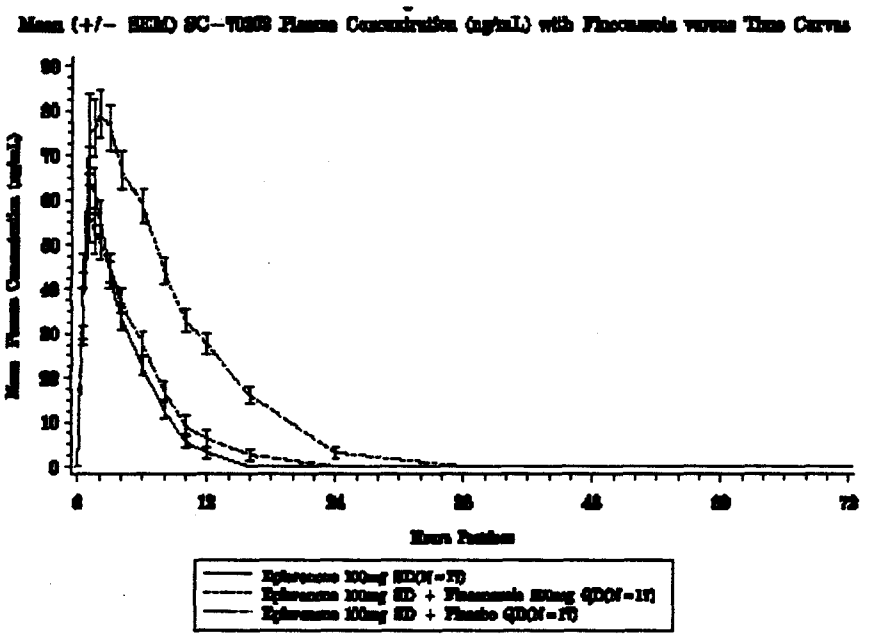
| | | | | | | |
|---|---|---|---|---|---|---|
| (ng/mL)*hr | | | | | | |
| Cmax (ng/mL) | 101.53 | 68.01 | 1.493 | (1.2637, 1.7634) | (1.3014, 1.7123) | <0.001 |
| XU0-72 (μg) | 17191.68 | 4979.12 | 3.453 | (2.9286, 4.0707) | (3.0149, 3.9541) | <0.001 |

***Effect of Fluconazole on SC-70303 Pharmacokinetics:***

**Table 10: Arithmetic Mean SC-70303 Pharmacokinetic Parameters: Fluconazole/ Placebo Co-administration**

| SC-70303 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 | 750.54 (33.3) | 332.84 (41.4) |
| AUC0-inf (ng/mL)*hr | 868.43 (32.6) | 391.83 (39.5) |
| Cmax (ng/mL) | 93.19 (25.4) | 64.81 (33.9) |
| Tmax (hr) | 1.53 (48.1) | 1.41 (60.3) |
| Kel (1/hr) | 0.13 (21.2) | 0.21 (26.8) |
| T ½ (hr) | 5.76 (23.0) | 3.76 (46.1) |



Coadministration with 200 mg QD fluconazole significantly increased $AUC_{0\text{-}inf}$ for SC-70303 (inactive open-ring form of eplerenone) by 2.3-fold compared to placebo. Mean $C_{max}$ for SC-70303 also significantly increased by 1.5-fold with multiple doses of fluconazole compared to placebo coadministration. Also, mean $XU_{0\text{-}72}$ for SC-70303 increased 2.1-fold with coadministration with fluconazole compared to placebo.

**Table 11: Ratios and 90% Confidence Intervals for SC-70303 Pharmacokinetic Parameters: Fluconazole 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 + Fluconazole 200 mg QD (Test) | Eplerenone 100 mg SD + Placebo (Reference) | | | | |
| AUC0-lqc (ng/mL)*hr | 723.00 | 310.93 | 2.325 | (2.1278, 2.5410) | (2.1616, 2.5013) | <0.001 |
| AUC0-inf (ng/mL)*hr | 837.52 | 367.55 | 2.279 | (2.0767, 2.5004) | (2.1112, 2.4595) | <0.001 |
| Cmax (ng/mL) | 91.05 | 62.34 | 1.461 | (1.2973, 1.6444) | (1.3249, 1.6102) | <0.001 |
| XU0-72 (µg) | 10122.67 | 4754.02 | 2.129 | (1.9123, 2.3709) | (1.9491, 2.3261) | <0.001 |

## CONCLUSIONS:

Eplerenone is substantially metabolized by CYP450 3A4 as evidenced by the significant 5.5 fold increase in eplerenone AUC and 1.7 fold increase in eplerenone Cmax caused by inhibition of metabolism by ketoconazole a CYP 3A4 inhibitor. 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 sponsor's recommendation to decrease eplerenone dose to 25 mg QD when ketoconazole is coadministered is acceptable.

Fluconazole reduced mean CL/F for eplerenone by about 2.2-fold and increased eplerenone AUC by 2.2 fold and Cmax by 1.4-fold. The dose of eplerenone should be reduced to 50 mg when coadministered with fluconazole. The sponsor's recommendation to lower eplerenone dose to 50 mg QD when fluconazole is coadministered is acceptable.

## COMMENTS:

1. This study assessed the effect of multiple dose ketoconazole on single dose eplerenone. Eplerenone is anticipated to be used chronically as an antihypertensive agent. The effect of inhibition of steady-state eplerenone metabolism and its effect on accumulation, time to steady-state is not known.
2. The magnitude of interaction between eplerenone and ketoconazole/fluconazole should be reported in the label.
3. Eplerenone dose should be reduced to 25 mg QD with ketoconazole and to 50 mg QD with fluconazole.

**ASSESSMENT OF THE EFFECT OF EPLERENONE (SC-66110) ON THE STEADY-STATE PHARMACOKINETIC PROFILE OF VERAPAMIL HCL IN HEALTHY ADULT SUBJECTS**

**STUDY INVESTIGATORS AND SITES:**

Protocol Number: NE3-00-02-031

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## OBJECTIVES:

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

## FORMULATIONS:

Eplerenone - 100 mg film-coated tablets (Lot # RCT 11631) by Searle
Verapamil HCl - Calan® SR 240 mg sustained-release caplets (Lot number 0F897K)

## STUDY DESIGN:

This was an open-label, randomized, multiple-dose, six sequence, three-period and three-treatment crossover design study conducted in 24 healthy adult subjects, 15 M/9 F, age range 19 years to 44 years and weight range 56 kg to 89 kg. Subjects were randomized to one of the following six treatment sequences for Period 1 (Days 1-7), Period 2 (Days 9-15), and Period 3 (Days 17-23):

| | Period 1 Days 1-7 | Period 2 Days 9-15 | Period 3 Days 17-23 |
|---|---|---|---|
| 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 = Verapamil HCl (Calan® SR) 240 mg QD
C = Verapamil HCl (Calan® SR) 240 mg QD + Eplerenone 100 mg QD

Each subject received oral doses of all three treatments: **Treatment A** = Eplerenone 100 mg QD for 7 days; **Treatment B** = Verapamil HCl (Calan® SR) 240 mg QD for 7 days; **Treatment C** = Eplerenone 100 mg QD + verapamil HCl (Calan® SR) 240 mg QD for 7 days) in a crossover manner. On Days 1-6, 9-14, and 17-22, subjects were administered

eplerenone and/or verapamil HCl doses in the morning, approximately 30 minutes following breakfast, while, on study Days 7, 15 and 23, doses were administered following an overnight fast. Standard low-fat meals were served each day.

**ASSAY:**

Sample Collection

Blood samples for R- and S- verapamil, R- and S-norverapamil, eplerenone, SC-71597 and SC-70303 analysis were drawn on Day 1 and on Days 4-6, 12-14, 20-22 at predose for trough concentration measurements. Also, on Days 7, 15 and 23, blood samples were drawn predose (-10 minutes) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hours postdose.

**RESULTS**

***Effect of Eplerenone on Verapamil Pharmacokinetics***

The following table lists the steady-state pharmacokinetic parameters of eplerenone, SC-70303 (open ring form of eplerenone) and SC-71597 following administration of eplerenone 100 mg QD alone or in the presence of verapamil 240 mg QD.

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

| Pharmacokinetic Parameter | Eplerenone 100 mg QD Alone | | | Verapamil HCl 240 mg QD + Eplerenone 100 mg QD | | |
|---|---|---|---|---|---|---|
| | N | Mean | (%CV) | N | Mean | (%CV) |
| **Eplerenone** | | | | | | |
| AUC(0-24) (hr*ng/mL) | 24 | 12266.55 | ( 36%) | 24 | 23625.22 | ( 26%) |
| Cmax (ng/mL) | 24 | 1939.21 | ( 23%) | 24 | 2633.42 | ( 24%) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Tmax (hr) | 24 | 1.69 | ( 50%) | 24 | 1.77 | ( 49%) |
| Cmin (ng/mL) | 24 | 60.80 | (102%) | 24 | 278.32 | ( 54%) |
| T(1/2) (hr) | 24 | 4.50 | ( 22%) | 21 | 7.84 | ( 19%) |
| CL/F (L/hr) | 24 | 9.14 | ( 33%) | 24 | 4.55 | ( 29%) |
| CL/F/WT (L/hr/70kg) | 24 | 8.70 | ( 36%) | 24 | 4.32 | ( 31%) |
| XU(0-24) (μg) | 24 | 1850.28 | ( 38%) | 24 | 3797.14 | ( 43%) |
| **SC-70303** | | | | | | |
| AUC(0-24) (hr*ng/mL) | 24 | 698.92 | ( 33%) | 24 | 1431.33 | ( 27%) |
| Cmax (ng/mL) | 24 | 129.16 | ( 26%) | 24 | 179.05 | ( 37%) |
| Tmax (hr) | 24 | 1.58 | ( 56%) | 24 | 1.63 | ( 50%) |
| Cmin (ng/mL) | 24 | 0.00 | (NAP) | 24 | 9.61 | ( 89%) |
| T(1/2) (hr) | 24 | 3.50 | ( 27%) | 24 | 6.69 | ( 29%) |
| XU(0-24) (μg) | 24 | 5826.02 | ( 52%) | 24 | 10436.06 | ( 48%) |
| **SC-71597** | | | | | | |
| AUC(0-24) (hr*ng/mL) | 24 | 5702.82 | ( 23%) | 24 | 6389.84 | ( 19%) |
| Cmax (ng/mL) | 24 | 564.70 | ( 23%) | 24 | 501.89 | ( 25%) |
| Tmax (hr) | 24 | 2.83 | ( 38%) | 24 | 3.23 | ( 51%) |
| Cmin (ng/mL) | 24 | 53.95 | ( 64%) | 24 | 119.12 | ( 34%) |
| T(1/2) (hr) | 23 | 5.66 | ( 22%) | 19 | 11.43 | ( 31%) |
| XU(0-24) (μg) | 24 | 20406.93 | ( 35%) | 24 | 21789.97 | ( 34%) |

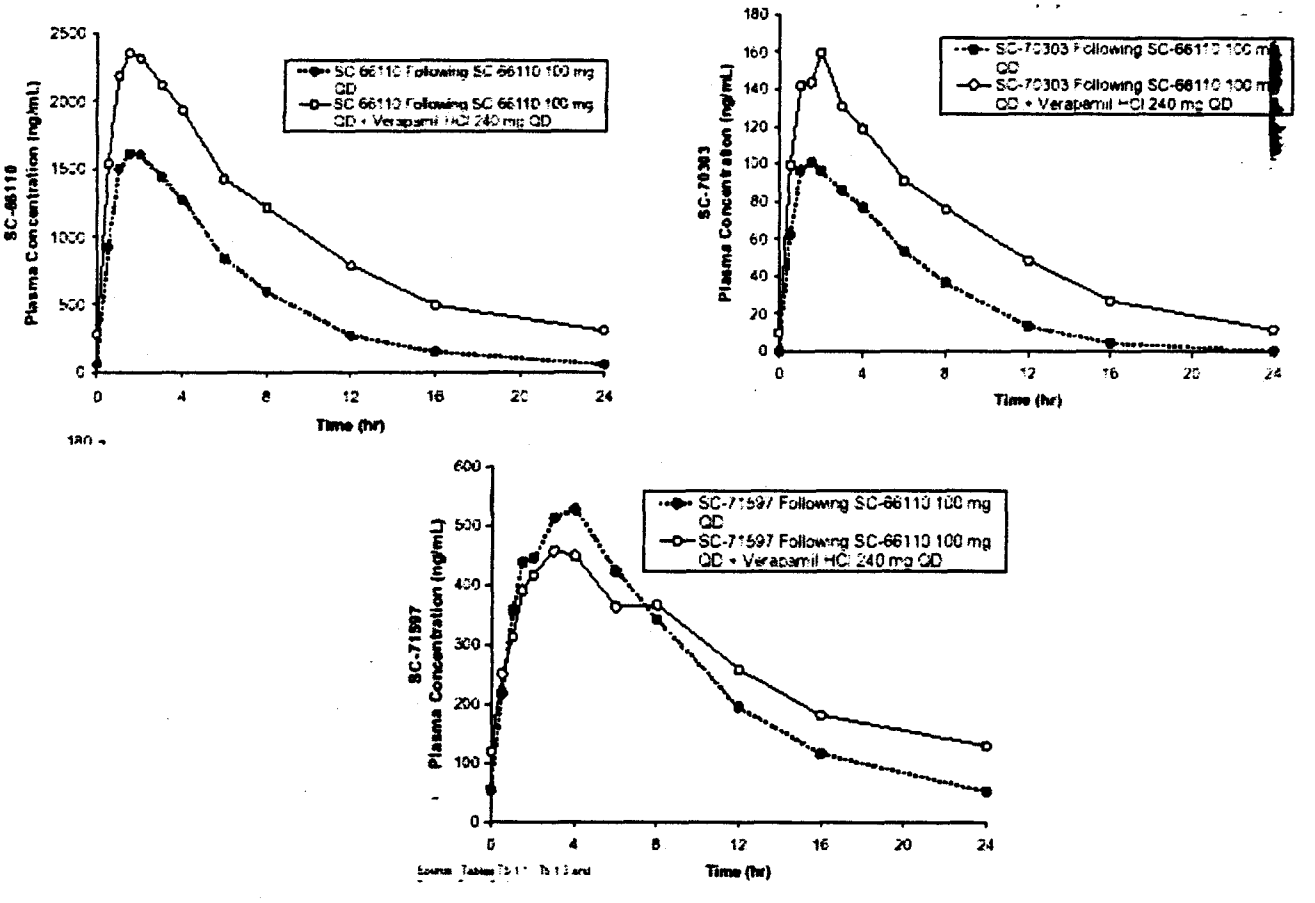
Coadministration of verapamil HCl 240 mg QD with eplerenone 100 mg QD had a statistically significant effect on the pharmacokinetic profile of eplerenone. Eplerenone $C_{max}$, $C_{min}$ and $AUC_{0-24}$ increased by 35.5%, 455.5% and 97.5% in the presence of verapamil. Also, coadministration of verapamil increased SC-70303 (open-ring form of eplerenone) $C_{max}$ (36.0%) and $AUC_{0-24}$ (109.0%), and increased SC-71597, the primary metabolite of eplerenone, $AUC_{0-24}$ (12.7%) and $C_{min}$ (136.9%).

