and multiple dosing was lower by 29% and 24%, respectively, in elderly black subjects compared to Caucasian subjects.



Comparison of steady-state AUC to single dose AUC_{inf} for eplerenone, SC-70303 and SC-71597 indicated time-related linearity in pharmacokinetics of eplerenone and SC-71597 in both Blacks and Caucasians. However, for SC-70303 there was a 30% and 60% increase in AUC at steady-state in Blacks and Caucasians subjects.

Linear Pharmacokinetics Assessment

Analyte/ Racial Group	Least Squares Means		Ratio of Means AUC(0-24)/AUC(0-∞)	95% CI for Ratio of Means
	Multiple-Dose AUC(0-24)	Single-Dose AUC(0-inf)		
Eplerenone				
Blacks	10049.91	10689.18	0.940	(0.696, 1.269)
Caucasians	13881.69	12359.00	1.123	(1.021, 1.235)
SC-70303				
Blacks	1090.26	831.49	1.311	(0.729, 2.358)
Caucasians	1279.04	799.30	1.600	(1.215, 2.107)
SC-71597				
Blacks	4745.24	6062.22	0.783	(0.645, 0.950)
Caucasians	5796.44	6198.93	0.935	(0.825, 1.060)

CONCLUSIONS

Following single and multiple dose administration of 100 mg eplerenone, mean Cmax in elderly black subjects was lower by 11% and 19%, respectively, and mean eplerenone AUC were lower by 14% and 26%, respectively, compared to elderly Caucasian subjects. Apparent oral clearance of eplerenone adjusted for 70-kg body weight following single

and multiple dosing was higher by 14% and 36%, respectively, in elderly black subjects. The higher CL/F of eplerenone in black subjects is probably attributable to either decreased bioavailability or increased metabolism, since a lower, 39% and 40%, mean amount of eplerenone was recovered in the urine following single and multiple dosing, respectively, in elderly black subjects compared to Caucasian subjects.

Following multiple dose administration of 100 mg eplerenone, mean SC-70303 (open-ring form of eplerenone) AUC were lower by 17% and mean amount recovered in the urine was lower by 20% in elderly Blacks compared to elderly Caucasian subjects. Similarly, following multiple dosing, mean SC-71597 (major inactive metabolite) AUC were lower by 19% and mean amount of SC-70303 excreted in urine was lower by 24% in elderly Black subjects compared to Caucasian subjects.

COMMENTS:

1. Peak concentration of eplerenone following both single and multiple dosing is lower in elderly Black subjects compared to Caucasians with a higher CL/F (36%) in Blacks. This difference should be listed in the label. In order to obtain a similar reduction in blood pressure, elderly Black subjects may need a higher eplerenone dose compared to elderly Caucasians.

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PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSIS PERFORMED BY CLINICAL PHARMACOLOGY REVIEWER

The following report is the summary of the results of population pharmacokinetic (PK) and pharmacodynamic (PD) modeling performed by the clinical pharmacology reviewer on submitted eplerenone PK and PD data.

CHARACTERIZATION OF EPLERENONE PHARMACOKINETICS IN ADULTS

BACKGROUND:

The pharmacokinetics of eplerenone in adults was characterized by the sponsor using non-compartmental methods. Modeling of pharmacokinetics of eplerenone in healthy adult subjects was not performed by the sponsor. The absence of a pharmacokinetic model defining the concentration-time profile of eplerenone in adults makes comparison of pediatric pharmacokinetics obtained using sparse sampling strategy difficult. Therefore, the clinical pharmacology reviewer obtained eplerenone data from the ketoconazole/fluconazole in vivo drug interaction study, where sufficient blood samples were collected from 36 healthy individuals to characterize the pharmacokinetics of eplerenone.

OBJECTIVES:

1. To identify a pharmacokinetic model for eplerenone in healthy adults.
2. Evaluate the influence of body weight on apparent oral clearance and volume of distribution of eplerenone in adults.

METHODS:

Eplerenone plasma concentration data was obtained from study titled "**THE EFFECT OF FLUCONAZOLE AND KETOCONAZOLE ON THE SINGLE DOSE PHARMACOKINETIC PROFILE OF EPLRENONE IN HEALTHY SUBJECTS** (Protocol #: NE3-98-02-027)". Eplerenone plasma concentration data on Day 1, where all subjects received a single 100 mg dose of eplerenone, was analyzed from 36 healthy adult subjects, 33 Male/3 Female, mean age 33 years (range: 22-45 years) and mean weight 80 kg (range: 61-104 kg). On Day 1, a 7 mL blood sample for analysis of eplerenone were obtained 30 minutes predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, and 72 hours postdose.

Data analysis was performed using NONMEM version V,
4.2.1. One and two compartment models were explored. The variance structure was partitioned into two components, inter-individual variability and residual variability. The individual pharmacokinetic parameters were expressed as,

$$\theta_i = \theta_0 * \exp(\eta_j) + \varepsilon_{ij}$$

where θ_i represents the value of the PK parameter (e.g. CL/F, V/F) for patient i, θ_0 represents the population mean (typical value), and η_i denotes a random deviation from θ_0 for patient 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). Residual intra-subject random error is denoted by ε_{ij} which is assumed to be independent and have a zero mean. ε_{ij} had both a proportional and an additive component, with variances of $\sigma^2_{proportional}$ and $\sigma^2_{additive}$.

The first-order conditional estimation (FOCE) method was used to estimate the population mean parameters and variance components.

The models and covariates were subjected to a step-wise selection algorithm using a likelihood ratio test based on the change in the extended least squares objective function (ELS). The significance level (0.005) was chosen a priori which is equivalent to ΔELS of 7.88.

RESULTS:

The 1-compartment and 2-compartment pharmacokinetic models with first order absorption were fit to the observed eplerenone data points.

The ΔELS objective function values for the different pharmacokinetic models tested are presented in the following table.

MODEL	OBJECTIVE FUNCTION	Δ OBJECTIVE FUNCTION
2-compartment	4549.303	
1-compartment	4541.588	-7.715
1-compartment with absorption lag time	4211.053	-330.535**

**Significance defined a priori at p=0.005 equivalent to a change in OBJ FUNC of 7.88

The objective function values for the 1-compartment model and the 2-compartment model with first order absorption were similar with a difference of –7.715, however, the 2-compartment model had 4 additional parameters compared to the 1-comparment model. With a view toward parsimony of parameters in modeling, the 1-compartment model with first order absorption was chosen for further exploration. Further, graphical display clearly favored a monoexponential decline. Addition of absorption lag time to the basic 1-compartment model improved the model significantly as evidenced by a ΔELS of 330.535. Therefore the 1-compartment model with absorption lag time was chosen as the base model for exploring the effect of weight on CL/F and V/F.

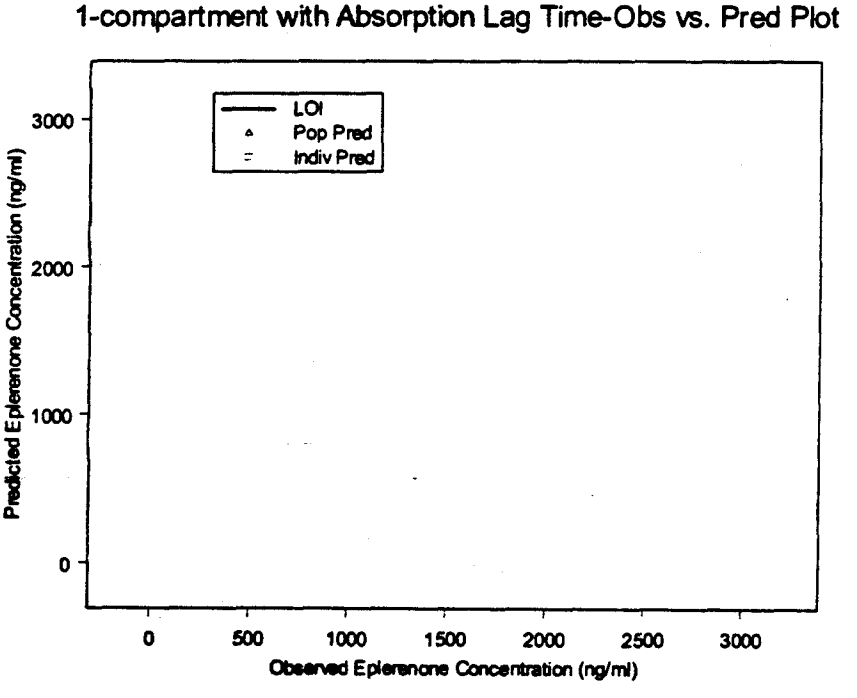
The estimates of the apparent CL/F, V/F, first order absorption rate constant, Ka, and absorption lag time and their respective inter-individual variability for eplerenone from the 1-compartment model with absorption lag time are presented in the table below.

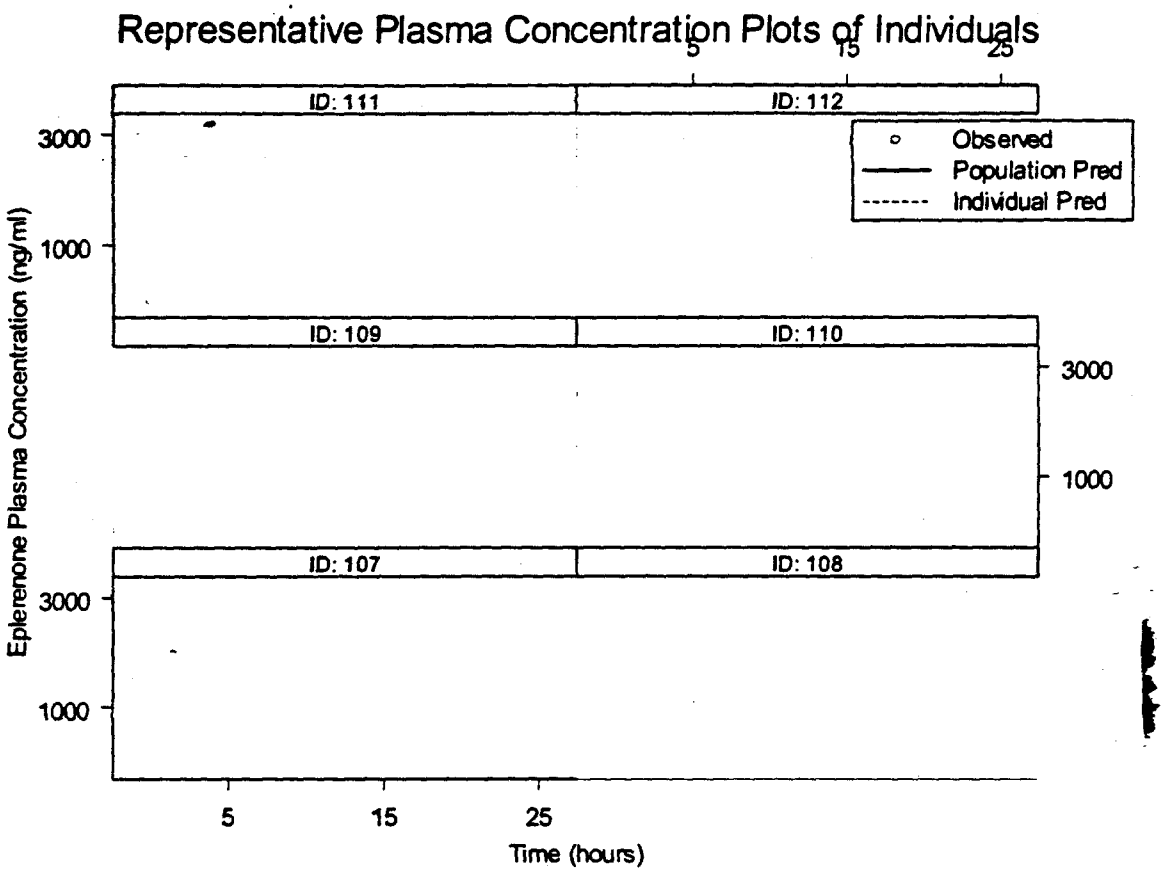
Parameter	Typical Value (CV%)
CL/F (L/h)	9.84 (39.5%)
V/F (L)	45.4 (19.6%)
Ka (h-1)	2.23 (51.5%)
Absorption Lag Time (h)	0.263 (69.6%)
σ proportional	%CV=8.8%
σ additive	Std.Dev=7.7 ng/ml

Standard error of the estimates were not estimable (covariance step aborted)

The population predicted CL/F of eplerenone was 9.84 L/h with interindividual variability of 40%, which is similar to the values obtained using non-compartmental analysis. Absorption of eplerenone was rapid with a Ka of 2.23 h^{-1}. Although the typical value of absorption lag time in healthy individuals was only about 16 minutes, its inclusion in the model significantly improved the fit of the plasma concentration data.

A representative *fit* of the plasma concentration-time data and the observed vs. predicted plots are presented below. (LOI = line of identity).





Effect of Body Weight on CL/F and V/F:

The covariate model building was performed on the 1-compartment model with first order absorption and absorption lag time. The covariates tested were body weight and age on CL/F and V/F. Gender was not tested because only 3 of the 36 subjects were female.

The ΔELS objective function values following addition of different covariates are presented in the following table.

MODEL	OBJECTIVE FUNCTION	Δ OBJECTIVE FUNCTION
Base model	4211.053	
Body weight on CL/F	4502.346	+291.293
Body weight on V/F (BWV) -	4199.509	-11.544**
Model BWV + age on CL/F	4260.517	+61.008
Model BWV + age on V/F	4198.554	-0.955

**Significance defined a priori at p=0.005 equivalent to a change in OBJ FUNC of 7.88

Of the covariates tested, only body weight on volume was statistically significant. Interestingly, the model with body weight on CL/F yielded higher ELS objective function values demonstrating poor fit. The reason for this anomaly is not clear.

The final parameter estimates for eplerenone CL/F, V/F, Ka, and absorption lag time and their associated inter-individual variability (CV%) following addition of covariate body weight on volume of distribution is presented in the table below.

Parameter	Typical Value (CV%)
CL/F (L/h)	11.1 (39.5%)
V/F in 45 kg adult (L)	37.2 (16.2%)
Exponent of body weight and V/F Relationship (L/Kg)	0.398
Ka (h-1)	2.15 (49.0%)
Absorption Lag Time (h)	0.277 (48.9%)
σ^2 proportional	%CV=8.9%
σ^2 additive	Std.Dev=7.6 ng/ml

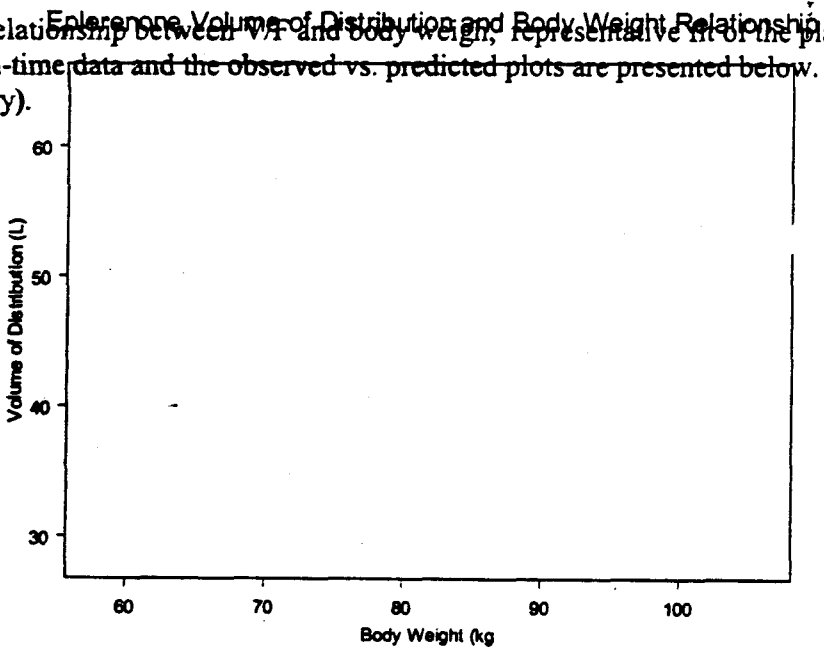
Standard error of the estimates were not estimable (covariance step aborted)

The equation describing the relationship of V/F and body weight is,

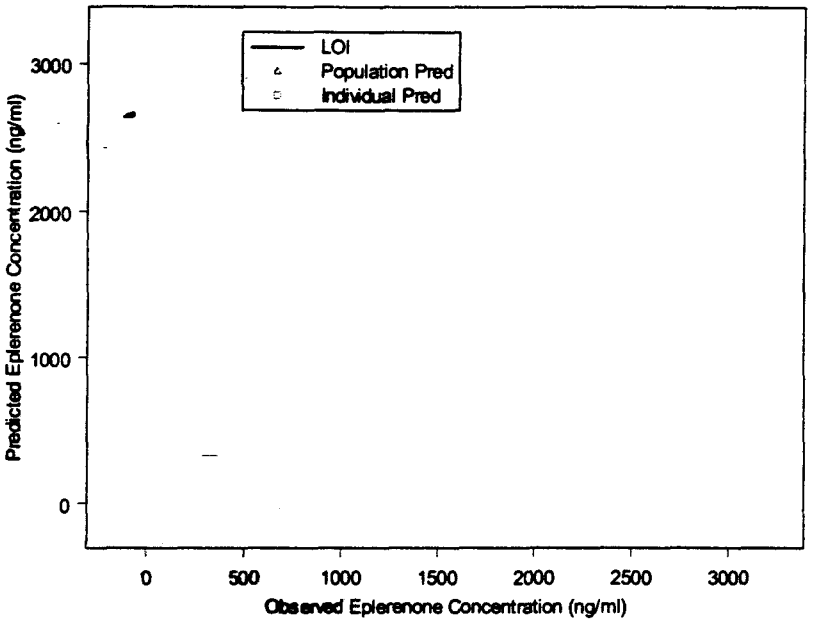
$$V/F = 37.2\,L * \left[\frac{Body\ Weight\ (kg)}{45}\right]^{0.398}$$

The typical value of V/F for a 45 kg individual is 37.2 L which will increase with an exponent of 0.398 with increasing body weight. The predicted V/F for a 70 kg individual is about 44.4 L. Addition of the influence of body weight to the pharmacokinetic model decreased the interindividual variability in V/F from 20% to 16% only and did not impact residual variability.