**Table 3: Ratios and 90% Confidence Intervals for Eplerenone, SC-70303, and SC-71597 Pharmacokinetic Parameters**

| Pharmacokinetic Parameter | Least Squares Means | | | | Ratio Coadmin./ Eplerenone | 90% Confidence Interval | p-value |
|---|---|---|---|---|---|---|---|
| | Eplrenone 100 mg QD + Verapamil HCl 240 mg QD | | Eplerenone 100 mg QD | | | | |
| | N | LS Mean | N | LS Mean | | | |
| **Eplerenone** | | | | | | | |
| AUC (0-24) (hr*ng/mL) | 24 | 22831.52 | 24 | 11561.77 | 1.975 | (1.836, 2.124) | <0.001 |
| Cmax (ng/mL) | 24 | 2564.69 | 24 | 1892.26 | 1.355 | (1.293, 1.421) | <0.001 |
| Cmin (ng/mL) | 24 | 238.73 | 22 | 42.98 | 5.555 | (3.928, 7.856) | <0.001 |
| CL/F (L/hr) | 24 | 4.38 | 24 | 8.65 | 0.506 | (0.471, 0.545) | <0.001 |
| CL/F/WT (L/hr/70kg) | 24 | 4.13 | 24 | 8.15 | 0.506 | (0.471, 0.545) | <0.001 |
| XU(0-24) (μg) | 24 | 3456.41 | 24 | 1715.49 | 2.015 | (1.747, 2.324) | <0.001 |
| Tmax (hr) | 24 | 1.77 | 24 | 1.69 | -- | -- | 0.729 |
| T(1/2) (hr) | 21 | 8.00 | 24 | 4.50 | -- | -- | <0.001 |
| **SC-70303** | | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| AUC (0-24) (hr*ng/mL) | 24 | 1378.85 | 24 | 659.89 | 2.090 | (1.934, 2.258) | <0.001 |
| Cmax (ng/mL) | 24 | 169.43 | 24 | 124.55 | 1.360 | (1.271, 1.456) | <0.001 |
| XU(0-24) (µg) | 24 | 9230.87 | 24 | 5057.46 | 1.825 | (1.452, 2.294) | <0.001 |
| Tmax (hr) | 24 | 1.63 | 24 | 1.58 | -- | -- | 0.850 |
| T(1/2) (hr) | 24 | 6.69 | 24 | 3.50 | -- | -- | <0.001 |
| **SC-71597** | | | | | | | |
| AUC (0-24) (hr*ng/mL) | 24 | 6269.52 | 24 | 5562.31 | 1.127 | (1.043, 1.218) | 0.015 |
| Cmax (ng/mL) | 24 | 487.57 | 24 | 551.42 | 0.884 | (0.816, 0.958) | 0.016 |
| Cmin (ng/mL) | 24 | 110.06 | 23 | 46.45 | 2.369 | (1.795, 3.128) | <0.001 |
| XU(0-24) (µg) | 24 | 20393.59 | 24 | 18905.23 | 1.079 | (0.891, 1.306) | 0.503 |
| Tmax (hr) | 24 | 3.23 | 24 | 2.83 | -- | -- | 0.326 |
| T(1/2) (hr) | 19 | 11.47 | 23 | 5.87 | -- | -- | <0.001 |

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




***Effect of Eplerenone on Verapamil and Norverapamil Pharmacokinetics***

**Table 5. Arithmetic Mean (%CV) Verapamil and Norverapamil Pharmacokinetic Parameters**

| Pharmacokinetic Parameter | Verapamil HCl 240 mg QD Alone | | | Verapamil HCl 240 mg QD + Eplerenone 100 mg QD | | |
|---|---|---|---|---|---|---|
| | N | Mean | (%CV) | N | Mean | (%CV) |
| **R-Verapamil** | | | | | | |
| AUC(0-24) (hr*ng/mL) | 24 | 2507.07 | (40%) | 24 | 2231.80 | (30%) |
| Cmax (ng/mL) | 24 | 221.26 | (39%) | 24 | 181.83 | (37%) |
| Tmax (hr) | 24 | 4.92 | (41%) | 24 | 5.38 | (45%) |
| Cmin (ng/mL) | 24 | 44.14 | (61%) | 24 | 43.67 | (46%) |
| T(1/2) (hr) | 22 | 10.00 | (34%) | 20 | 10.17 | (28%) |
| CL/F (L/hr) | 24 | 110.91 | (41%) | 24 | 118.38 | (34%) |
| CL/F/WT (L/hr/70kg) | 24 | 105.13 | (42%) | 24 | 111.87 | (33%) |
| **R-Norverapamil** | | | | | | |
| AUC(0-24) (hr*ng/mL) | 24 | 2290.85 | (26%) | 24 | 2093.46 | (27%) |
| Cmax (ng/mL) | 24 | 137.15 | (22%) | 24 | 118.62 | (27%) |
| Tmax (hr) | 24 | 7.00 | (35%) | 24 | 8.25 | (36%) |
| Cmin (ng/mL) | 24 | 59.51 | (46%) | 24 | 59.34 | (39%) |
| T(1/2) (hr) | 17 | 14.70 | (32%) | 11 | 16.45 | (60%) |
| CL/F (L/hr) | 24 | 112.55 | (30%) | 24 | 122.42 | (26%) |
| CL/F/WT (L/hr/70kg) | 24 | 106.80 | (31%) | 24 | 115.69 | (27%) |
| **S-Verapamil** | | | | | | |
| AUC(0-24) (hr*ng/mL) | 24 | 617.63 | (50%) | 24 | 529.71 | (37%) |
| Cmax (ng/mL) | 24 | 57.64 | (48%) | 24 | 46.01 | (45%) |
| Tmax (hr) | 24 | 5.63 | (41%) | 24 | 6.46 | (44%) |
| Cmin (ng/mL) | 24 | 9.77 | (76%) | 24 | 9.19 | (64%) |
| T(1/2) (hr) | 20 | 8.49 | (38%) | 19 | 10.23 | (46%) |
| CL/F (L/hr) | 24 | 510.14 | (67%) | 24 | 530.58 | (47%) |
| CL/F/WT (L/hr/70kg) | 24 | 483.18 | (66%) | 24 | 499.82 | (45%) |
| **S-Norverapamil** | | | | | | |
| AUC(0-24) (hr*ng/mL) | 24 | 894.41 | (31%) | 24 | 803.81 | (28%) |
| Cmax (ng/mL) | 24 | 58.55 | (28%) | 24 | 50.15 | (31%) |
| Tmax (hr) | 24 | 6.83 | (30%) | 24 | 8.08 | (31%) |
| Cmin (ng/mL) | 24 | 20.62 | (50%) | 24 | 19.80 | (42%) |
| T(1/2) (hr) | 22 | 11.54 | (26%) | 16 | 14.56 | (51%) |
| CL/F (L/hr) | 24 | 297.03 | (36%) | 24 | 320.90 | (28%) |
| CL/F/WT (L/hr/70kg) | 24 | 280.60 | (36%) | 24 | 301.42 | (25%) |

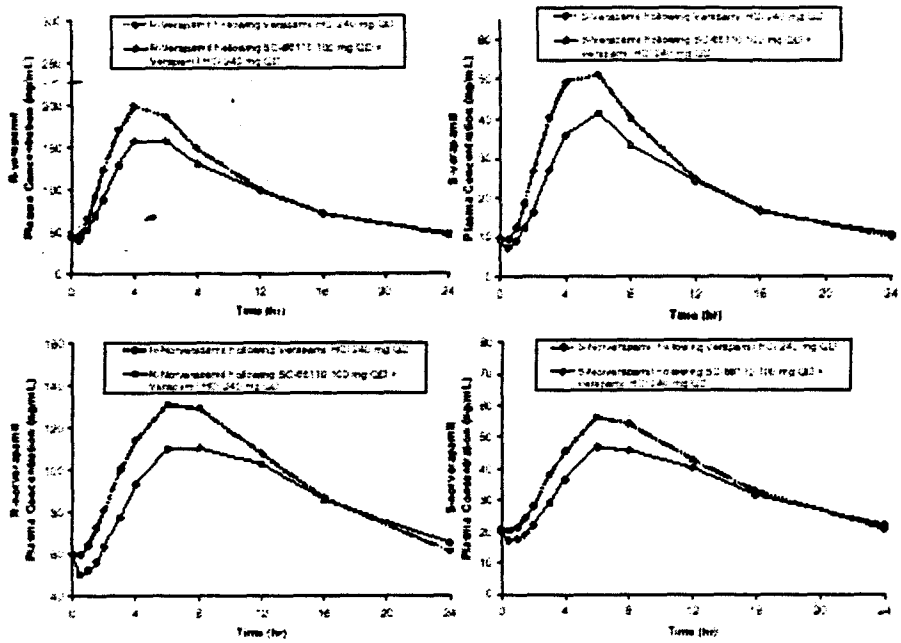
Coadministration of eplerenone 100 mg QD with 240 mg QD verapamil HCl did not have a significant effect on the pharmacokinetic profile of verapamil. Coadministration with eplerenone decreased verapamil and norverapamil concentrations. Mean Cmax of R-verapamil and R-norverapamil decreased by 18% and 14%, respectively, while mean Cmax of S-verapamil and S-norverapamil decreased by 20% and 15%, respectively. Similarly, coadministration with eplerenone decreased mean $AUC_{0-24}$ of R-verapamil and R-norverapamil by 9% and 8%, respectively, while mean $AUC_{0-24}$ of S-verapamil and S-norverapamil decreased by 10% and 9%, respectively.