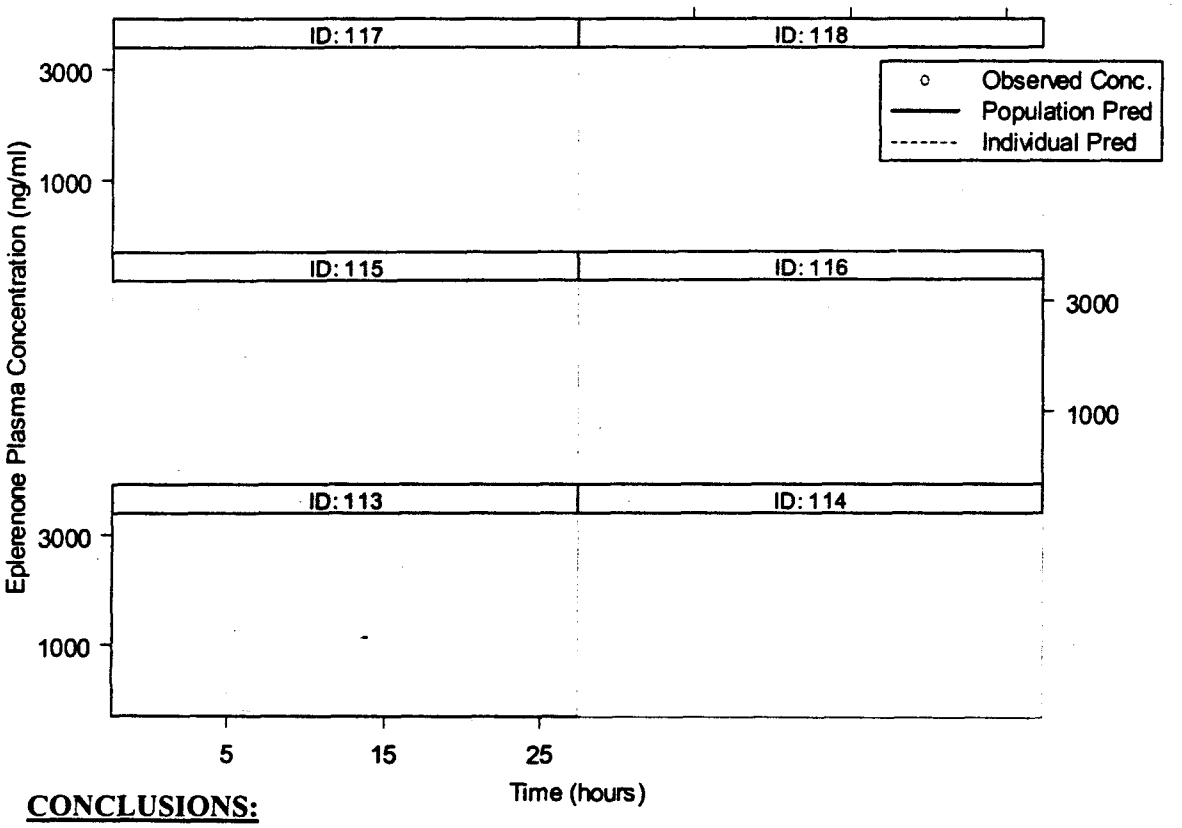
Plots of the relationship between V/F and body weight, representative fit of the plasma concentration-time data and the observed vs. predicted plots are presented below. (LOI = line of identity).



Observed vs. Predicted Eplerenone Concentration Plot
Body Weight Influence on V/F (1-compartment with Absorption Lag)



Representative Individual Plasma Concentration-Time Profiles of Eplerenone



CONCLUSIONS:

Eplerenone pharmacokinetics can be described by an 1-compartment model with first order absorption and absorption lag time, predicted a typical value for eplerenone CL/F of 9.84 L/h and V/F of 45.4 L with inter-individual variability of 40% and 20%, respectively. Eplerenone was rapidly absorbed following a short mean lag time of about 16 minutes. Covariate model testing indicated that body weight significantly influenced eplerenone V/F. The covariate model with body weight predicted a typical value of eplerenone V/F of 37 L in an adult weighing 45 kg increasing with body weight with an exponent of 0.398. For a 70 kg individual the predicted V/F is about 44 L. Model incorporating the influence of body weight on volume decreased the inter-individual variability of eplerenone V/F from 20% to 16% only.

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AN OPEN-LABEL, RANDOMIZED, MULTIPLE DOSE, THREE-WAY CROSSOVER STUDY TO ASSESS THE EFFECT OF EPLERENONE ON THE STEADY-STATE PHARMACOKINETIC PROFILE OF DIGOXIN IN HEALTHY ADULT SUBJECTS

STUDY INVESTIGATORS AND SITES:

Protocol No.: NE3-99-02-007

OBJECTIVES:

1. To assess the effect of eplerenone coadministration on the steady-state pharmacokinetic profile of digoxin in healthy adults.
2. To assess the effect of digoxin coadministration on the steady-state pharmacokinetic profile of eplerenone and to assess the safety and tolerability of concomitant administration of eplerenone and digoxin in healthy adult subjects.

FORMULATIONS:

Eplerenone – 100 mg film-coated tablets by Searle (Lot number RCT 11326)
Lanoxicap® - Digoxin solution in capsules, 0.2 mg capsules, Glaxo Wellcome (Lot # SF089303).

STUDY DESIGN:

This was an open-label, randomized, multiple-dose, six-sequence, three-period and three-treatment crossover design study conducted in twenty-four (24) healthy adult subjects, 12 M/12 F, age range 19 to 45 years. Subjects were randomized to one of the following six treatment sequences for Period 1 (Days 1-10), Period 2 (Days 21-30), and Period 3 (Days 41-50):

	Days 1-10	(Days 21-30)	(Days 41-50)
Sequence I	A	B	C
Sequence II	B	C	A
Sequence III	C	A	B
Sequence IV	A	C	B
Sequence V	B	A	C
Sequence VI	C	B	A

A = Eplerenone 100 mg QD
B = Digoxin 200 g QD
C = Digoxin 200 g QD + Eplerenone 100 mg QD

Each subject received 3 treatments in a crossover manner, with each treatment separated by a ten-day washout period. **Treatment A:** Eplerenone 100 mg QD for 10 consecutive days, **Treatment B:** Digoxin 200 µg QD for 10 consecutive days, **Treatment C:** Eplerenone 100 mg QD and digoxin 200 µg QD for 10 consecutive days. On Days 10, 30 and 50, subjects received study medication following an overnight fast.

ASSAY:

Sample Collection

Blood samples were drawn on the following days and times:

· Days 1, 21 and 41 at predose for analyses for digoxin, eplerenone and SC-70303 predose plasma concentrations;

· Days 7-9, 27-29 and 47-49 at predose (trough) for analysis for digoxin and/or eplerenone and SC-70303 predose (trough) plasma concentrations, depending on the treatment being administered;

· Days 10, 30 and 50 at 0 hour predose and at 30 minutes, 1, 1.5, 2, 3, 4, 6, 8, 12,16 and 24 hours postdose for analysis for digoxin and/or eplerenone and SC-70303 plasma concentrations, depending on the treatment being administered.

Urine samples were collected and pooled on Day -1 (-12 hours to 0 hour predose) and on Days 10, 30 and 50 (0-4, 4-8, 8-12 and 12-24 hours postdose). Aliquots of pooled urine samples were analyzed for eplerenone, SC-70303 and/or unchanged digoxin.

RESULTS

Effect on Digoxin Pharmacokinetics:

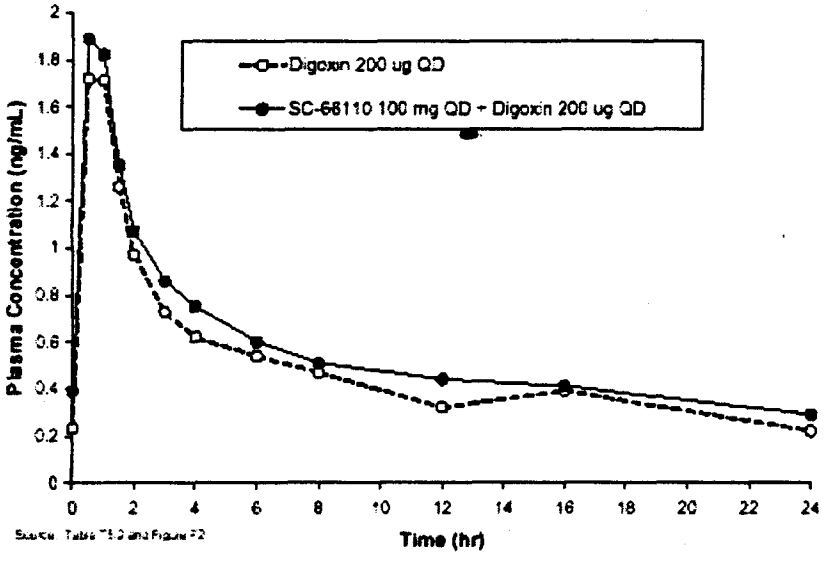
The pharmacokinetic parameters of digoxin in the absence and presence of eplerenone are listed in the following table.

Table 2. Arithmetic Mean (%CV) Digoxin Pharmacokinetic Parameters

Mean Pharmacokinetic Parameters of Digoxin	Digoxin 200 mg QD			Eplerenone 100 mg QD + Digoxin 200 mg QD		
	N	Mean	(%CV)	N	Mean	(%CV)
AUC(0-24) (hr*ng/mL)	24	11.80	(35%)	24	13.53	(29%)
Cmax (ng/mL)	24	2.05	(31%)	24	2.16	(34%)
Tmax (hr)	24	0.75	(48%)	24	0.79	(74%)
T(1/2) (hr)	23	41.59	(80%)	24	50.43	(111%)
CL/F (L/hr)	24	19.16	(40%)	24	16.41	(41%)
CL/F/WT (L/hr/70kg)	24	19.01	(33%)	24	16.65	(44%)

AUMC(0-24) (hr^2*ng/mL)	24	101.82	(48%)	24	118.58	(41%)
MRT (hr)	24	8.25	(19%)	24	8.40	(22%)
XU(0-24) (mg)	24	106.27	(19%)	24	111.26	(26%)
XUT(0-24) (mg/hr)	24	4.43	(19%)	24	4.64	(26%)

Figure 8.a. Mean Digoxin Plasma Concentrations



Coadministration of eplerenone for 10 days decreased the apparent oral clearance of digoxin estimated at steady state from 19 L/h to 16 L/h which consequently increased digoxin AUC by 16%. Coadministration of eplerenone increased digoxin Cmax by 5%. This elevation in overall plasma digoxin exposure was not accompanied by clinical effects of digoxin toxicity.

Table 3 Ratios and 90% Confidence Intervals for Digoxin Pharmacokinetic Parameters

Digoxin Parameter	Least Squares Means				Ratio Coadmin./ Digoxin	90% Conf Interval	p-value
	Eplerenone 100 mg QD + Digoxin 200 mg QD		Digoxin 200 mg QD				
	N	LS Mean	N	LS Mean			
AUC(0-24) (hr*ng/mL)	24	12.92	24	11.13	1.16	(1.036, 1.301)	0.0349
Cmax (ng/mL)	24	2.05	24	1.96	1.05	(0.947, 1.157)	0.4410
Tmax (hr)	24	0.79	24	0.75	--	--	0.7481
T(1/2) (hr)	24	50.43	23	41.53	--	--	0.5278
CL/F (L/hr)	24	15.48	24	17.98	0.86	(0.768, 0.965)	0.0349
CL/F/WT (L/hr/70kg)	24	15.55	24	18.05	0.86	(0.768, 0.965)	0.0350
XU(0-24) (mg)	24	107.69	24	104.31	1.03	(0.942, 1.131)	0.5550

Effect on Eplerenone Pharmacokinetics:

The pharmacokinetic parameters of eplerenone and its metabolite SC-70303 at steady-state obtained following administration of 100 mg eplerenone QD for 10 days alone and in the presence of 200 µg of digoxin for 10 days is presented in the table below.

Table 4. Arithmetic Mean Eplerenone and SC-70303 Pharmacokinetic Parameters

Pharmacokinetic Parameter	Eplerenone				SC-70303			
	Eplerenone 100 mg QD		Eplerenone 100 mg QD + Digoxin 200 mg QD		Eplerenone 100 mg QD		Eplerenone 100 mg QD + Digoxin 200 mg QD	
	N	Mean	N	Mean	N	Mean	N	Mean
AUC(0-24) (hr*ng/mL)	24	12766.67	24	12142.73	24	516.52	24	549.95
Cmax (ng/mL)	24	2073.75	24	1931.67	24	99.82	24	122.22
Tmax (hr)	24	1.75	24	1.88	24	1.88	24	1.65
T(1/2) (hr)	24	4.01	24	3.83	23	3.53	24	3.18
CL/F (L/hr)	24	8.61	24	9.62	--	--	--	--
CL/F/WT (L/hr/70kg)	24	8.87	24	9.97	--	--	--	--
AUMC(0-24) (hr^2*ng/mL)	24	71841.68	24	68440.58	24	2526.67	24	2416.18
MRT (hr)	24	5.32	24	5.32	24	4.56	24	4.26
XU(0-24) (mg)	24	2712.32	24	2529.30	24	5651.17	24	5357.35
XUT(0-24) (mg)	24	113.01	24	105.39	24	235.47	24	223.22

Coadministration of 200 µg digoxin for 10 days did not affect eplerenone pharmacokinetics. Eplerenone AUC_{0-24} and C_{max} values decreased slightly by 7-8% with digoxin coadministration, and the 90% confidence intervals for the ratios (eplerenone + digoxin/eplerenone alone) of these parameters indicated the two treatments were bioequivalent with respect to AUC_{0-24} and C_{max}.

Figure 8.b. Mean SC-66110 Plasma Concentrations

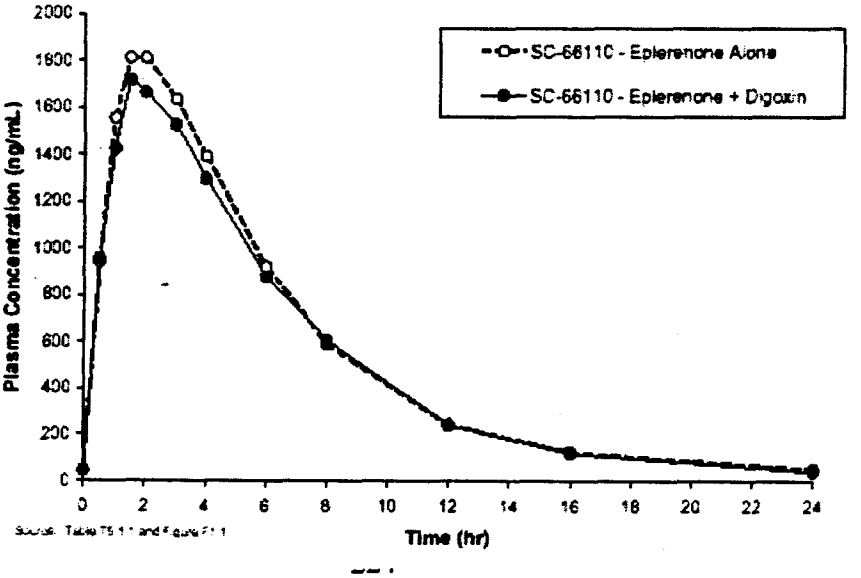


Table 5. Ratios and 90% Confidence Intervals for Eplerenone and SC-70303 Pharmacokinetic Parameters

Pharmacokinetic Parameter	Least Squares Means				Ratio Coadmin./ Eplerenone	90% Confidence Interval	p-value
	Eplerenone 100 mg QD + Digoxin 200 mg QD		Eplerenone 100 mg QD				
	N	LS Mean	N	LS Mean			
Eplerenone							
AUC(0-24) (hr*ng/mL)	24	11343.25	24	12166.64	0.93	(0.857, 1.014)	0.1670
Cmax (ng/mL)	24	1874.38	24	2038.44	0.92	(0.865, 0.977)	0.0276
Tmax (hr)	24	1.87	24	1.75	--	--	0.5380
T(1/2) (hr)	24	3.83	24	4.01	--	--	0.4392
CL/F (L/hr)	24	8.82	24	8.22	1.07	(0.986, 1.167)	0.1670
CL/F/WT (L/hr/70kg)	24	8.85	24	8.25	1.07	(0.986, 1.167)	0.1672
XU(0-24) (mg)	24	2235.58	24	2423.77	0.92	(0.793, 1.073)	0.3688
SC-70303							
AUC(0-24) (hr*ng/mL)	24	530.89	24	491.59	1.08	(1.013, 1.151)	0.0500
Cmax (ng/mL)	24	113.53	24	96.14	1.18	(1.070, 1.303)	0.0086
Tmax (hr)	24	1.65	24	1.87	--	--	0.3210
T(1/2) (hr)	24	3.18	23	3.55	--	--	0.0790

Coadministration of 200 µg digoxin for 10 days did not affect SC-70303 AUC_{0-24} but slightly increased C_{max} values by 18%. The difference in C_{max} is not expected to be clinically significant since the contribution of SC-70303 to the overall activity of eplerenone is low.

Effect of Digoxin and Eplerenone alone and Digoxin + Eplerenone on ECG Parameters

Digoxin and eplerenone when administered alone or in combination decreased heart rate. Neither eplerenone alone nor digoxin alone affected the mean length of the PR interval, although the combination resulted in a slight prolongation of the PR interval (+4.5 msec) on Day 10. Neither digoxin nor eplerenone alone or in combination had any prolongation effect on cardiac repolarization. No subject had a QTc interval greater than 500 msec or a change from Baseline in the QTc interval greater than 60 msec. Using Fridericia's correction, one subject while on eplerenone alone and one subject while on eplerenone + digoxin had a change from Baseline in the QTc interval between 31 msec and 60 msec.

Table 6: Mean (±SEM) Change From Baseline in ECG Parameters at Steady State – Day 10

Parameter	Digoxin 200 mg QD mean ± SEM	Eplerenone 100 mg QD mean ± SEM	Digoxin 200 mg QD + Eplerenone 100 mg QD mean ± SEM	P-Value[a]

	N = 24	N = 24	N = 24	
HR (bpm)	-6 .1 ± 1.2 [b]	-3.5 ± 1.1 [b]	-5.9 ± 1.6 [b]	NS
PR (msec)	1.5 ± 1.6	0.3 ± 1.4	4.5 ± 1.5	NS
QRS (msec)	0.9 ± 1.0	-0.5 ± 0.9	0.8 ± 1.0	NS
QT (msec)	-1.9 ± 2.3	1.7 ± 2.2	-0.2 ± 3.0	NS
QTc[c] (msec)	-13.0 ± 1.6 [b]	-4.7 ± 1.8 [b]	-10.8 ± 1.7	0.0026
QTc[d] (msec)	-18.9 ± 2.1 [b]	-8.2 ± 2.3 [b]	-16.4 ± 2.2 [b]	0.0051
MaxQTc[c] (msec)	-13.0 ± 1.6	-4.7 ± 1.8	-10.8 ± 1.7	NS
MaxQTc[d] (msec)	-18.9 ± 2.1	-8.2 ± 2.3	-16.4 ± 2.2	NS

a – P-values >0.05 indicates statistically significant difference in mean change from Baseline across treatments
b - indicates statistically significantly different from Baseline
c – calculated using Fridericia's formula
d – calculated using Bazett's formula
Max=mean maximum change from Baseline
NS – not statistically significant across treatments

CONCLUSIONS:

Coadministration of 100 mg QD eplerenone for 10 days did not affect digoxin Cmax and slightly increased digoxin $AUC_{0\text{-}24}$ by 16%. This increase is not expected to be clinically relevant and in the present study were not accompanied by clinical evidence of digoxin toxicity.

Coadministration of digoxin 200 µg QD for 10 days did not have a significant effect on the pharmacokinetic disposition of eplerenone and its open-ring form SC-70303.

Both digoxin and eplerenone administered alone decreased heart rate by –6 bpm and –4 bpm, respectively. When coadministered mean heart rate decreased by 6 bpm. Digoxin and eplerenone when administered alone or in combination did not affect ECG parameters significantly.

A SINGLE-BLIND ASSESSMENT OF THE PHARMACOKINETICS AND PHARMACODYNAMICS OF WARFARIN IN THE PRESENCE OF STEADY-STATE LEVELS OF EPLERENONE IN HEALTHY ADULT SUBJECTS

STUDY INVESTIGATORS AND SITES:

Protocol Number: NE3-99-02-032

OBJECTIVES:

1. To examine the effect of multiple doses of eplerenone on prothrombin time (PT) in subjects stabilized on warfarin, and to assess the effect of multiple doses of eplerenone on the steady-state pharmacokinetics of warfarin.
2. To evaluate the safety and tolerability of multiple doses of eplerenone in subjects stabilized on warfarin.