**Table 6. Ratios and 90% Confidence Intervals for Verapamil and Norverapamil Pharmacokinetic Parameters**

| Verapamil | Least Squares Means | Ratio | 90% | p- |
|---|---|---|---|---|

| Pharmacokinetic Parameters | Eplerenone 100 mg QD + Verapamil HCl 240 mg QD | | Verapamil HCl 240 mg QD Alone | | Coadmin./ Verapamil | Confidence Interval | value |
|---|---|---|---|---|---|---|---|
| | N | LS Mean | N | LS Mean | | | |
| **R-Verapamil** | | | | | | | |
| AUC (0-24) (hr*ng/mL) | 24 | 2130.79 | 24 | 2331.47 | 0.914 | (0.812, 1.029) | 0.204 |
| Cmax (ng/mL) | 24 | 168.47 | 24 | 204.47 | 0.824 | (0.703, 0.966) | 0.048 |
| Cmin (ng/mL) | 24 | 38.82 | 22 | 41.17 | 0.943 | (0.730, 1.217) | 0.695 |
| CL/F (L/hr) | 24 | 112.63 | 24 | 102.94 | 1.094 | (0.972, 1.231) | 0.204 |
| CL/F/WT (L/hr/70kg) | 24 | 106.18 | 24 | 97.04 | 1.094 | (0.972, 1.231) | 0.204 |
| Tmax (hr) | 24 | 5.38 | 24 | 4.92 | -- | -- | 0.459 |
| T(1/2) (hr) | 20 | 10.44 | 22 | 10.00 | -- | -- | 0.427 |
| **R-Norverapamil** | | | | | | | |
| AUC (0-24) (hr*ng/mL) | 24 | 2025.59 | 24 | 2213.50 | 0.915 | (0.826, 1.014) | 0.152 |
| Cmax (ng/mL) | 24 | 114.63 | 24 | 133.70 | 0.857 | (0.772, 0.952) | 0.020 |
| Cmin (ng/mL) | 24 | 54.79 | 22 | 60.20 | 0.910 | (0.752, 1.102) | 0.405 |
| CL/F (L/hr) | 24 | 118.48 | 24 | 108.43 | 1.093 | (0.986, 1.211) | 0.152 |
| CL/F/WT (L/hr/70kg) | 24 | 111.70 | 24 | 102.21 | 1.093 | (0.986, 1.211) | 0.152 |
| Tmax (hr) | 24 | 8.25 | 24 | 7.00 | -- | -- | 0.061 |
| T(1/2) (hr) | 11 | 18.58 | 17 | 14.14 | -- | -- | 0.130 |
| **S-Verapamil** | | | | | | | |
| AUC (0-24) (hr*ng/mL) | 24 | 492.75 | 24 | 546.37 | 0.902 | (0.785, 1.036) | 0.214 |
| Cmax (ng/mL) | 24 | 40.94 | 24 | 51.07 | 0.802 | (0.676, 0.950) | 0.036 |
| Cmin (ng/mL) | 20 | 10.70 | 19 | 11.16 | 0.959 | (0.881, 1.043) | 0.389 |
| CL/F (L/hr) | 24 | 487.06 | 24 | 439.26 | 1.109 | (0.965, 1.274) | 0.214 |
| CL/F/WT (L/hr/70kg) | 24 | 459.16 | 24 | 414.10 | 1.109 | (0.965, 1.274) | 0.214 |
| Tmax (hr) | 24 | 6.46 | 24 | 5.63 | -- | -- | 0.187 |
| T(1/2) (hr) | 19 | 10.26 | 20 | 8.10 | -- | -- | 0.108 |
| **S-Norverapamil** | | | | | | | |
| AUC (0-24) (hr*ng/mL) | 24 | 775.33 | 24 | 852.49 | 0.909 | (0.824, 1.004) | 0.113 |
| Cmax (ng/mL) | 24 | 47.78 | 24 | 56.06 | 0.852 | (0.761, 0.954) | 0.024 |
| Cmin (ng/mL) | 24 | 18.29 | 22 | 20.66 | 0.886 | (0.723, 1.084) | 0.312 |
| CL/F (L/hr) | 24 | 309.54 | 24 | 281.53 | 1.100 | (0.996, 1.214) | 0.113 |
| CL/F/WT (L/hr/70kg) | 24 | 291.81 | 24 | 265.40 | 1.100 | (0.996, 1.214) | 0.113 |
| Tmax (hr) | 24 | 8.08 | 24 | 6.83 | -- | -- | 0.039 |
| T(1/2) (hr) | 16 | 15.08 | 22 | 11.61 | -- | -- | 0.086 |

## Mean Verapamil and Norverapamil Plasma Concentrations



***Effect of Verapamil and Eplerenone alone and Verapamil + Eplerenone on ECG Parameters***

Both verapamil and eplerenone administered alone or in combination produced a decrease in heart rate (-6 to 8 bpm). Suppression of atrioventricular conduction by verapamil was manifest by a large prolongation (+ 23 msec to +27 msec) of the PR interval. Eplerenone alone prolonged PR interval slightly, +6.35 msec. Analysis of the QRS duration indicated no effect of either agent alone or in combination. Likewise, neither agent alone nor in combination exhibited any effect on cardiac repolarization. At Baseline, the mean (SEM) QTc duration was 376 (4) msec using Fridericia's correction and 388 (5) msec using Bazett's correction. Using Fridericia's correction, 3 subjects while on verapamil, 2 subjects while on verapamil + eplerenone, and 1 subject while on eplerenone had a change from Baseline in QTc duration between 31 msec and 60 msec. No subject had a QTc interval duration over 500 msec or a change from Baseline of 60 or more msec.

**Table 7: Mean (±SEM) Change From Baseline To Day Seven in ECG Parameters**

| Parameter | Verapamil 240 mg QD Mean ± SEM | Eplerenone 100 mg QD Mean ± SEM | Verapamil 240 mg QD + Eplerenone 100 mg QD Mean ± SEM | P-Value[a] |
|---|---|---|---|---|
| | N = 24 | N = 24 | N = 24 | |
| HR (bpm) | -7.45 ± 1.95 [b] | -6.32 ± 1.71 [b] | -7.39 ± 1.91 [b] | NS |
| PR (msec) | 27.33 ± 3.86 [b] | 6.35 ± 2.25 [b] | 23.21 ± 4.05 [b] | 0.0000 |
| QRS (msec) | 2.19 ± 1.23 | 1.45 ± 1.16 | 2.51 ± 1.26 | NS |
| QT (msec) | 17.21 ± 4.02 [b] | 5.94 ± 3.68 | 12.39 ± 4.04 [b] | 0.0005 |
| QTc[c] (msec) | 4.61 ± 2.65 | -4.56 ± 2.87 | -0.10 ± 2.76 | 0.0040 |
| QTc[d](msec) | -2.13 ± 3.27 | -10.34 ± 3.53 [b] | -6.85 ± 3.36 | 0.0004 |
| MaxQTc[c] (msec) | 4.67 ± 2.35 [b] | 6.33 ± 3.00 [b] | 12.46 ± 2.76 [b] | 0.0173 |

| | | | | |
|---|---|---|---|---|
| MaxQTc[d] (msec) | 10.79 ± 2.87 [b] | 1.04 ± 3.69 | 6.75 ± 3.56 | 0.0133 |

a – P-values < 0.05 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
NS – not statistically significant across treatments

## CONCLUSIONS:

Both eplerenone and verapamil are metabolized by CYP3A4. Coadministration of verapamil HCl 240 mg QD with eplerenone 100 mg QD had a statistically and clinically significant effect on eplerenone pharmacokinetics. Verapamil increased eplerenone AUC by 98%, $C_{max}$ by 36%, $C_{min}$ by 455%, and $XU_{0-24}$ by 102%. Verapamil also increased SC-70303, inactive, open-ring form of eplerenone, AUC by 109%, $C_{max}$ by 36% and $XU_{0-24}$ by 83%. In addition, the primary metabolite SC-71597, had statistically significant changes on AUC (+13%) and $C_{min}$ (+137%).

Coadministration of eplerenone 100 mg QD with verapamil HCl 240 mg QD did not have a significant effect on the pharmacokinetic profile of verapamil. Coadministration with eplerenone decreased mean Cmax of R-verapamil, R-norverapamil, S-verapamil and S-norverapamil by <20%. Similarly, coadministration with eplerenone decreased mean $AUC_{0-24}$ of R-verapamil, R-norverapamil, S-verapamil and S-norverapamil by <10%.

Both verapamil and eplerenone administered alone or in combination produced a decrease in heart rate (-6 to 8 bpm). Suppression of atrioventricular conduction by verapamil was manifest by a large prolongation (+23 msec to +27 msec) of the PR interval. Eplerenone alone prolonged PR interval slightly, +6.35 msec. Verapamil and eplerenone when administered alone or in combination did not affect other ECG parameters.

## COMMENTS:

1. Eplerenone dose should be reduced to 50 mg QD when coadministered with verapamil.

**ASSESSMENT OF THE EFFECT OF EPLERENONE ON THE STEADY-STATE PHARMACOKINETIC AND PHARMACODYNAMIC PROFILE OF GLYBURIDE IN SUBJECTS WITH TYPE II NON-INSULIN DEPENDENT DIABETES MELLITUS**

**STUDY INVESTIGATORS AND SITES:**

Protocol Number: NE3-00-02-033

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## OBJECTIVES:

1. To determine the effect of multiple doses of Eplerenone (100 mg QD) on the steady-state pharmacodynamic profile of glyburide in Type II, non-insulin dependent diabetes mellitus (NIDDM) subjects.
2. To determine the safety and tolerability of multiple doses of SC-66110 (100 mg QD) on the steady-state pharmacokinetic profile of glyburide in Type II NIDDM subjects.

## FORMULATIONS:

Eplerenone – 100 mg tablets by Searle (Lot number RCT 11530)
Placebo – matching eplerenone tablets (Lot number RCT 11535) by Searle
Glyburide - Diaβeta® - 5 mg tablets by Hoechst-Roussel (Lot # 3005837)

## STUDY DESIGN:

This was a single-blind, randomized, multiple-dose, two-treatment, two-sequence and two-period crossover design study in 16 subjects, 6 F/10 M, age range 47 years to 67 years: Group I, 8 subjects with well- controlled NIDDM who had been stabilized on a 5 mg QD glyburide dose for a minimum of three months, and Group II, 8 subjects, with well-controlled NIDDM who had been stabilized on a 10 mg BID glyburide dose for a minimum of three months. Diabetic subjects taking an approved oral hypoglycemic medication other than glyburide prior to the start of the study (including, but not limited to, glipizide, metformin, pioglitazone, rosiglitazone, tolbutamide or chlorpropamide) participated if they consented to discontinue their oral hypoglycemic medication and switched to a stable regimen of either glyburide 5 mg QD or 10 mg BID for a period of at least three months prior to admission to the research center for the study. The entire treatment duration lasted 20 days. Subjects were randomized to one of the following 2 treatment sequences for Days 1-7 and Days 12-18:

| | Days 1-7 | Days 12-18 |
|---|---|---|
| Sequence I | A | B |
| Sequence II | B | A |
| A = Glyburide + Eplerenone 100 mg QD<br>B = Glyburide + Eplerenone placebo QD | | |

Each subject received oral doses of both treatments: **Treatment A** = Glyburide + eplerenone 100 mg QD for 7 days; **Treatment B** = Glyburide + eplerenone placebo QD for seven days) in a crossover manner.

On Days 1-7 and 12-18, subjects received eplerenone or placebo and glyburide doses immediately prior to a standard low-fat diet breakfast and their second dose of glyburide (if receiving 10 mg BID) 12 hours after the first dose immediately prior to dinner. On Days 8-11, subjects received only glyburide prior to meals.

**ASSAY:**

Sample Collection

Blood samples for glyburide concentrations were drawn on Days -1, 7 and 18, 30 minutes predose and at 1, 2, 3, 4, 6, 8, 12, 13, 14, 15, 16, 18, 20 and 24 hours postdose for all subjects.

On Days 7 and 18, blood samples for eplerenone and SC-70303 concentrations were also drawn at 30 minutes predose and at 1, 2, 3, 4, 6, 8, 12 and 24 hours postdose for subjects receiving eplerenone only. On Days 4-6 and 15-17, predose blood samples were drawn for all subjects for trough glyburide determination, and additional predose samples were drawn on these same days for subjects receiving eplerenone for determination of eplerenone and SC-70303 trough concentrations.

Blood samples for blood glucose and insulin concentrations were drawn on Days -1, 7 and 18 at 30 minutes predose and at 1, 2, 3, 4, 6, 8, 12, 16 and 24 hours postdose. In addition, fasting blood samples for glucose monitoring were drawn predose on Days 3, 5, 14 and 16.

**RESULTS**

Glyburide, a sulfonylurea oral hypoglycemic agent, is extensively bound to plasma proteins (about 99%). Coadministration of certain medications has resulted in displacement of glyburide from plasma proteins and lead to hypoglycemia. This study was performed to assess the effect of coadministration of eplerenone 100 mg QD on the pharmacodynamics of glyburide (glucose and insulin concentrations) and pharmacokinetics of both glyburide and eplerenone.

As shown in the following figure, mean glucose plasma concentrations were similar among subjects receiving the same glyburide dose, regardless of eplerenone or placebo coadministration. Glucose concentrations in subjects stabilized with glyburide 10 mg BID were higher compared to subjects receiving glyburide 5 mg QD.

Mean insulin plasma concentrations in both glyburide groups tended to be greater with coadministration of eplerenone compared to the period where subjects in the group received placebo. Insulin concentrations in subjects stabilized with glyburide 10 mg BID was lower compared to subjects receiving glyburide 5 mg QD.