FORMULATIONS:

Eplerenone (SC-66110) - 100 mg tablets, packaging lot number RCT 11209 by Searle
Eplerenone (SC-66110) placebo tablets, packaging lot number RCT 11204 by Searle
Coumadin®. (warfarin) -1 mg tablets, DuPont lot number EMH442A
Coumadin®. (warfarin) - 2 mg tablets, DuPont lot number EMK556A
Coumadin®. (warfarin) - 5 mg tablets, DuPont lot number EML565A

STUDY DESIGN:

This was a single-blind, randomized, multiple-dose, parallel group study conducted in 25 healthy adult subjects between 23 and 45 years of age (mean: 32 years) with a mean body weight of 83 kg. Predose blood samples for warfarin pharmacokinetic measurements were drawn prior to receipt of a 10 mg (2 x 5 mg tablets) oral warfarin dose. On the morning of Day -6, an additional 5 mg warfarin was administered, and then individualized doses of warfarin (1-15 mg QD) required to achieve and maintain target PT values were administered on Days -5 to 0. If the PT was stabilized for three consecutive days at 1.2x to 1.7x the pretreatment value, the subjects began Day 0, then on Days 1-7 received the warfarin dose found to achieve the target PT.

Subjects were randomized to receive on the following treatments on Days 1-7 (n=12 per treatment):
Treatment A = 100 mg eplerenone QD + 1-15 mg warfarin QD
Treatment B = Eplerenone placebo QD + 1-15 mg warfarin QD

ASSAY:

NP = not provided by sponsor

Sample Collection

Blood samples for total and free R- and S-warfarin plasma concentrations were drawn on the following days and times: Day -7 at predose; Day -6 through Day -1 at 15 minutes predose; and Days 0 and 7 at 15 minutes predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16 and 24 hours postdose.

Blood samples for plasma eplerenone and SC-70303 concentrations were drawn prior to the morning dose on Days 1-8 for determination of steady-state.

Urine samples for eplerenone and SC-70303 pharmacokinetic measurements were collected and pooled on Days 1 and 7 during the following time periods: -10 to 0, 0-4, 4-8, 8-12 and 12-24 hours postdose.

Blood samples for prothrombin (PT) measurements were drawn on Days -7 to 0 at 15 minutes prior to warfarin dosing and at five and 12 hours postdose. On Days 1-7, blood samples for PT measurements were drawn at 15 minutes predose and 11 hours postdose. PT samples were analyzed within 12 hours of collection.

RESULTS

The following table lists the pharmacokinetic parameter values for total and free R- and S- warfarin administered alone and in the presence of 100 mg QD eplerenone.

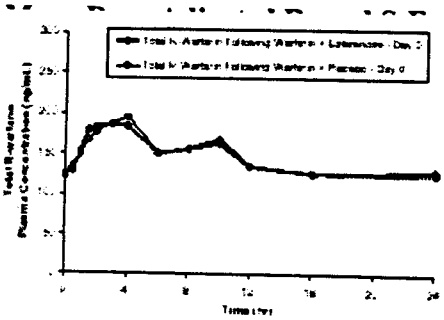
Table 4. Summary Statistics for Total and Free R- and S-Warfarin Pharmacokinetic Parameters

Analyte	Total Warfarin	Free Warfarin

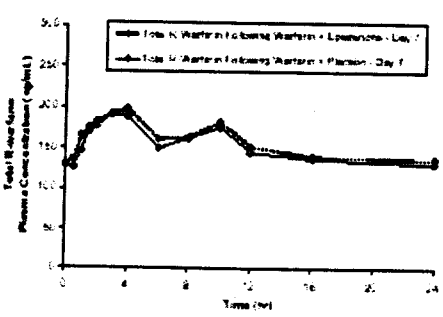
PK Parameter	Eplerenone 100 mg QD + Warfarin 1-15 mg QD			Placebo QD + Warfarin 1-15 mg QD		Eplerenone 100 mg QD + Warfarin 1-15 mg QD			Placebo QD + Warfarin 1-15 mg QD	
	N	Mean	(%CV)	N	Mean (%CV)	N	Mean	(%CV)	N	Mean (%CV)
R-Warfarin (Day 0)										
AUC(0-24) (hr*ng/mL)	13	3427.82	(21%)	12	3455.79 (31%)	13	17.63	(29%)	12	18.09 (32%)
Cmax (ng/mL)	13	201.96	(25%)	12	203.31 (30%)	13	1.01	(21%)	12	1.01 (29%)
Tmax (hr)	13	3.24	(71%)	12	5.28 (115%)	13	1.73	(53%)	12	2.33 (83%)
CL/F (L/hr)	13	0.31	(25%)	12	0.32 (32%)	13	60.95	(26%)	12	59.68 (26%)
CL/F/WT (L/hr/70kg)	13	0.26	(31%)	12	0.28 (36%)	13	50.18	(25%)	12	51.78 (28%)
Vss/F (L)	13	3.37	(23%)	12	3.47 (29%)	13	634.15	(21%)	12	664.17 (25%)
R-Warfarin (Day 7)										
AUC(0-24) (hr*ng/mL)	11	3909.48	(29%)	12	3569.75 (25%)	11	19.70	(42%)	12	18.09 (31%)
Cmax (ng/mL)	11	211.45	(19%)	12	206.83 (29%)	11	1.08	(18%)	12	1.14 (30%)
Tmax (hr)	11	5.18	(68%)	12	3.42 (68%)	11	2.18	(67%)	12	4.31 (147%)
CL/F (L/hr)	11	0.27	(23%)	12	0.30 (25%)	11	57.45	(34%)	12	60.37 (30%)
CL/F/WT (L/hr/70kg)	11	0.22	(27%)	12	0.26 (28%)	11	46.02	(26%)	12	52.20 (28%)
Vss/F (L)	11	3.01	(23%)	12	3.33 (24%)	11	564.43	(27%)	12	599.47 (27%)
S-Warfarin (Day 0)										
AUC(0-24) (hr*ng/mL)	13	2619.06	(31%)	12	2363.55 (43%)	13	10.95	(29%)	12	10.28 (35%)
Cmax (ng/mL)	13	168.70	(30%)	12	145.74 (36%)	13	0.67	(19%)	12	0.64 (31%)
Tmax (hr)	13	2.00	(46%)	12	3.30 (56%)	13	1.77	(52%)	12	1.54 (35%)
CL/F (L/hr)	13	0.42	(36%)	12	0.48 (34%)	13	99.32	(31%)	12	106.77 (29%)
CL/F/WT (L/hr/70kg)	13	0.36	(41%)	12	0.42 (39%)	13	82.72	(35%)	12	93.09 (32%)
Vss/F (L)	13	4.50	(33%)	12	5.11 (31%)	13	1009.70	(24%)	12	1154.92 (27%)
S-Warfarin (Day 7)										
AUC(0-24) (hr*ng/mL)	11	2635.94	(32%)	12	2345.57 (39%)	11	11.38	(38%)	12	10.10 (36%)
Cmax (ng/mL)	11	155.39	(24%)	12	143.35 (32%)	11	0.70	(16%)	12	0.66 (26%)
Tmax (hr)	11	4.09	(85%)	12	3.13 (77%)	11	1.77	(41%)	12	2.17 (60%)
CL/F (L/hr)	11	0.41	(29%)	12	0.47 (27%)	11	96.79	(28%)	12	108.52 (28%)
CL/F/WT (L/hr/70kg)	11	0.34	(36%)	12	0.41 (30%)	11	78.92	(29%)	12	94.31 (27%)
Vss/F (L)	11	4.43	(28%)	12	5.07 (27%)	11	937.19	(28%)	12	1051.63 (24%)

Statistically significant differences in Day 0 total or free R- and S- warfarin AUC_{0-24}, C_{max}, CL/F or CL/F/WT values were not observed upon coadministration with 100 mg QD eplerenone. Similarly, coadministration of 100 mg QD eplerenone did not result in statistically significant differences in Day 7 total or free R- and S-warfarin AUC_{0-24}, C_{max}, CL/F, CL/F/WT or T_{max} values compared to coadministration for 7 days with placebo.

For total R-enantiomer, Day 7 AUC_{0-24} was 10.2% greater and C_{max} was 7.6% greater with coadministration of eplerenone relative to placebo. Similarly, for the S-enantiomer, which is 5 times more potent than R-enantiomer, Day 7 AUC_{0-24} was 13.2% greater and C_{max} was 11.4% greater with coadministration of eplerenone relative to placebo.



ntiomer



For the free R-enantiomer, Day 7 AUC_{0-24} was 12.1% greater and C_{max} was 0.7% greater with coadministration of eplerenone relative to placebo. Similarly, for the free S-enantiomer, Day 7 AUC_{0-24} was 15.1% greater and C_{max} was 8.2% greater with coadministration of eplerenone relative to placebo. These increases are not expected to be clinically relevant.

Table 5. Ratios and 90% Confidence Intervals for Total and Free R- and S-Warfarin Pharmacokinetic Parameters

Pharmacokinetic Parameter	Least Squares Means				Ratio Eplerenone/ Placebo	90% Confidence Interval	P-Value
	Eplerenone + Warfarin		Placebo + Warfarin				
TOTAL WARFARIN	**N**	**LSM**	**N**	**LSM**			
R-Enantiomer (Day 0)							
AUC(0-24) (hr*ng/mL)	13	3340.85	12	3309.39	1.010	(0.8297, 1.2282)	0.935
Cmax (ng/mL)	13	196.33	12	194.74	1.008	(0.8271, 1.2288)	0.944
CL/F (L/hr)	13	0.30	12	0.30	0.991	(0.8141, 1.2052)	0.935
CL/F/WT (L/hr/70 kg)	13	0.25	12	0.26	0.986	(0.8124, 1.1974)	0.904
Tmax (hr)	13	3.27	12	5.24	--	--	0.304
R-Enantiomer (Day 7)							
AUC(0-24) (hr*ng/mL)	11	3802.78	12	3450.54	1.102	(0.9104, 1.3339)	0.390
Cmax (ng/mL)	11	211.54	12	196.57	1.076	(0.9101, 1.2724)	0.459
CL/F (L/hr)	11	0.26	12	0.29	0.907	(0.7496, 1.0983)	0.390
CL/F/WT (L/hr/70 kg)	11	0.22	12	0.24	0.905	(0.7482, 1.0936)	0.373
Tmax (hr)	11	5.21	12	3.39	--	--	0.175
S-Enantiomer (Day 0)							
AUC(0-24) (hr*ng/mL)	13	2469.73	12	2224.08	1.110	(0.8654, 1.4247)	0.478
Cmax (ng/mL)	13	160.86	12	139.65	1.152	(0.9281, 1.4293)	0.273
CL/F (L/hr)	13	0.40	12	0.45	0.901	(0.7018, 1.1554)	0.478
CL/F/WT (L/hr/70 kg)	13	0.34	12	0.38	0.897	(0.7010, 1.1467)	0.455
Tmax (hr)	13	1.98	12	3.33	--	--	0.032
S-Enantiomer (Day 7)							
AUC(0-24) (hr*ng/mL)	11	2517.56	12	2224.95	1.132	(0.8919, 1.4353)	0.381
Cmax (ng/mL)	11	152.50	12	136.95	1.114	(0.9172, 1.3517)	0.350
CL/F (L/hr)	11	0.40	12	0.45	0.884	(0.6966, 1.1210)	0.381
CL/F/WT (L/hr/70 kg)	11	0.33	12	0.38	0.881	(0.6965, 1.1145)	0.364
Tmax (hr)	11	4.08	12	3.14	--	--	0.475
FREE WARFARIN							
R-Enantiomer (Day 0)							
AUC(0-24) (hr*ng/mL)	13	17.20	12	17.13	1.004	(0.8310, 1.2140)	0.968
Cmax (ng/mL)	13	1.00	12	0.96	1.045	(0.8939, 1.2206)	0.635
CL/F (L/hr)	13	58.13	12	58.39	0.996	(0.8236, 1.2032)	0.968
CL/F/WT (L/hr/70 kg)	13	49.06	12	49.49	0.991	(0.8208, 1.1969)	0.937
Tmax (hr)	13	1.80	12	2.27	--	--	0.432
R-Enantiomer (Day 7)							
AUC(0-24) (hr*ng/mL)	11	18.93	12	16.88	1.121	(0.8903, 1.4125)	0.402

Cmax (ng/mL) (b)	11	1.08	12	1.08	1.007	(0.8508, 1.1910)	0.946
CL/F (L/hr)	11	52.81	12	59.23	0.892	(0.7079, 1.1231)	0.402
CL/F/WT (L/hr/70 kg)	11	44.41	12	49.96	0.889	(0.7044, 1.1218)	0.393
Tmax (hr)	11	2.12	12	4.37	--	--	0.284
S-Enantiomer (Day 0)							
AUC(0-24) (hr*ng/mL)	13	10.56	12	9.73	1.086	(0.8719, 1.3515)	0.527
Cmax (ng/mL)	13	0.66	12	0.61	1.078	(0.9062, 1.2814)	0.466
CL/F (L/hr)	13	94.68	12	102.78	0.921	(0.7398, 1.1468)	0.527
CL/F/WT (L/hr/70 kg)	13	79.90	12	87.12	0.917	(0.7378, 1.1400)	0.502
Tmax (hr)	13	1.78	12	1.54	--	--	0.456
S-Enantiomer (Day 7)							
AUC(0-24) (hr*ng/mL)	11	10.93	12	9.50	1.151	(0.9094, 1.4561)	0.316
Cmax (ng/mL)	11	0.69	12	0.64	1.082	(0.9269, 1.2636)	0.389
CL/F (L/hr)	11	91.49	12	105.28	0.869	(0.6867, 1.0995)	0.316
CL/F/WT (L/hr/70 kg)	11	76.93	12	88.80	0.866	(0.6843, 1.0966)	0.306
Tmax (hr)	11	1.81	12	2.13	--	--	0.497

PHARMACODYNAMICS:

The following table lists the mean prothrombin time values in subjects receiving warfarin + placebo for 7 days or warfarin + eplerenone for 7 days.

Table 6. Mean (SD) Changes in PT Values at 15 Minutes Predose and 11 Hours Postdose

Prothrombin Time (sec)	Eplerenone 100 mg QD + Warfarin 1-15 mg QD		Placebo QD + Warfarin 1-15 mg QD		P-Value
	N	Mean ± SD	N	Mean + SD	
15 Min Predose					0.7169
Day 2	13	0.58 ± 0.724	12	0.27 ± 0.680	
Day 3	11	-0.15 ± 0.696	12	-0.14 ± 1.148	
Day 4	11	-0.36 ± 0.785	12	-0.21 ± 1.030	
Day 5	11	-0.73 ± 0.875	12	-0.52 ± 1.337	
Day 6	11	-0.29 ± 0.842	12	-0.02 ± 1.647	
Day 7	11	-0.78 ± 1.124	12	-0.35 ± 1.795	
11 Hours Postdose					0.3622
Day 1	13	-0.66 ± 0.632	12	-0.53 ± 0.959	
Day 2	12	-0.89 ± 0.607	12	-0.83 ± 1.057	
Day 3	11	-1.11 ± 0.785	12	-0.70 ± 1.091	
Day 4	11	-1.30 ± 0.909	12	-0.76 ± 1.167	
Day 5	11	-0.52 ± 0.981	12	-0.03 ± 1.768	
Day 6	11	-1.45 ± 1.061	12	-0.84 ± 1.781	
Day 7	11	-0.95 ± 1.283	12	-0.30 ± 2.280	

Overall, mean PT values in both treatment groups, placebo and eplerenone, decreased slightly from baseline throughout the randomized treatment period. No statistically

significant treatment effects were observed for the mean changes in PT at 15 minutes predose or 11 hours postdose on Days 3 through 7. The largest mean increases in PT values at 15 minutes predose were observed on Day 2 (0.58 seconds following eplerenone + warfarin dosing, and 0.27 seconds following placebo + warfarin dosing). These increases were not considered to appreciably increase the bleeding risk. At 11 hours postdose, all of the mean PT values from Days 2 through 7 were decreased compare to baseline (Day 0).

CONCLUSIONS:

Statistically significant differences in Day 0 and Day 7 total or free R- and S- warfarin $AUC_{0\text{-}24}$, C_{max}, CL/F or CL/F/WT values were not observed upon coadministration with 100 mg QD eplerenone.

Coadministration of eplerenone 100 mg QD with warfarin 2-6 mg QD for 7 days did not have a statistically or clinically significant effect on prothrombin time (PT). Overall, minor decreases in mean PT values were observed over time compared to baseline.

THE EFFECT OF FLUCONAZOLE AND KETOCONAZOLE ON THE SINGLE DOSE PHARMACOKINETIC PROFILE OF EPLRENONE IN HEALTHY SUBJECTS

STUDY INVESTIGATORS AND SITES:

Protocol Number: NE3-98-02-027

OBJECTIVES:

1. To examine the single-dose pharmacokinetics of eplerenone in the presence of steady-state fluconazole or ketoconazole.
2. To compare the safety and tolerability of single doses of eplerenone and steady state fluconazole or ketoconazole in healthy subjects.

FORMULATIONS:

Eplerenone - 100 mg IR tablets (Lot No. RCT 10904) by Searle
Placebo - placebo gray capsules, Size No.— (Lot No. RCT 10903) by Searle
Fluconazole - (Diflucan®) 200 mg tablets (Lot No. 84P005E) by Pfizer
Ketoconazole - (Nizoral®) 200 mg tablets (Lot No. 98P0579E) by Janssen.

STUDY DESIGN:

This was a single-blind, randomized, multiple-dose, two period crossover study conducted in 36 healthy subjects (33 M/3 F), mean age 33 years and mean weight 80 kg. Subjects were assigned to either Group I or Group II, and within each group were randomized to one of two treatment sequences (n=9 per sequence, 18 per group):

Treatment Group	Treatment Sequence	TREATMENTS	
		PERIOD 1	PERIOD 2
I	i	Ketoconazole 200 mg BID	Placebo BID
	ii	Placebo BID	Ketoconazole 200 mg BID
II	i	Fluconazole 200 mg QD	Placebo QD
	ii	Placebo QD	Fluconazole 200 mg QD

On Day 1, subjects received a single 100 mg dose of eplerenone. During Treatment Period 1 (Days 4-10), subjects received either ketoconazole 200 mg or placebo twice daily (Group I), or fluconazole 200 mg or placebo (Group II) once daily. On Days 13-19, subjects received the crossover treatment of either ketoconazole 200 mg or placebo twice daily (Group I), or fluconazole 200 mg or placebo (Group II) once daily. On Days 10 and 19, subjects were to be administered 100 mg of eplerenone as a single dose at the same time as the morning dose of fluconazole, ketoconazole, or placebo.

ASSAY:

[redacted]

Sample Collection

On Days 1, 10, and 19, a 7 mL blood sample for analysis of eplerenone and SC-70303 concentrations were obtained 30 minutes predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, and 72 hours postdose.

On Day 1 a 7 mL blood sample for the analysis of ketoconazole (Group I) or fluconazole (Group II) was obtained at 30 minutes pre-eplerenone dose and 1.5 hours post-eplerenone dose.

On Days 7-9, and Days 16-18, a 7 mL blood sample was obtained from subjects receiving active ketoconazole (Group I) or fluconazole (Group II) 30 minutes prior to study drug dose for the assessment of trough levels of ketoconazole and fluconazole.

On Days 10 and 19, a 7 mL blood sample for the assessment of ketoconazole (Group I) or fluconazole (Group II) concentrations was collected from subjects receiving active ketoconazole or fluconazole treatment 30 minutes predose, and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, and 72 hours postdose.