**Mean Glucose and Insulin Plasma Concentrations**

**e 8.a. Mean Glucose and Insulin Plasma Concentrations**

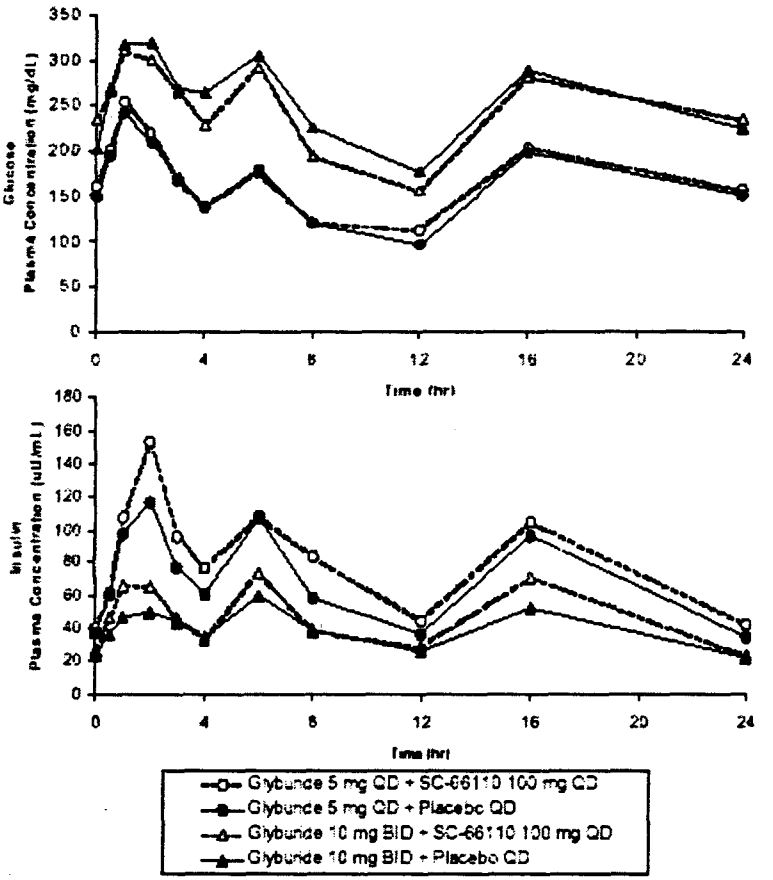



**Table 1: Ratios and 90% Confidence Intervals for Glucose and Insulin Pharmacodynamic Parameters**

| Pharmacodynamic Parameter | Least Squares Means | | Ratio of Means | 90% CI | Treatment Effect |
|---|---|---|---|---|---|
| | Eplerenone 100 mg QD | Placebo QD | Eplerenone/Placebo | Ratio of Means | |
| GLUCOSE PARAMETERS | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| **Glyburide 5 mg QD** | | | | | |
| AUC (0-24) (hr*mg/dL) | 3723.19 | 3597.95 | 1.035 | (0.985, 1.087) | 0.229 |
| Cmax (mg/dL) | 244.42 | 235.21 | 1.039 | (0.987, 1.094) | 0.196 |
| Cave (mg/dL) | 153.06 | 144.55 | 1.059 | (1.015, 1.105) | 0.039 |
| Tmax (hr) | 1.00 | 1.13 | -- | -- | 0.356 |
| **Glyburide 10 mg BID** | | | | | |
| AUC (0-24) (hr*mg/dL) | 5612.38 | 5574.45 | 1.007 | (0.941, 1.077) | 0.851 |
| Cmax (mg/dL) | 316.59 | 326.07 | 0.971 | (0.900, 1.047) | 0.476 |
| Cave (mg/dL) | 227.67 | 195.93 | 1.162 | (1.042, 1.296) | 0.037 |
| Tmax (hr) | 2.50 | 4.63 | -- | -- | 0.341 |
| **INSULIN PARAMETERS** | | | | | |
| **Glyburide 5 mg QD** | | | | | |
| AUC (0-24) (hr*:U/mL) | 1790.29 | 1526.38 | 1.173 | (1.058, 1.301) | 0.024 |
| Cmax (:U/mL) | 141.16 | 118.90 | 1.187 | (0.976, 1.444) | 0.139 |
| Cave (:U/mL) | 38.45 | 32.07 | 1.199 | (1.048, 1.372) | 0.040 |
| Tmax (hr) | 3.63 | 4.75 | -- | -- | 0.652 |
| **Glyburide 10 mg BID** | | | | | |
| AUC (0-24) (hr*:U/mL) | 972.68 | 797.22 | 1.220 | (1.058, 1.408) | 0.035 |
| Cmax (:U/mL) | 70.75 | 54.89 | 1.289 | (1.118, 1.486) | 0.013 |
| Cave (:U/mL) | 22.70 | 18.80 | 1.208 | (1.078, 1.353) | 0.018 |
| Tmax (hr) | 6.94 | 5.00 | -- | -- | 0.431 |

Mean insulin $AUC_{0-24}$ and Cmax in the group stabilized with 5 mg QD glyburide was higher by 17% and 19%, respectively, when eplerenone 100 mg QD was coadministered compared to coadministration with placebo QD. Similarly, mean insulin $AUC_{0-24}$ and Cmax in the group stabilized with 10 mg BID glyburide was higher by 22% and 29%, respectively, when eplerenone 100 mg QD was coadministered compared to coadministration with placebo.

***Effect of Eplerenone on Glyburide Pharmacokinetics***

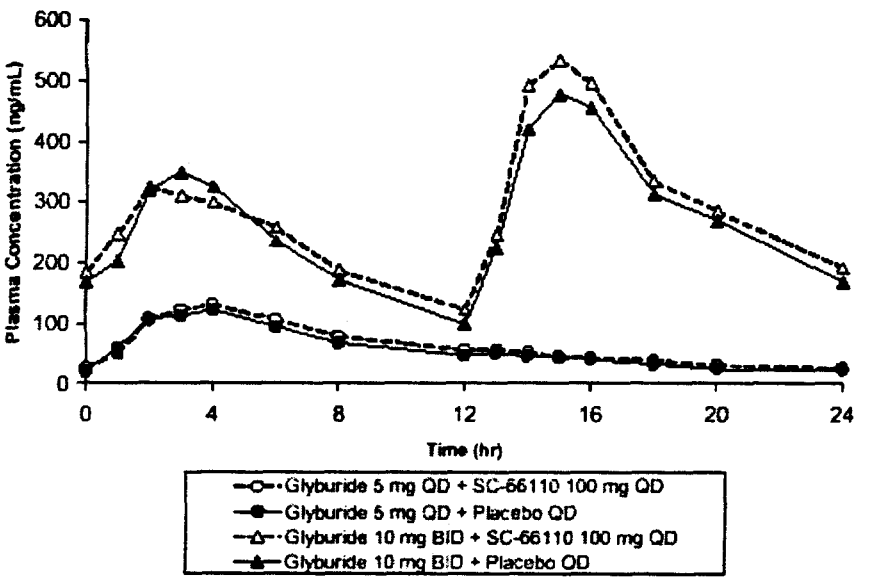
Mean glyburide $AUC_{0-24}$ and Cmax in the glyburide 5 mg QD group were slightly higher by about 11% following eplerenone coadministration. In the glyburide 10 mg BID group, mean glyburide plasma concentrations were similar between the two treatment groups (eplerenone or placebo) following the first dose of glyburide, but were slightly greater following the evening dose of glyburide when eplerenone was coadministered.

**Table 2: Ratios and 90% Confidence Intervals for Glyburide Pharmacokinetic Parameters**

| Pharmacokinetic Parameters | Least Squares Means | | | | Ratio of Means Eplerenone/ Placebo | 90% CI for Ratio of Means | Treatment Effect |
|---|---|---|---|---|---|---|---|
| | Eplerenone 100 mg QD | | Placebo QD | | | | |
| | N | LSM | N | LSM | | | |
| **Glyburide 5 mg QD** | | | | | | | |
| AUC (0-24) (hr*ng/mL) | 7 | 1280.69 | 7 | 1168.46 | 1.096 | (0.920, 1.306) | 0.327 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Cmax (ng/mL) | 8 | 137.27 | 8 | 124.08 | 1.106 | (0.955, 1.282) | 0.231 |
| Cmin (ng/mL) | 7 | 17.40 | 8 | 16.08 | 1.082 | (0.744, 1.573) | 0.689 |
| CL/F (L/hr) | 7 | 3.90 | 7 | 4.28 | 0.912 | (0.766, 1.087) | 0.327 |
| CL/F/WT (L/hr/70kg) | 7 | 3.54 | 7 | 3.88 | 0.912 | (0.766, 1.087) | 0.327 |
| Tmax (hr) | 8 | 3.63 | 8 | 3.50 | -- | -- | 0.823 |
| MRT (hr) | 7 | 8.72 | 7 | 8.71 | -- | -- | 0.960 |
| **Glyburide 10 mg BID** | | | | | | | |
| AUC (0-12) (hr*ng/mL) | 8 | 2695.08 | 8 | 2661.00 | 1.013 | (0.879, 1.166) | 0.867 |
| Cmax (ng/mL) | 8 | 360.04 | 8 | 367.23 | 0.980 | (0.821, 1.171) | 0.836 |
| Cmin (ng/mL) | 8 | 186.61 | 8 | 171.27 | 1.090 | (0.795, 1.493) | 0.615 |
| CL/F (L/hr) | 8 | 3.71 | 8 | 3.76 | 0.987 | (0.857, 1.137) | 0.867 |
| CL/F/WT (L/hr/70kg) | 8 | 3.37 | 8 | 3.41 | 0.987 | (0.857, 1.137) | 0.867 |
| Tmax (hr) | 8 | 2.75 | 8 | 2.88 | -- | -- | 0.870 |
| MRT (hr) | 8 | 5.11 | 8 | 4.99 | -- | -- | 0.469 |

**gure 8.b. Mean Glyburide Plasma Concentrations**




## Effect of Glyburide on Eplerenone and SC-70303 Pharmacokinetics

Eplerenone concentrations when administered alone were not determined in this study. Eplerenone mean $AUC_{0-24}$ and Cmax in the group receiving glyburide 5 mg QD were 20502 ng.h/ml and 2577 ng/ml, respectively, and in the gyburide 10 mg BID group were, 16814 ng.h/ml and 2366 ng/ml, respectively. These values are higher than the values observed in previous studies were eplerenone was administered alone. Eplerenone mean $AUC_{0-24}$ and Cmax in the verapamil drug interaction study following 100 mg QD

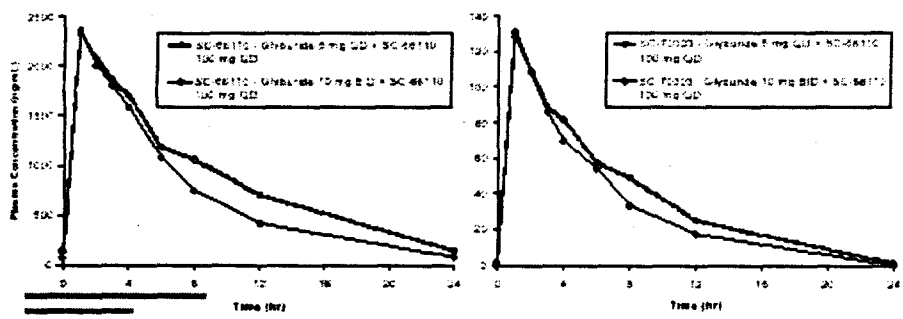
administration to steady state were 11562 ng.h/ml and 1892 ng/ml; in the ketoconazole study eplerenone mean $AUC_{0-24}$ and Cmax were 10110 ng.h/ml and 1583 ng/ml, respectively, and in the fluconazole study they were 10374 ng.h/ml and 1577 ng/ml, respectively.

Based on eplerenone pharmacokinetics in other studies, we can conclude that glyburide 5 mg QD increases eplerenone AUC approximately 90% and Cmax by approximately 50%. Similarly, glyburide 10 mg BID increases eplerenone AUC by approximately 60% and Cmax increases by approximately 40%. The effect of this increase on the blood pressure lowering effect of eplerenone is not known.

**Table 4: Arithmetic Mean (%CV) Eplerenone and SC-70303 Pharmacokinetic Parameters**

| Pharmacokinetic Parameter | EPLERENONE | | | | SC-70303 | | | |
|---|---|---|---|---|---|---|---|---|
| | Glyburide 5 mg QD + Eplerenone 100 mg QD | | Glyburide 10 mg BID + Eplerenone 100 mg QD | | Glyburide 5 mg QD + Eplerenone 100 mg QD | | Glyburide 10 mg BID + Eplerenone 100 mg QD | |
| | N = 8 | | N = 8 | | N = 8 | | N = 8 | |
| AUC(0-24) (hr*ng/mL) | 20501.74 | ( 35%) | 16814.47 | ( 27%) | 920.57 | ( 37%) | 772.42 | ( 32%) |
| Cmax (ng/mL) | 2577.50 | ( 28%) | 2366.25 | ( 16%) | 148.63 | ( 32%) | 131.73 | ( 22%) |
| Cmin (ng/mL) | 140.18 | ( 68%) | 73.84 | ( 81%) | 1.55 | (283%) | 0.00 | |
| MRT (hr) | 6.73 | ( 17%) | 6.03 | ( 13%) | 5.63 | ( 27%) | 5.16 | ( 16%) |
| Tmax (hr) | 1.25 | ( 37%) | 1.00 | ( 0%) | 1.38 | ( 54%) | 1.25 | ( 37%) |
| CL/F (L/hr) | 5.56 | ( 42%) | 6.34 | ( 26%) | 128.50 | ( 48%) | 141.78 | ( 34%) |
| CL/F/WT (L/hr/70kg) | 5.01 | ( 41%) | 5.85 | ( 33%) | 115.44 | ( 45%) | 130.09 | ( 36%) |

**Figure 8.c. Mean SC-66110 and SC-70303 Plasma Concentrations**



## CONCLUSIONS:

Coadministration of eplerenone 100 mg QD did not alter glucose concentrations compared to placebo. Mean insulin $AUC_{0-24}$ and Cmax in the group stabilized with 5 mg QD glyburide were higher by 17% and 19%, respectively, when eplerenone 100 mg QD was coadministered compared to placebo QD. Similarly, mean insulin $AUC_{0-24}$ and Cmax

in the group stabilized with 10 mg BID glyburide was higher by 22% and 29%, respectively, when eplerenone 100 mg QD was coadministered compared to placebo. This increase is not expected to be clinically significant.

Mean glyburide $AUC_{0-24}$ and Cmax in the glyburide 5 mg QD group were similar following both eplerenone and placebo coadministration.

Based on eplerenone pharmacokinetics in other studies (verapamil interaction study eplerenone Cmax and AUC were 1892 ng/ml and 11562 ng.h/ml, respectively) we can conclude that glyburide 5 mg QD increases eplerenone AUC approximately 90% and Cmax by approximately 50%. Similarly, glyburide 10 mg BID increased eplerenone AUC by approximately 60% and Cmax by approximately 40%.