On Days 1, 10, and 19, urine was collected at the 0 to 24 hour, 24 to 48 hour, and 48 to 72 hour time intervals and analyzed for eplerenone and SC-70303 concentrations.

RESULTS

Effect of Ketoconazole on Eplerenone Pharmacokinetics:

Baseline plasma pharmacokinetic parameters of eplerenone based on Day 1 dosing for all evaluable subjects is presented in the following table.

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

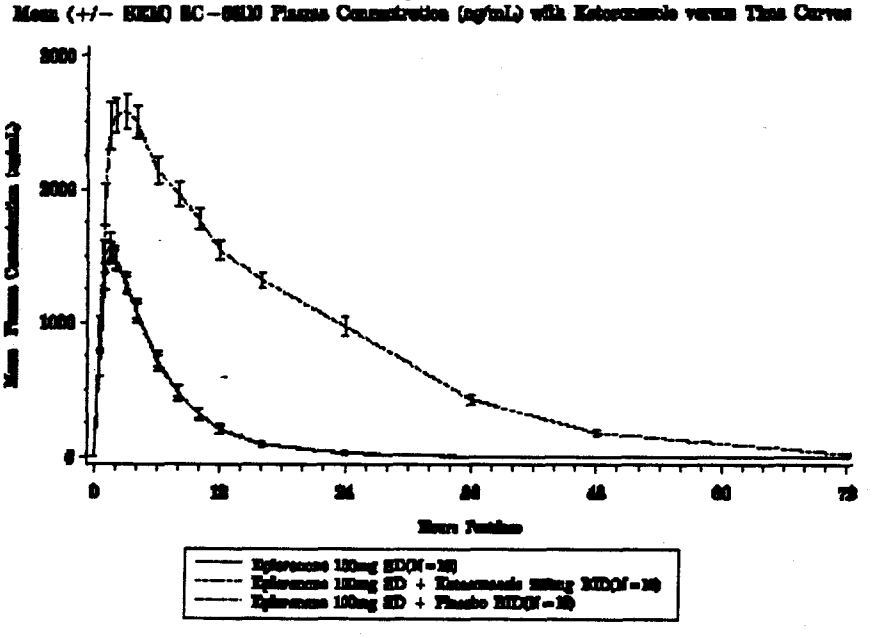
Pharmacokinetic Parameter	Eplerenone Mean (%CV)		SC-70303 Mean (%CV)	
	Ketoconazole Trt Group (N=18)	Fluconazole Trt Group (N=17)	Ketoconazole Trt Group (N=18)	Fluconazole Trt Group (N=17)
AUC0-lqc (ng/mL)*hr	10278.04 (32.0)	8732.47 (29.5)	353.85 (38.2)	293.63 (38.0)

AUC0-inf (ng/mL)*hr	10391.34 (31.6)	8838.18 (29.6)	401.01 (35.2)	337.62 (35.1)
Cmax (ng/mL)	1669.06 (26.2)	1665.62 (19.0)	74.86 (30.7)	73.40 (31.9)
Tmax (hr)	1.7 (52.7)	1.44 (38.6)	1.47 (58.7)	1.21 (38.8)
Kel (1/hr)	0.2 (23.1)	0.25 (28.9)	0.22 (21.0)	0.25 (18.6)
T ½ (hr)	3.6 (24.3)	3.01 (35.9)	3.30 (21.4)	2.91 (18.4)
CL/F (L/hr)	10.54 (30.0)	12.25 (28.2)	--	--
CL/F/WT (L/hr/70 kg)	9.17 (33.1)	11.37 (30.0)	--	--

The following table lists the pharmacokinetic parameters of eplerenone following coadministration of ketoconazole 200 mg BID or placebo BID for 10 days.

Table 2: Arithmetic Mean Eplerenone Pharmacokinetic Parameters: Ketoconazole/ Placebo Co-administration

Pharmacokinetic Parameter	Eplerenone Mean (%CV)		Eplerenone Mean (%CV)	
	Ketoconazole 200 mg BID + Eplerenone 100 mg SD (N=18)	Placebo + Eplerenone 100 mg SD (N=18)	Fluconazole 200 mg QD + Eplerenone 100 mg SD (N=17)	Placebo + Eplerenone 100 mg SD (N=17)
AUC0-lqc (ng/mL)*hr	52894.22 (24.1)	10110.41 (37.9)	22187.00 (30.4)	10250.28 (42.1)
AUC0-inf (ng/mL)*hr	53712.33 (23.5)	10224.81 (37.5)	22412.99 (30.6)	10374.37 (41.7)
Cmax (ng/mL)	2679.46 (23.3)	1583.28 (20.4)	2228.61 (21.6)	1576.91 (20.6)
Tmax (hr)	2.53 (34.2)	1.72 (37.6)	1.77 (38.7)	1.76 (40.2)
Kel (1/hr)	0.08 (18.1)	0.21 (29.4)	0.12 (23.9)	0.22 (30.6)
T ½ (hr)	9.21 (22.0)	3.63 (35.7)	5.99 (23.2)	3.47 (36.7)
CL/F (L/hr)	1.95 (21.4)	10.81 (27.8)	4.85 (29.1)	10.99 (33.6)
CL/F/WT (L/hr/70 kg)	1.68 (21.2)	9.29 (27.4)	4.46 (26.8)	10.17 (33.7)



Ketoconazole inhibits the metabolism of CYP 3A4 substrates. Co-administration of multiple doses of ketoconazole altered the single-dose pharmacokinetics of eplerenone. Coadministration of ketoconazole 200 mg BID for 10 days increased eplerenone AUC, and C_{max} by 5.4 fold- and 1.7 fold, respectively. The elimination T1/2 of eplerenone increased approximately 3 fold from 3.6 hours to 9.2 hours. The CL/F adjusted to 70 kg body weight decreased 5.5-fold from 9.3 L/h/70 kg to 1.7 L/h/70 kg in the presence of ketoconazole compared to placebo.

The highest mean (%CV) eplerenone plasma concentration of 2585.39 (21.0) ng/mL was observed 3 hours postdose in subjects receiving ketoconazole and eplerenone which decreased to 23.11 (133.4) ng/mL by 72 hours postdose. In contrast, subjects receiving placebo and eplerenone, the mean (%CV) eplerenone plasma concentration was highest (1512.32 [22.5] ng/mL) at 1.5 hours postdose, and was below the lower limit of assay detection at 72 hours postdose.

Upon coadministration with ketoconazole, mean XU_{0-72} for eplerenone increased by 4.2-fold compared to the mean XU_{0-72} during multiple doses of placebo co-administration. Upon coadministration with ketoconazole mean (%CV) XU_{0-24} for eplerenone increased approximately 4-fold to 8066.06 (37.4) µg. The mean XU_{24-48} and XU_{48-72} for eplerenone in subjects receiving ketoconazole was 1748.90 (34.5) µg and 164.82 (90.2) µg, respectively. The mean XU_{0-72} for eplerenone in subjects receiving ketoconazole was 9979.78 (32.3) µg. In subjects receiving placebo, mean (%CV) XU_{0-24} and XU_{24-48} were 2498.71 (47.7) µg and 4.56 (424.3) µg, respectively. The concentration of eplerenone in the urine was below the lower limit of assay detection in the 48 to 72 hours postdose urine sample. The mean XU_{0-72} for SC-66110 in subjects receiving placebo was 2503.27 (48.0) µg.

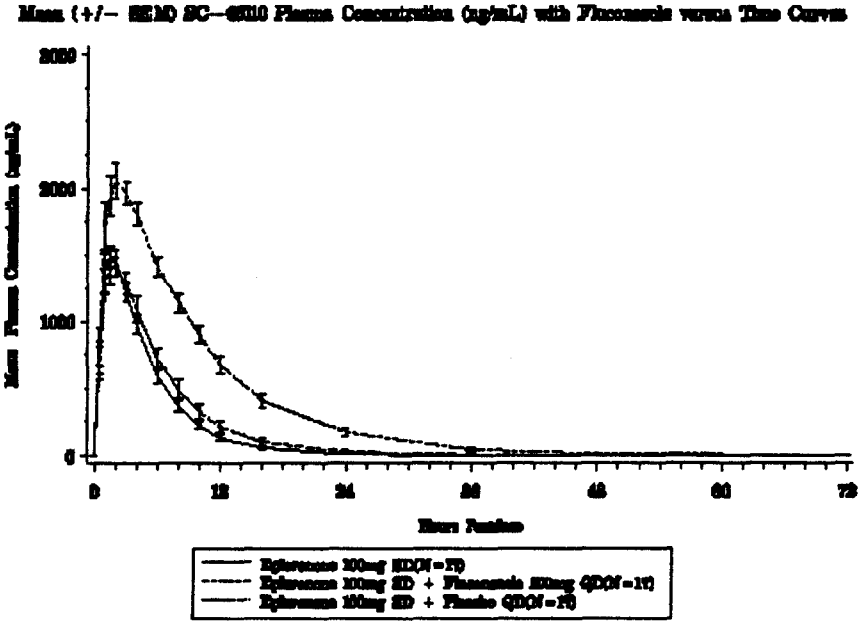
Table 3: Ratios and 90% Confidence Intervals for Eplerenone Pharmacokinetic Parameters: Ketoconazole vs. Placebo Co-administration

Eplerenone Parameter	Least Squares Means		Ratio of Means (Test/Ref)	95% CI for Ratio of Means	90% CI for Ratio of Means	p-Value
	Eplerenone 100 mg SD + Ketoconazole 200 mg BID (Test)	Eplerenone 100 mg SD + Placebo BID (Reference)				
AUC0-lqc (ng/mL)*hr	51538.91	9562.17	5.390	(4.8181, 6.0295)	(4.9144, 5.9113)	<0.001
AUC0-inf (ng/mL)*hr	52405.56	9679.67	5.414	(4.8522, 6.0408)	(4.9469, 5.9252)	<0.001
Cmax (ng/mL)	2613.27	1554.71	1.681	(1.5455, 1.8280)	(1.5686, 1.8012)	<0.001
XU0-72 (µg)	9477.39	2237.19	4.236	(3.5092, 5.1141)	(3.6277, 4.9470)	<0.001
CL/F (L/hr)	1.91	10.33	0.185	(0.1655, 0.2061)	(0.1688, 0.2021)	<0.001
CL/F/WT (L/hr/70 kg)	1.65	8.92	0.185	(0.1655, 0.2061)	(0.1688, 0.2021)	<0.001