**COMMENTS:**

1. Following comparison of eplerenone pharmacokinetics in previous studies with the present study, we can conclude that glyburide 5 mg QD increases eplerenone AUC approximately 90% and Cmax by approximately 50%. Similarly, glyburide 10 mg BID increases eplerenone AUC by approximately 60% and Cmax increases by approximately 40%. This is contrary to the sponsor's claim of no interaction.
2. This interaction should be incorporated in the label.
3. Eplerenone dose should be reduced to 50 mg QD when coadministered with glyburide.
4. Since SC-70303 is formed by conversion from eplerenone, it is not possible to calculate the CL/F of SC-70303. The sponsor has reported a CL/F of 128.5 L/h for SC-70303 in this study which is incorrect.

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

**STUDY INVESTIGATORS AND SITE:**

Protocol Number: NE3-99-02-036

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**OBJECTIVES:**

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

**FORMULATIONS:**

Eplerenone – 100 mg tablets (lot numbers RCT 11187 and RCT 11148)
Simvastatin - Zocor® 40 mg tablets (Merck manufacturing lot number J0998)

**STUDY DESIGN:**

This was an open-label, randomized, multiple-dose, six sequence, three-period and three-treatment crossover design study conducted in 18 healthy adult subjects, 16 M/2 F, age range 22 years to 43 years. Each subject received oral doses of all three treatments: **Treatment A** = eplerenone 100 mg QD for 7 days, **Treatment B** = simvastatin 40 mg QD for 7 days, **Treatment C** = eplerenone 100 mg QD + simvastatin 40 mg QD for 7 days in a crossover manner.

| | Period 1 Days 1-7 | Period 2 Days 9-15 | Period 3 Days 17-23 |
|---|---|---|---|
| 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 = Simvastatin 40 mg QD
C = Simvastatin 40 mg QD + Eplerenone 100 mg QD

On Days 1-6, 9-14, and 17-22, subjects were administered their eplerenone and/or simvastatin doses in the morning, approximately 15 minutes following breakfast. On

Days 7, 15 and 23, subjects received their medication under fasted conditions. Standard low-fat meals were served each day.

**ASSAY:**

Sample Collection

Blood samples for plasma simvastatin, β-hydroxysimvastatin, eplerenone and SC-70303 were drawn on Days 4-6, 12-14, 20-22 at predose for trough concentration measurements. Relative to dosing on Days 7, 15 and 23, blood samples were drawn at predose (-15 minutes), and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36 and 48 hours postdose.

**RESULTS:**

Simvastatin (Zocor®) is an inactive lactone which is converted in vivo to β-hydroxysimvastatin, an effective lipid-lowering agent via HMG-CoA reductase inhibition. Simvastatin undergoes extensive first-pass metabolism via CYP3A4. Since eplerenone is also a substrate for hepatic CYP3A4, this study evaluated the potential for an interaction with simvastatin.

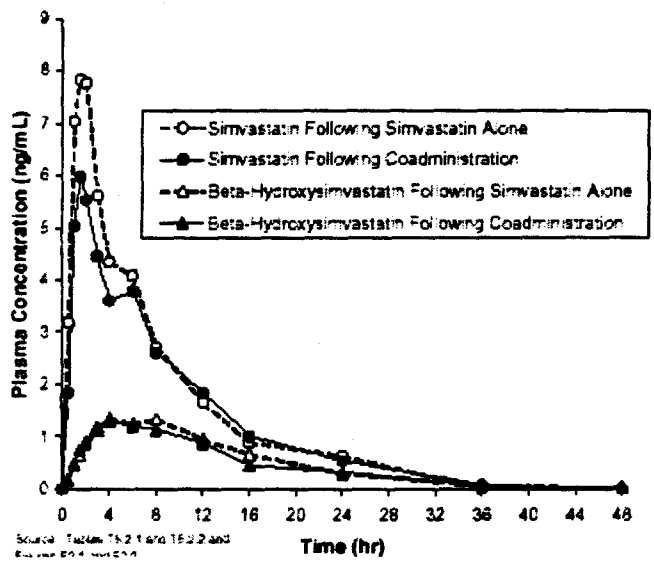
***Effect of Eplerenone on Simvastatin and β-hydroxy Simvastatin Pharmacokinetics***

The following table lists the pharmacokinetic parameters of simvastatin and β-hydroxy simvastatin when administered alone and in the presence of 100 mg QD eplerenone.

**Table 1: Arithmetic Mean Simvastatin and β-Hydroxysimvastatin Pharmacokinetic Parameters**

| Pharmacokinetic Parameter | Simvastatin | | | | β-Hydroxysimvastatin | | | |
|---|---|---|---|---|---|---|---|---|
| | Simvastatin 40 mg QD | | Eplerenone 100 mg QD + Simvastatin 40 mg QD | | Simvastatin 40 mg QD | | Eplerenone 100 mg QD + Simvastatin 40 mg QD | |
| | N | Mean | N | Mean | N | Mean | N | Mean |
| AUC(0-24) (hr*ng/mL) | 18 | 57.76 | 17 | 50.16 | 18 | 19.77 | 18 | 17.75 |
| Cmax (ng/mL) | 18 | 10.12 | 18 | 7.63 | 18 | 1.70 | 18 | 1.60 |
| Tmax (hr) | 18 | 2.72 | 18 | 3.64 | 18 | 6.96 | 18 | 7.06 |
| T(1/2) (hr) | 17 | 5.82 | 17 | 7.52 | 15 | 7.55 | 15 | 7.26 |
| Kel (1/hr) | 17 | 0.21 | 17 | 0.12 | 15 | 0.11 | 15 | 0.11 |
| MRT (hr) | 18 | 6.32 | 17 | 6.99 | 18 | 9.50 | 18 | 9.55 |
| CL/F (L/hr) | 18 | 902.35 | 17 | 1060.48 | | NAP | | NAP |
| CL/F/WT (L/hr/70kg) | 18 | 844.47 | 17 | 973.54 | | NAP | | NAP |
| XU(0-48) (:g) | 18 | 0 | 18 | 0 | 18 | 0 | 18 | 0 |

**Mean Simvastatin and β-Hydroxysimvastatin Plasma Concentrations**




Coadministration of multiple dose 100 mg QD eplerenone decreased simvastatin Cmax and $AUC_{0-24}$ by 32% and 14%, respectively. Simvastatin $C_{max}$ values decreased from 9.09 ng/ml to 6.17 ng/ml. Eplerenone increased simvastatin oral apparent clearance by 16%.

In contrast to simvastatin, coadministration of eplerenone did not affect the Cmax or $AUC_{0-24}$ of β-hydroxysimvastatin, the active metabolite of simvastatin.

**Table 2. Ratios and 90% Confidence Intervals for Simvastatin and β-Hydroxysimvastatin Pharmacokinetic Parameters**

| Parameter | Least Squares Means | | | | Ratio Coadmin./ Simvastatin | 90% Confidence Interval | p-value |
|---|---|---|---|---|---|---|---|
| | Eplerenone 100 mg QD + Simvastatin 40 mg QD | | Simvastatin 40 mg QD | | | | |
| | N | LS Mean | N | LS Mean | | | |
| **Simvastatin** | | | | | | | |
| AUC (0-24) (hr*ng/mL) | 17 | 43.92 | 18 | 50.95 | 0.862 | (0.7271, 1.0221) | 0.147 |
| Cmax (ng/mL) (b) | 18 | 6.17 | 18 | 9.09 | 0.679 | (0.5887, 0.7833) | <0.001 |
| Tmax (hr) | 18 | 3.64 | 18 | 2.72 | -- | -- | 0.248 |
| T(1/2) (hr) | 17 | 7.47 | 17 | 5.87 | -- | -- | 0.153 |
| CL/F (L/hr) (b) | 17 | 910.66 | 18 | 785.12 | 1.160 | (0.9782, 1.3752) | 0.147 |
| CL/F/WT (L/hr/70kg) | 17 | 878.24 | 18 | 757.17 | 1.160 | (0.9782, 1.3752) | 0.147 |
| **β-Hydroxysimvastatin** | | | | | | | |
| AUC (0-24) (hr*ng/mL) | 18 | 16.44 | 18 | 16.92 | 0.972 | (0.8505, 1.1100) | 0.710 |
| Cmax (ng/mL) | 18 | 1.38 | 18 | 1.47 | 0.941 | (0.7946, 1.1132) | 0.534 |
| Tmax (hr) | 18 | 7.06 | 18 | 6.96 | -- | -- | 0.897 |
| T(1/2) (hr) | 15 | 7.18 | 15 | 7.18 | -- | -- | 0.996 |

***Effect of Coadministration of Simvastatin on Eplerenone Pharmacokinetics***

Simvastatin did not affect the pharmacokinetics of eplerenone or SC-70303, the open-ring form of eplerenone. In the presence of simvastatin, eplerenone $AUC_{0-24}$ and $C_{max}$ increased slightly by 3% and 6%, respectively.

Coadministration of simvastatin increased SC-70303 $AUC_{0-24}$ and $C_{max}$ by 9%.

**Mean Eplerenone and SC-70303 Plasma Concentrations**

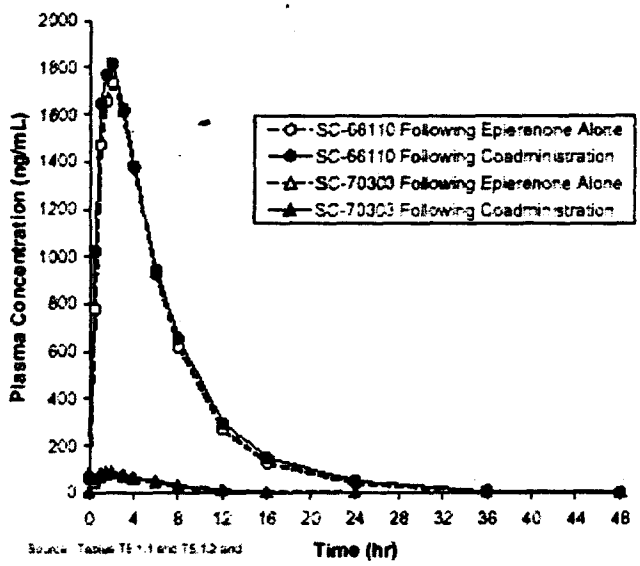



**Table 3. Arithmetic Mean (%CV) Eplerenone and SC-70303 Pharmacokinetic Parameters**

| Pharmacokinetic Parameter | EPLERENONE | | SC-70303 | |
|---|---|---|---|---|
| | Eplerenone 100 mg QD | Eplerenone 100 mg QD + Simvastatin 40 mg QD | Eplerenone 100 mg QD | Eplerenone 100 mg QD + Simvastatin 40 mg |
| | N = 18 | N = 18 | N = 18 | N = 18 |
| AUC(0-24) (hr*ng/mL) | 12651.69 (31.96) | 13373.00 (40.98) | 550.28 (31.04) | 602.30 (32.64) |
| Cmax (ng/mL) | 1848.89 (29.61) | 1983.33 (36.81) | 93.58 (20.74) | 102.52 (25.46) |
| Tmax (hr) | 2.11 (37.63) | 1.78 (43.38) | 1.85 (47.16) | 1.61 (51.66) |
| T(1/2) (hr) | 4.19 (28.69) | 5.05 (50.97) | 3.49 (13.40) | 3.51 (14.70) |
| Kel (1/hr) | 0.18 (24.42) | 0.16 (37.15) | 0.20 (14.07) | 0.20 (16.25) |
| CL/F (L/hr) | 8.44 (22.58) | 8.31 (29.16) | NAP | NAP |
| CL/F/WT (L/hr/70kg) | 8.10 (21.28) | 7.99 (29.34) | NAP | NAP |
| MRT (hr) | 5.69 (12.66) | 5.66 (14.43) | 4.64 (19.58) | 4.79 (19.99) |
| XU(0-48) (:g) | 1732.79 (68.94) | 2247.04 (96.28) | 4135.70 (53.15) | 4927.92 (52.33) |

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

| Parameter | Least Squares Means | | Ratio Coadmin./ Eplerenone | 90% Confidence Interval | p-value |
|---|---|---|---|---|---|
| | Eplerenone 100 mg QD + Simvastatin 40 mg QD | Eplerenone 100 mg QD | | | |
| | N = 18 | N = 18 | | | |
| **Eplerenone** | | | | | |
| AUC(0-24) (hr*ng/mL) | 12609.33 | 12200.57 | 1.034 | (1.0019, 1.0660) | 0.082 |
| Cmax (ng/mL) | 1892.91 | 1787.87 | 1.059 | (0.9964, 1.1249) | 0.120 |
| Tmax (hr) | 1.78 | 2.11 | -- | -- | 0.148 |
| T(1/2) (hr) | 5.05 | 4.19 | -- | -- | 0.075 |
| CL/F (L/hr) (b) | 7.93 | 8.20 | 0.968 | (0.9380, 0.9980) | 0.082 |

| | | | | | |
|---|---|---|---|---|---|
| CL/F/WT (L/hr/70kg) (b) | 7.65 | 7.90 | 0.968 | (0.9380, 0.9980) | 0.082 |
| XU(0-48) (μg) | 1433.83 | 1294.63 | 1.108 | (0.6403, 1.9156) | 0.748 |
| **SC-70303** | | | | | |
| AUC(0-24) (hr*ng/mL) | 575.79 | 527.19 | 1.092 | (1.0415, 1.1453) | 0.005 |
| Cmax (ng/mL) | 99.61 | 91.70 | 1.086 | (1.0127, 1.1652) | 0.056 |
| Tmax (hr) | 1.61 | 1.85 | -- | -- | 0.351 |
| T(1/2) (hr) | 3.51 | 3.49 | -- | -- | 0.826 |
| XU(0-48) (μg) | 4157.02 | 3384.76 | 1.228 | (0.8296, 1.8179) | 0.373 |

## CONCLUSIONS:

Coadministration of multiple dose 100 mg QD eplerenone decreased simvastatin Cmax and AUC by 32% and 14%, respectively. Eplerenone increased simvastatin oral apparent clearance by 16% but did not affect Cmax or $AUC_{0-24}$ of β-hydroxysimvastatin, the active metabolite of simvastatin. This decrease is not expected to be clinically significant.

Simvastatin did not affect the pharmacokinetics of eplerenone or SC-70303, the open-ring form of eplerenone.

## COMMENTS:

1. Coadministration of eplerenone affects only simvastatin, the inactive lactone. The pharmacokinetic parameters of active metabolite β-hydroxy simvastatin were not affected in the presence of eplerenone. Therefore, this interaction is not expected to be clinically significant.

**EFFECT OF MULTIPLE DOSES OF EPLERENONE ON THE SINGLE DOSE PHARMACOKINETIC PROFILE OF MIDAZOLAM IN HEALTHY SUBJECTS**

**STUDY INVESTIGATORS AND SITE:**

Protocol Number: NE3-00-02-037

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**OBJECTIVES:**

1. To investigate the effect of multiple doses of eplerenone on the single dose disposition kinetics of a prototype CYP3A4 substrate, midazolam.
2. To determine the safety and tolerability of single doses of midazolam in combination with steady-state eplerenone in healthy adult subjects.

**FORMULATIONS:**

Eplerenone – 100 mg tablets (lot number RCT 11525) by Searle.
Placebo matching eplerenone – Tablets (lot number RCT 11526) by Searle.
Midazolam hydrochloride - Versed® Syrup by Roche –Lot number 0004.

**STUDY DESIGN:**

This was a single blind, randomized, multiple dose, two-period crossover study conducted in 20 healthy adult subjects, 12 M/8 F, age range 19-41 years. Subjects received a single oral dose of midazolam 10 mg (5 ml) on Day 1. On Days 4-10, subjects received oral doses of either eplerenone 100 mg QD or placebo QD, with coadministration of midazolam 10 mg on Day 10. After a two-day washout period, subjects were crossed over to the alternate dosing regimen (eplerenone 100 mg or placebo on Days 13-19, with coadministration of midazolam 10 mg on Day 19). On Days 10 and 19, subjects took their morning dose of eplerenone or placebo with midazolam 10 mg (5 mL) following an overnight fast of at least ten hours.

**ASSAY:**

C

Sample Collection

Blood samples for total midazolam and total 1-hydroxy-midazolam determination were collected on Days 1, 10 and 19 at the following timepoints: 15 minutes predose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, 16, 24, 36 and 48 hours postdose.

Blood samples for eplerenone and SC-70303 analysis were collected on Day 1 prior to and 1.5 hr following midazolam dosing for all subjects, and at 15 minutes predose and at 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24, 36 and 48 hours postdose on Days 10 and 19 for subjects receiving eplerenone only. Blood collection for trough level concentrations for SC-66110 and SC-70303 were collected 15 minutes predose on Days 7 or 16, 8 or 17, and 9 or 18.

Urine samples were collected for 12-hours predose on Day -1, and at 0-4, 4-8, 8-12, 12-24 and 24-48 hours postdose on Days 10 and 19 for midazolam, free 1-hydroxy-midazolam and total 1-hydroxy-midazolam analyses.

## RESULTS

Midazolam (Versed®) is a benzodiazepine sedative that is metabolized primarily by CYP 3A4. Since eplerenone is a substrate for CYP3A4, this study assessed the potential for a pharmacokinetic interaction following coadministration of eplerenone and midazolam.

### *Effect of Eplerenone on Midazolam and 1-hydroxy Midazolam Pharmacokinetics*

Single dose pharmacokinetic parameters of 10-mg midazolam and its metabolite 1-hydroxy midazolam when administered alone and in the presence of multiple dose 100 mg QD eplerenone is listed in the following table.

**Table 1: Ratios and 90% Confidence Intervals for Midazolam and 1-Hydroxy-Midazolam Pharmacokinetic Parameters**

| Parameter | Least Squares Means | | | | Ratio Eplerenone/ Placebo | 90% Confidence Interval | p-value |
|---|---|---|---|---|---|---|---|
| | Midazolam 10 mg + Eplerenone 100 mg | | Midazolam 10 mg + Placebo | | | | |
| | N | LS Mean | N | LS Mean | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Total Midazolam** | | | | | | | |
| Cmax (ng/mL) | 20 | 48.51 | 20 | 49.24 | 0.99 | (0.861, 1.127) | 0.8490 |
| AUC (0-lqc) (hr*ng/mL) | 20 | 114.28 | 20 | 118.73 | 0.96 | (0.893, 1.037) | 0.3878 |
| $AUC_{(0-\infty)}$ (hr*ng/mL) | 20 | 123.80 | 20 | 128.25 | 0.97 | (0.891, 1.046) | 0.4540 |
| CL/F (L/hr) | 20 | 80.77 | 20 | 77.97 | 1.04 | (0.956, 1.122) | 0.4540 |
| CL/F/WT (L/hr) | 20 | 81.96 | 20 | 79.12 | 1.04 | (0.956, 1.122) | 0.4540 |
| Tmax (hr) | 20 | 0.55 | 20 | 0.61 | -- | -- | 0.5909 |
| XU (0-48) (μg) | 16 | 4.05 | 13 | 4.59 | 0.88 | (0.695, 1.118) | 0.3546 |
| **1-Hydroxy-Midazolam** | | | | | | | |
| Cmax (ng/mL) | 20 | 34.51 | 20 | 34.57 | 1.00 | (0.833, 1.196) | 0.9864 |
| AUC (0-lqc) (hr*ng/mL) | 20 | 86.56 | 20 | 84.39 | 1.03 | (0.934, 1.126) | 0.6446 |
| AUC (0-∞) (hr*ng/mL) | 20 | 88.41 | 19 | 85.91 | 1.03 | (0.937, 1.131) | 0.6034 |
| Tmax (hr) | 20 | 0.61 | 20 | 0.66 | -- | -- | 0.6466 |
| XU (0-48) (μg) | 16 | 4.37 | 14 | 3.92 | 1.12 | (0.879, 1.414) | 0.4233 |

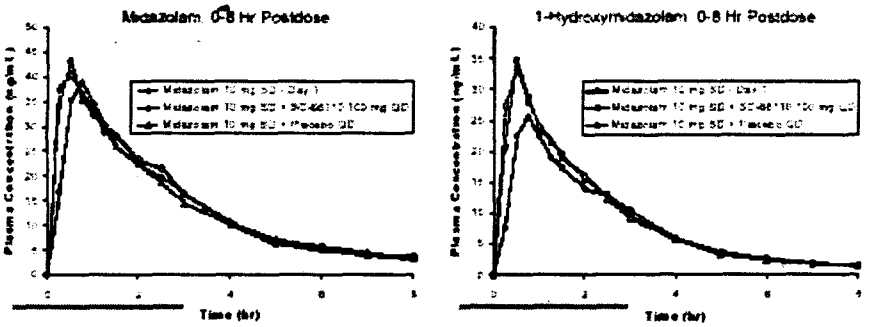
Coadministration of 100 mg QD eplerenone did not alter the single dose pharmacokinetics of midazolam or its metabolite 1-hydroxy midazolam.

As shown in the following table, urinary excretion of midazolam and its metabolite was quite variable. The baseline excretion of midazolam and its metabolite is substantially different from the amount excreted in the presence of placebo. In light of this variability, it is difficult to conclude if the increase in amount of free 1-hydroxy midazolam excreted in the urine in the presence of eplerenone is a "true" effect or an artifact. Based on the absence of interaction as judged from plasma concentrations it is reasonable to conclude an absence of interaction based on urinary data as well.

**Table 3: Mean Amount (μg) of Total Midazolam, Free 1-Hydroxy-Midazolam and Total 1-Hydroxy-Midazolam Excreted in Urine**

| | Midazolam 10 mg SD Day 1 | Midazolam 10 mg SD + Eplerenone 100 mg QD | Midazolam 10 mg SD + Placebo QD |
|---|---|---|---|
| | N = 20 | N = 20 | N = 20 |
| **Total Midazolam** | | | |
| 0-4 | 4.46 | 3.68 | 3.21 |
| 4-8 | 0.0 | 0.0 | 0.0 |
| 8-12 | 0.0 | 0.0 | 0.0 |
| 12-24 | 0.0 | 0.0 | 0.0 |
| 24-48 | 0.0 | 0.0 | 0.0 |
| **Free 1-Hydroxy-Midazolam** | | | |
| 0-4 | 5.03 | 3.55 | 2.88 |
| 4-8 | 0.36 | 0.03 | 0.09 |
| 8-12 | 0.0 | 0.0 | 0.0 |
| 12-44 | 0.0 | 0.0 | 0.0 |
| 24-28 | 0.0 | 0.0 | 0.0 |
| **Total 1-Hydroxy-Midazolam** | | | |
| 0-4 | 4221.78 | 4123.79 | 4195.20 |
| 4-8 | 1205.80 | 881.41 | 858.05 |
| 8-12 | 535.28 | 536.62 | 483.49 |
| 12-24 | 640.00 | 724.08 | 711.97 |
| 24-48 | 289.74 | 280.14 | 263.87 |

**Mean Total Midazolam and Total 1-hydroxy Midazolam Plasma Concentrations**




***Effect of Midazolam on Eplerenone and SC-70303 Pharmacokinetics***

The steady-state pharmacokinetic parameters of eplerenone and SC-70303 obtained in the present study in the presence of single 10 mg dose of midazolam are similar to those obtained in the absence of interacting drugs in other studies. Coadministration of midazolam does not seem to affect the pharmacokinetics of eplerenone or SC-70303.

**Table 4: Arithmetic Mean (%CV) Eplerenone and SC-70303 Pharmacokinetic Parameters Following Midazolam 10 mg SD + Eplerenone 100 mg QD for Seven Days**

| Pharmacokinetic Parameter | Midazolam 10 mg SD + Eplerenone 100 mg QD | |
|---|---|---|
| | Eplerenone | SC-70303 |
| AUC(0-24) (hr*ng/mL) | 11130.037 | 505.815 |
| Cmax (ng/mL) | 1697.500 | 86.705 |
| Tmax (hr) | 2.70 | 2.70 |
| CL/F (L/hr) | 10.61 | N/A |
| CL/F/WT (L/hr/70kg) | 10.81 | N/A |
| T 1/2 (hr) | 3.46 | 3.00 |

**CONCLUSIONS:**

Coadministration of eplerenone 100 mg QD for 7 days did not alter the single dose pharmacokinetics of midazolam and its primary metabolite 1-hydroxy midazolam. Similarly, single 10 mg dose of midazolam did not affect the steady-state pharmacokinetics of eplerenone or its open ring form SC-70303.

## THE EFFECT OF EPLERENONE ON THE PHARMACOKINETIC PROFILE OF CISAPRIDE (PROPULSID) IN HEALTHY SUBJECTS

## STUDY INVESTIGATORS AND SITE:

Protocol Number: NE3-99-02-038

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## OBJECTIVES:

1. To examine the multiple-dose effect of eplerenone on the pharmacokinetic profile of cisapride, and the multiple-dose effect of cisapride on the pharmacokinetic profile of eplerenone in healthy adult subjects.
2. To evaluate the safety and tolerability of multiple doses of eplerenone in combination with cisapride.

## FORMULATIONS:

Eplerenone – 100 mg tablets (lot number RCT 11149) by Searle.
Cisapride - Propulsid® 20 mg tablets by Janssen Pharmaceutica, Piscataway, NJ, Lot number RCT 99P0309.

## STUDY DESIGN:

This was an open-label, randomized, multiple-dose, three-treatment, six-sequence, three-period, crossover study to be completed by at least 18 healthy adult subjects, 8 M/10 F, age range 20-44 years. Each subject received each of the following treatments, according to their assigned treatment sequence:
**Treatment A:** Eplerenone 100 mg QD for six days
**Treatment B:** Cisapride 20 mg BID for six days (QD on Days 6, 13, and 20)
**Treatment C:** Eplerenone 100 mg QD + cisapride 20 mg BID for six days (QD on Days 6, 13, and 20).

Cisapride (20 mg) dosing was administered twice daily, approximately 12 hours apart. On Days 6, 13, and 20, cisapride was administered in the morning only. On Days 1-5, 8-12, and 15-19, subjects were to be administered study doses within 30 minutes after breakfast. On Days 6, 13, and 20, subjects received their morning dose following an overnight fast.

| Treatment Sequence | Period | | |
|---|---|---|---|
| | 1 (Days 1-6) | 2 (Days 8-13) | 3 (Days 15-20) |
| I | A | B | C |
| II | B | C | A |
| III | C | A | B |
| IV | A | C | B |
| V | B | A | C |
| VI | C | B | A |

A = 100 mg eplerenone QD
B = 20 mg cisapride BID (QD on Days 6, 13, and 20)
C = 100 mg eplerenone QD + 20 mg cisapride BID (QD on Days 6, 13, and 20)

**ASSAY:**

[redacted]

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Sample Collection

Each subject was to have two 7 mL samples drawn 30 minutes prior to the first dose on Day 1 (Baseline).