Effect of Fluconazole on Eplerenone Pharmacokinetics:

Table 4: Arithmetic Mean Eplerenone Pharmacokinetic Parameters: Fluconazole/ Placebo Co-administration

Parameter	Treatment Mean (%CV)	
	Eplerenone 100 mg SD + Fluconazole 200 mg QD	Eplerenone 100 mg SD + Placebo QD
	(N=17)	(N=17)
AUC0-lqc (ng/mL)*hr	22187.00 (30.4)	10250.28 (42.1)
AUC0-inf (ng/mL)*hr	22412.99 (30.6)	10374.37 (41.7)
Cmax (ng/mL)	2228.61 (21.6)	1576.91 (20.6)
Tmax (hr)	1.77 (38.7)	1.76 (40.2)
Kel (1/hr)	0.12 (23.9)	0.22 (30.6)
T ½ (hr)	5.99 (23.2)	3.47 (36.7)
CL/F (L/hr)	4.85 (29.1)	10.99 (33.6)
CL/F/WT (L/hr/70 kg)	4.46 (26.8)	10.17 (33.7)



Fluconazole inhibit the metabolism of CYP 2C9 substrates. Co-administration of multiple doses of fluconazole altered the single-dose pharmacokinetics of eplerenone. Mean $AUC_{0\text{-}inf}$ for eplerenone increased significantly by 2.2-fold with fluconazole compared to placebo co-administration. The mean C_{max} and $XU_{0\text{-}72}$ for eplerenone increased significantly by 1.4-fold and 2.6-fold, respectively, compared to placebo. Fluconazole reduced mean CL/F for eplerenone by about 2.2-fold.

Table 5: Ratios and 90% Confidence Intervals for Eplerenone Pharmacokinetic Parameters: Fluconazole vs. Placebo Co-administration

Eplerenone	Least Squares Means	Ratio	95% CI for Ratio	90% CI for	p-Value

Parameter	Eplerenone 100 mg SD + Fluconazole 200 mg QD (Test)	Eplerenone 100 mg SD + Placebo (Reference)	Means (Test/Ref)	of Means	Ratio of Means	
AUC0-lqc (ng/mL)*hr	21387.35	9548.37	2.240	(2.0631, 2.4318)	(2.0935, 2.3966)	<0.001
AUC0-inf (ng/mL)*hr	21603.82	9674.31	2.233	(2.0601, 2.4207)	(2.0898, 2.3862)	<0.001
Cmax (ng/mL)	2186.39	1549.71	1.411	(1.2727, 1.5639)	(1.2962, 1.5356)	<0.001
XU0-72 (μg)	3796.43	1479.61	2.566	(2.0503, 3.2109)	(2.1336, 3.0856)	<0.001
CL/F (L/hr)	4.63	10.34	0.448	(0.4131, 0.4854)	(0.4191, 0.4785)	<0.001
CL/F/WT (L/hr/70 kg)	4.28	9.57	0.448	(0.4131, 0.4854)	(0.4191, 0.4785)	<0.001

Upon coadministration with fluconazole 200 mg QD, mean eplerenone plasma concentration was highest (2059.79 [27.9] ng/mL) at 2 hours postdose and declined to below lower limit of assay detection at 72 hours postdose. Similarly, in subjects receiving placebo, mean eplerenone plasma concentration was highest (1409.61 [20.9] ng/mL) at 2 hours postdose and declined to below the lower limit of assay detection at 72 hours postdose.

Effect of Ketoconazole on SC-70303 Pharmacokinetics:

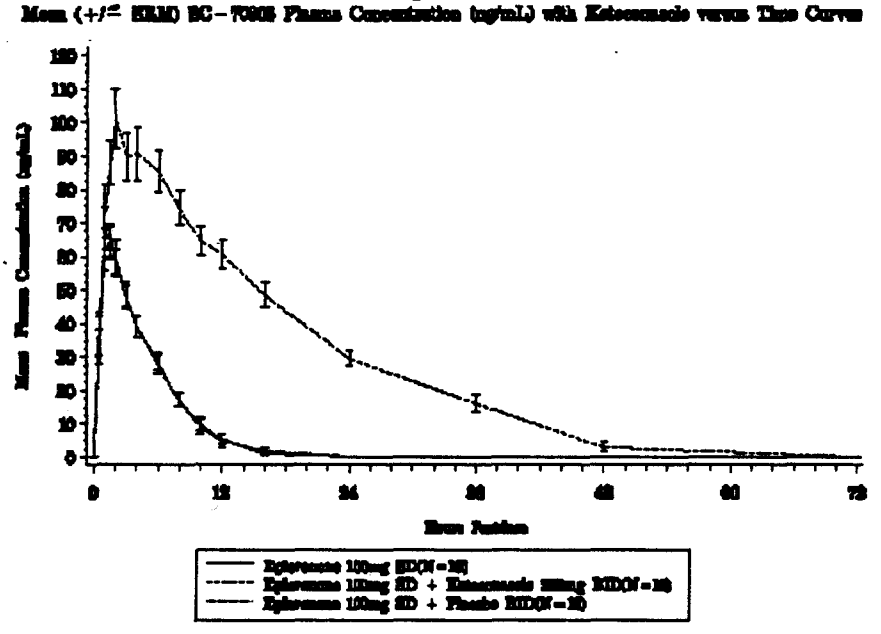
Table 6: Baseline Arithmetic Mean SC-70303 Pharmacokinetic Parameters

Parameter	Treatment Group Mean (%CV)	
	Ketoconazole Treatment Group	Fluconazole Treatment Group
	(N=18)	(N=17)
AUC0-lqc (ng/mL)*hr	353.85 (38.2)	293.63 (38.0)
AUC0-inf (ng/mL)*hr	401.01 (35.2)	337.62 (35.1)
Cmax (ng/mL)	74.86 (30.7)	73.40 (31.9)
Tmax (hr)	1.47 (58.7)	1.21 (38.8)
Kel (1/hr)	0.22 (21.0)	0.25 (18.6)
T ½ (hr)	3.30 (21.4)	2.91 (18.4)

Table 7: Arithmetic Mean SC-70303 Pharmacokinetic Parameters: Ketoconazole/ Placebo Co-administration

SC-70303 Pharmacokinetic Parameter	SC-70303 Mean (%CV)		SC-70303 Mean (%CV)	
	Ketoconazole 200 mg BID + Eplerenone 100 mg SD (N=18)	Placebo + Eplerenone 100 mg SD (N=18)	Fluconazole 200 mg QD + Eplerenone 100 mg SD (N=17)	Placebo + Eplerenone 100 mg SD (N=17)
AUC0-lqc (ng/mL)*hr	1761.34 (32.8)	350.18 (43.1)	750.54 (33.3)	332.84 (41.4)
AUC0-inf (ng/mL)*hr	2000.33 (31.9)	399.16 (40.3)	868.43 (32.6)	391.83 (39.5)
Cmax (ng/mL)	107.22 (34.6)	70.93 (30.9)	93.19 (25.4)	64.81 (33.9)
Tmax (hr)	2.03 (38.1)	1.59 (53.1)	1.53 (48.1)	1.41 (60.3)
Kel (1/hr)	0.06 (18.7)	0.22 (23.5)	0.13 (21.2)	0.21 (26.8)

T ½ (hr)	11.61 (24.2)	3.32 (26.2)	5.76 (23.0)	3.76 (46.1)



Coadministration with 200 mg BID ketoconazole increased mean $AUC_{0\text{-}inf}$ of SC-70303 (inactive open-ring form of eplerenone) significantly by 5-fold compared to coadministration with placebo. Also, mean C_{max} for SC-70303 was also significantly increased by 1.5-fold with ketoconazole. The mean $XU_{0\text{-}72}$ for SC-70303 increased by 3.5-fold with ketoconazole compared to placebo.

Upon coadministration with ketoconazole, mean (%CV) $XU_{0\text{-}24}$, $XU_{24\text{-}48}$, and $XU_{48\text{-}72}$ for SC-70303 were 13,481.82 (29.5) µg, 3,870.83 (42.0) µg and 564.73 (69.1) µg, respectively. The mean $XU_{0\text{-}72}$ for SC-70303 in subjects receiving ketoconazole was 17,917.38 (29.9) µg. In contrast, upon administering placebo, mean (%CV) $XU_{0\text{-}24}$, $XU_{24\text{-}48}$, and $XU_{48\text{-}72}$ for SC-70303 were 5,337.83 (43.4) µg, 72.33 (182.2) µg and 4.74 (424.3) µg, respectively. The mean $XU_{0\text{-}72}$ for SC-70303 in subjects receiving placebo was 5,414.91 (44.8) µg.

Table 8: Ratios and 90% Confidence Intervals for SC-70303 Pharmacokinetic Parameters: Ketoconazole vs. Placebo Co-administration

SC-70303 Parameter	Least Squares Means		Ratio of Means (Test/Ref)	95% CI for Ratio of Means	90% CI for Ratio of Means	p-Value
	Eplerenone 100 mg SD + Ketoconazole 200 mg BID (Test)	Eplerenone 100 mg SD + Placebo BID (Reference)				
AUC0-lqc (ng/mL)*hr	1680.26	325.64	5.160	(4.4893, 5.9305)	(4.6009, 5.7866)	<0.001
AUC0-inf	1888.04	374.95	5.035	(4.4026, 5.7592)	(4.5089, 5.6235)	<0.001