On Days 6, 13, or 20, for Treatments A and B, a 7 mL sample was to be collected for analysis of eplerenone and SC-70303 or cisapride and norcisapride concentrations 30 minutes predose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, and 48 hours postdose. dose

On Days 3-5, 10-12, or 17-19, trough samples were collected 30 minutes prior to the morning dose.

For Treatment C, two 7 mL samples were to be collected for analysis of eplerenone and SC-70303 and cisapride and norcisapride concentrations 30 minutes predose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, and 48 hours postdose on Day 6, 13, or 20. Two additional 7 mL samples for analysis of trough concentrations were to be collected 30 minutes prior to the morning dose on Days 3-5, 10-12, or 17-19.

On Days 6, 13, and 20, 48-hour urine was collected in the following intervals, 0-12, 12-24, and 24-48 hours postdose.

Twelve-lead EKGs were to be performed at the following times during the study:

| | |
|---|---|
| Day 0: | 24, 23, 22.5, 22, 21.5, 21, 20, 18, and 14 hours prior to the first dose on Day 1 |

| | |
|---|---|
| Days 1-5, 8-12, and 15-19: | 15 minutes predose and 1.5 hours postdose |
| Days 6,13, and 20: | 15 minutes predose and 1, 1.5, 2, 2.5, 3, 4, 6, and 10 hours postdose |
| Days 7, 14, and 21: | 24 hours postdose (± 15 minutes) |
| Day 22: | 48 hours postdose (± 15 minutes) |

## RESULTS:

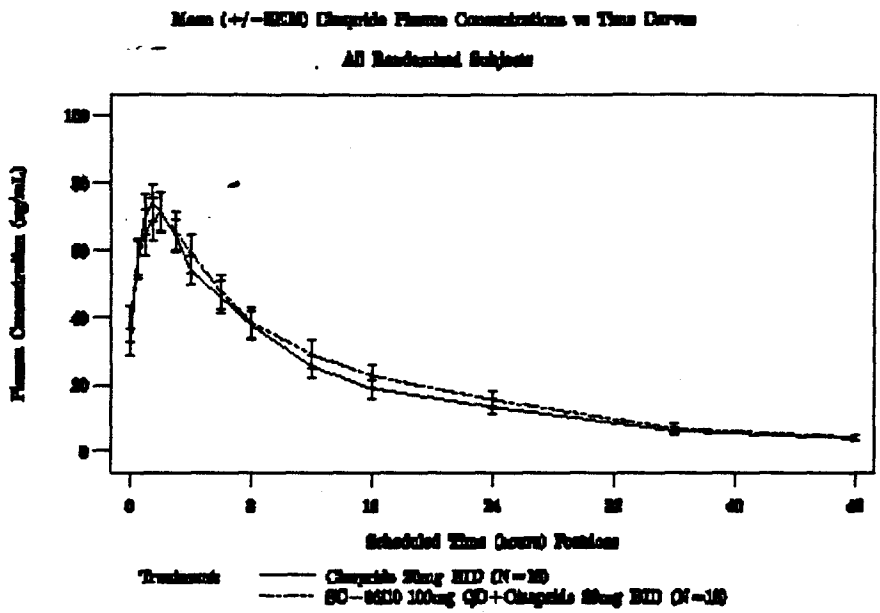
Cisapride (Propulsid®), an oral GI-motility agent, is metabolized primarily by CYP 3A4, to its primary metabolite norcisapride. Eplerenone is a substrate of CYP3A4. Inhibition of cisapride metabolism can cause has been associated with QT prolongation, syncopsal episodes, and cardiac dysrhythmias. Therefore, this study assessed the effect of eplerenone on cisapride pharmacokinetics, and the effect of cisapride on eplerenone pharmacokinetics.

### *Effect of Eplerenone on Cisapride and Norcisapride Pharmacokinetics*

Steady-state pharmacokinetic parameters of 20-mg cisapride when administered alone and in the presence of eplerenone 100 mg QD are listed in the following table.

**Table 1: Arithmetic Mean Cisapride and Norcisapride Pharmacokinetic Parameters**

| Pharmacokinetic Parameter | Cisapride Values by Treatment | | Norcisapride Values by Treatment | |
|---|---|---|---|---|
| | Cisapride 20 mg BID | Eplerenone 100 mg QD + Cisapride 20 mg BID | Cisapride 20 mg BID | Eplerenone 100 mg QD + Cisapride 20 mg BID |
| | N=18 | N=18 | N=18 | N=18 |
| AUC(0-12) (hr*ng/mL) | 594.12 | 654.27 | 188.99 | 192.89 |
| Cmax (ng/mL) | 86.05 | 92.34 | 22.97 | 23.34 |
| Tmax (hr) | 1.69 | 1.58 | 1.44 | 1.42 |
| T1/2 (hr) | 12.93 | 12.61 | 13.94 | 14.32 |
| CL/F (L/hr) | 42.66 | 41.54 | NA | NA |
| CL/F/WT (L/hr/70kg) | 44.68 | 43.62 | NA | NA |
| XU(0-48) (mcg) | 142.6 | 184.2 | 7643.6 | 7728.3 |



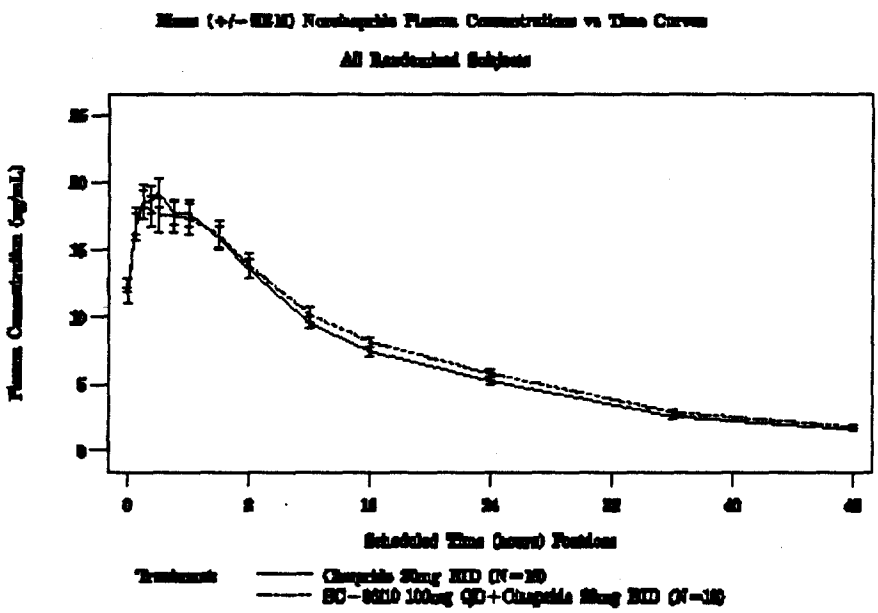


**Table 2: Ratios and 90% Confidence Intervals for Cisapride and Norcisapride Pharmacokinetic Parameters**

| Analyte Parameter | Least Squares Means | | Ratio of Means (Test/Ref) | 90% CI for Ratio of Means | p-Value |
|---|---|---|---|---|---|
| | Epierenone 100 mg QD + Cisapride 20 mg BID (Test) | Cisapride 20 mg BID (Reference) | | | |
| | N=18 | N=18 | | | |
| Cisapride | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| AUC(0-12) (hr*ng/mL) | 579.25 | 539.53 | 1.074 | (0.9899, 1.1643) | 0.146 |
| Cmax (ng/mL) | 84.10 | 80.52 | 1.045 | (0.9606, 1.1357) | 0.376 |
| Tmax (hr) | 1.58 | 1.69 | -- | -- | 0.506 |
| T1/2 (hr) | 12.61 | 12.93 | -- | -- | 0.621 |
| CL/F (L/hr) | 34.53 | 37.07 | 0.931 | (0.8588, 1.0101) | 0.146 |
| CL/F/WT (L/hr/70kg) | 34.61 | 37.16 | 0.931 | (0.8588, 1.0101) | 0.146 |
| XU(0-48) (mcg) | 144.89 | 106.96 | 1.355 | (1.0504, 1.7467) | 0.054 |
| **Norcisapride** | | | | | |
| AUC(0-12) (hr*ng/mL) | 186.44 | 184.48 | 1.011 | (0.9496, 1.0755) | 0.770 |
| Cmax (ng/mL) | 22.39 | 22.27 | 1.005 | (0.9274, 1.0900) | 0.907 |
| Tmax (hr) | 1.42 | 1.44 | -- | -- | 0.868 |
| T1/2 (hr) | 14.32 | 13.94 | -- | -- | 0.501 |
| XU(0-48) (mcg) | 7598.63 | 7485.11 | 1.015 | (0.9038, 1.1402) | 0.823 |

Coadministration of eplerenone 100 mg QD increased the AUC and Cmax of cisapride by 7% and 5%, respectively, which are not expected to be clinically significant. The AUC and Cmax of norcisapride were not affected by coadministration of 100 mg QD eplerenone.

***Effect of Cisapride on Eplerenone and SC-70303 Pharmacokinetics***

Steady-state pharmacokinetic parameters of eplerenone and SC-70303 when administered alone and in the presence of cisapride 20 mg BID is presented in the following table.

**Table 3: Arithmetic Mean Eplerenone and SC-70303 Pharmacokinetic Parameters**

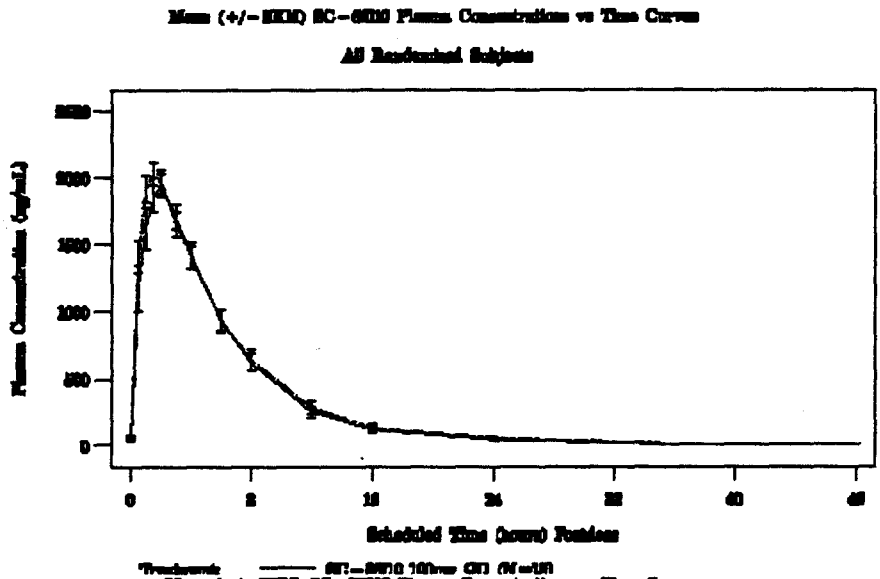
| Pharmacokinetic Parameter | Eplerenone Values by Treatment | | SC-70303 Values by Treatment | |
|---|---|---|---|---|
| | Eplerenone 100 mg QD | Eplerenone 100 mg QD + Cisapride 20 mg BID | Eplerenone 100 mg QD | Eplerenone 100 mg QD + Cisapride 20 mg BID |
| | N=18 | N=18 | N=18 | N=18 |
| $AUC_{(0-24)}$ (hr*ng/mL) | 13422.6 | 14061.6 | 465.14 | 484.02 |
| Cmax (ng/mL) | 2200.06 | 2245.02 | 93.44 | 93.35 |
| Tmax (hr) | 1.67 | 1.42 | 1.58 | 1.28 |
| T1/2 (hr) | 4.82 | 4.64 | 3.21 | 3.48 |
| CL/F (L/hr) | 8.19 | 7.99 | NA | NA |
| CL/F/WT (L/hr/70kg) | 8.33 | 8.11 | NA | NA |
| XU(0-48) (mcg) | 3061.7 | 2905.1 | 6485.7 | 5550.5 |

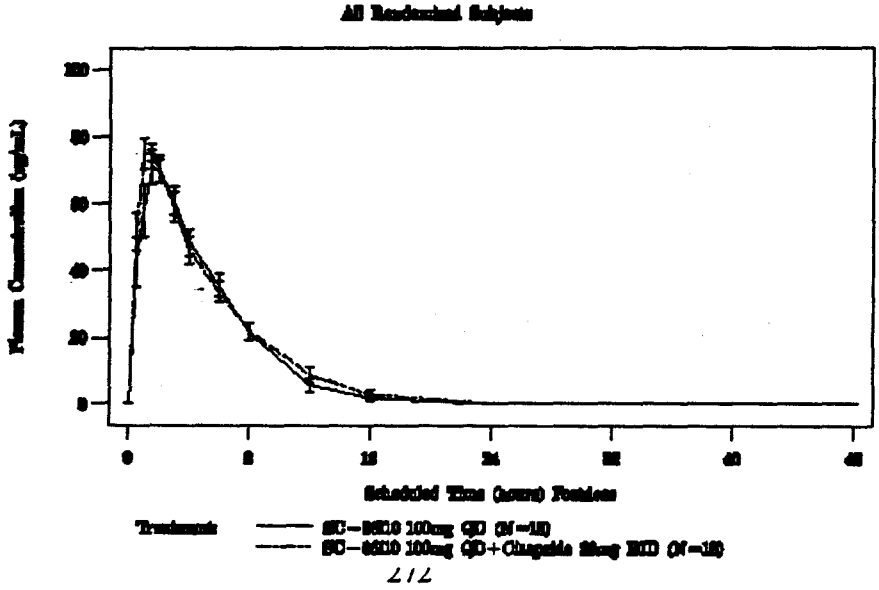
Coadministration of 20 mg BID cisapride had negligible effect (<4%) on steady-state AUC and Cmax of eplerenone and its open-ring form SC-70303.

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

| Analyte Parameter | Least Squares Means | | Ratio of Means (Test/Ref) | 90% CI for Ratio of Means | p-value |
|---|---|---|---|---|---|
| | Eplerenone 100 mg QD + Cisapride 20 mg BID (Test) | Eplerenone100 mg QD (Reference) | | | |
| | N=18 | N=18 | | | |

| | | | | | |
|---|---|---|---|---|---|
| **Eplerenone** | | | | | |
| $AUC_{(0-24)}$ (hr*ng/mL) | 13288.16 | 12806.63 | 1.038 | (0.9777, 1.1011) | 0.293 |
| Cmax (ng/mL) | 2214.67 | 2166.79 | 1.022 | (0.9749, 1.0715) | 0.430 |
| Tmax (hr) | 1.42 | 1.67 | -- | -- | 0.153 |
| T1/2 (hr) | 4.64 | 4.82 | -- | -- | 0.673 |
| CL/F (L/hr) | 7.53 | 7.81 | 0.964 | (0.9081, 1.0227) | 0.293 |
| CL/F/WT (L/hr/70kg) | 7.54 | 7.83 | 0.964 | (0.9081, 1.0227) | 0.293 |
| XU(0-48) (mcg) | 2477.30 | 2594.63 | 0.955 | (0.7934, 1.1488) | 0.667 |
| **SC-70303** | | | | | |
| $AUC_{(0-24)}$ (hr*ng/mL) | 452.66 | 439.73 | 1.029 | (0.9622, 1.1011) | 0.463 |
| Cmax (ng/mL) | 91.19 | 90.51 | 1.008 | (0.9443, 1.0749) | 0.842 |
| Tmax (hr) | 1.28 | 1.58 | -- | -- | 0.015 |
| T1/2 (hr) | 3.48 | 3.21 | -- | -- | 0.083 |
| XU(0-48) (mcg) | 5030.50 | 5897.74 | 0.853 | (0.7315, 0.9944) | 0.089 |





***Effect of Cisapride and Eplerenone Alone and in Combination on ECG Parameters***

Both cisapride and eplerenone when administered alone or in combination increased mean heart rate by 7 to 9 bpm. Neither cisapride nor eplereone alone or in combination, had an effect on the length of PR or QRS intervals. When corrected for heart rate, the mean changes in QTc interval length (calculated using either the Fridericia or Bazett method) following cisapride and eplerenone dosing indicated that eplerenone showed no evidence of lengthening cardiac repolarization, while cisapride, either alone or in combination with eplerenone resulted in an increase in the mean change from Baseline. Coadministration increased QTc interval from baseline by 13 msec based on Bazett's formula. Using Fridericia's correction, a change from Baseline in QTc between 31 msec and 60 msec was noted in 1 subject while on cisapride, 1 subject while on eplerenone, in 6 subjects while on cisapride + eplerenone. Using Bazett's correction, a change from Baseline in QTc between 31 msec and 60 msec was noted in 13 subjects while on cisapride, 13 on cisapride + eplerenone, and five subjects while on eplerenone. No subject, however, in any treatment group had a QTc interval duration over 500 msec or a change from Baseline of 60 or more msec.

**Table 5: Mean (±SEM) Change From Baseline in ECG Parameters**

| Parameter | Cisapride 20 mg BID/QD mean ± SEM | Eplerenone 100 mg QD mean ± SEM | Cisapride 20 mg BID/QD + Eplerenone 100 mg QD mean ± SEM | P-Value[a] |
|---|---|---|---|---|
| | N = 18 | N = 18 | N = 18 | |
| HR (bpm) | 6.82 ± 0.99 [b] | 6.72 ± 1.05 [b] | 9.32 ± 1.40 [b] | 0.0083 |
| PR (msec) | -5.69 ± 1.80 [b] | -0.33 ± 1.69 | -4.01 ± 2.39 | 0.0003 |
| QRS (msec) | -0.11 ± 0.78 | 0.14 ± 0.86 | -0.38 ± 0.78 | NS |
| QT (msec) | -12.81 ± 2.48 [b] | -22.65 ± 2.79 [b] | -15.15 ± 3.36 [b] | 0.0006 |
| QTc[c] (msec) | 1.16 ± 1.76 | -9.15 ± 1.43 | 3.70 ± 1.83 | 0.0000 |
| QTc[d] (msec) | 8.14 ± 2.23 [b] | -2.33 ± 1.58 [b] | 13.29 ± 2.31 [b] | 0.0000 |
| MaxQTc[d] (msec) | 7.78 ± 2.23 | -5.83 ± 1.93 | 6.17 ± 1.81 | 0.0000 |
| MaxQTc[e] (msec) | 18.50 ± 3.47 [b] | 1.83 ± 2.50 | 17.56 ± 3.41 | 0.0000 |

a – P-values < 0.05 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
NS – not statistically significant across treatments

## CONCLUSIONS:

The results of this study indicate the absence of an interaction between cisapride and eplerenone. Coadministration of eplerenone with cisapride had no statistically significant effects on the pharmacokinetic profile of either cisapride or its primary metabolite norcisapride. Moreover, coadministration of cisapride with eplerenone had no statistically significant effects on the pharmacokinetic profile of eplerenone or it open-ring form SC-70303.

Both cisapride and eplerenone when administered alone or in combination increased mean heart rate by 7-9 bpm. When corrected for heart rate, the mean changes in QTc

interval length (calculated using either the Fridericia or Bazett method) following cisapride and eplerenone dosing indicated that eplerenone showed no evidence of lengthening cardiac repolarization, while cisapride, either alone or in combination with eplerenone resulted in an increase in the mean change from Baseline. Coadministration increased QTc interval from baseline by 13 msec based on Bazett's formula. Using Fridericia's correction, a change from Baseline in QTc between 31 msec and 60 msec was noted in 1 subject while on cisapride, 1 subject while on eplerenone, in 6 subjects while on cisapride + eplerenone. Using Bazett's correction, a change from Baseline in QTc between 31 msec and 60 msec was noted in 13 subjects while on cisapride, 13 on cisapride + eplerenone, and five subjects while on eplerenone. No subject, however, in any treatment group had a QTc interval duration over 500 msec or a change from Baseline of 60 or more msec.

## THE EFFECT OF EPLERENONE ON THE PHARMACOKINETIC PROFILE OF CYCLOSPORINE IN HEALTHY ADULT SUBJECTS

## STUDY INVESTIGATORS AND SITE:

Protocol Number: NE3-00-02-039

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### OBJECTIVES:

1. To examine the effect of multiple-dose eplerenone on the single-dose pharmacokinetic profile of cyclosporine in healthy adult subjects.
2. To evaluate the safety and tolerability of multiple doses of eplerenone coadministration with a single dose of cyclosporine.

### FORMULATIONS:

Eplerenone – 100 mg tablets (lot number RCT 11431) by Searle.
Placebo –Tablets (lot number RCT 11430) by Searle.
Cyclosporine - Neoral® 100 mg softgel capsules by Novartis Pharmaceuticals,East Hanover, NJ. Lot number 305515-RCT 11431.

### STUDY DESIGN:

This was a single-blind, randomized, multiple-dose, two-sequence, two-period, crossover study to be conducted in 20 healthy adult subjects, 17 M/3 F, age range 19-43 years. Subjects were to be randomized in equal numbers to one of the following treatment sequences:

| Treatment Sequence | Period | | |
|---|---|---|---|
| | BASELINE | 1 | 2 |
| | (Days 1) | (Days 4-8) | (Days 11-15) |
| I | A | B | C |
| II | A | C | B |

A = Cyclosporine 400 mg (4x100 mg capsules) SD taken alone
B = Cyclosporine 400 mg (4x100 mg capsules) SD + eplerenone 100 mg tablet QD
C = Cyclosporine 400 mg (4x100 mg capsules) SD + eplerenone placebo tablet QD

Each subject received each of the following treatments, according to his or her assigned treatment sequence (ABC or ACB), with a 72-hour washout period between successive treatments:
**Treatment A:** Cyclosporine 400 mg single dose (SD) taken alone
**Treatment B:** Cyclosporine 400 mg SD + eplerenone 100 mg QD for five days
**Treatment C:** Cyclosporine 400 mg SD + eplerenone placebo QD for five days.

A single dose of cyclosporine 400 mg (4x100 mg capsules) was administered following an overnight fast on Days 1, 8, and 15 only. Eplerenone100 mg or placebo tablets were administered once daily on Days 4-8 or 11-15, according to each subject's assigned treatment sequence. On Days 8 and 15, cyclosporine and eplerenone/placebo were administered simultaneously.

**ASSAY:**

[

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Sample Collection

On Days 1, 8, and 15, a 7 mL blood sample were collected for analysis of cyclosporine concentration 30 minutes predose and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 16, 24, 48, and 72 hours postdose.

During active eplerenone treatment, on Day 8 or 15, subjects were to provide an additional 7 mL blood sample 30 minutes predose and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 16, and 24 hours postdose for analysis of eplerenone and SC-70303 concentrations. On Days 5-7 or 12-14, additional 7 mL blood samples were drawn 30 minutes predose for analysis of eplerenone and SC-70303 trough concentrations.

Subjects began a 12-hour urine collection period on the evening of Day 0. A 72-hour urine collection period began immediately following study drug administration on Days 1, 8, and 15: Urine was collected for the time intervals 0-12, 12-24, 24-48, and 48-72 hours postdose.

**RESULTS:**

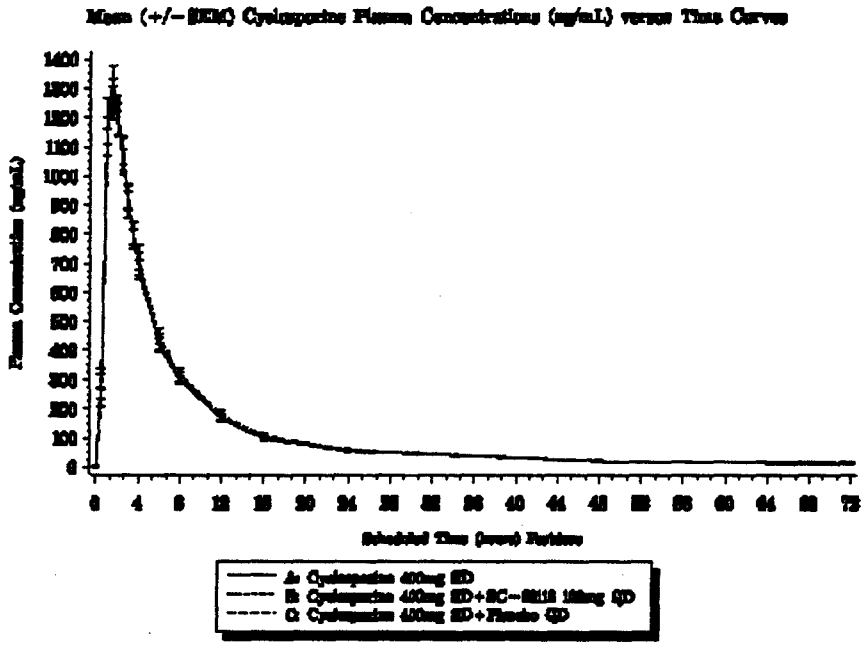
Cyclosporine (Neoral®), an immunosuppressive agent, is extensively metabolized by CYP3A4. Since eplerenone is also metabolized extensively by CYP3A4, this study assessed the potential for metabolism interaction between eplerenone and cyclosporine.

***Effect of Eplerenone on Cyclosporine Pharmacokinetics***

The following table lists the single dose pharmacokinetic parameters of 400-mg cyclosporine obtained following administration of cyclosporine alone and in the presence of 100-mg QD eplerenone.

**Table 1: Mean Single-Dose Cyclosporine Pharmacokinetic Parameters**

| Parameter | Treatment | | |
|---|---|---|---|
| | Cyclosporine 400 mg SD | Cyclosporine 400 mg SD + Eplerenone 100 mg QD | Cyclosporine 400 mg SD + Placebo QD |
| | N=20 | N=20 | N=20 |
| Cmax (ng/mL) | 1345.25 | 1304.55 | 1370.00 |
| AUC(0-lqc) (hr*ng/mL) | 8715.30 | 8977.98 | 8809.09 |
| AUC(0-inf) (hr*ng/mL) | 9031.90 | 9350.01 | 9225.85 |
| Tmax (hr) | 1.38 | 1.43 | 1.38 |
| T1/2 (hr) | 18.77 | 19.27 | 19.72 |
| Kel (1/hr) | 0.037 | 0.037 | 0.036 |
| CL/F (L/hr) | 45.78 | 45.61 | 45.83 |
| CL/F/WT (L/hr/70 kg) | 43.79 | 43.41 | 43.49 |



Coadministration of 100 mg QD eplerenone resulted in a small decrease in the Cmax of cyclosporine (5%) while, the AUC, CL/F and $T_{1/2}$ of cyclosporine was unaffected by coadministration of eplerenone.

**Table 2: Effect of Eplerenone on Single-Dose Cyclosporine Pharmacokinetics**

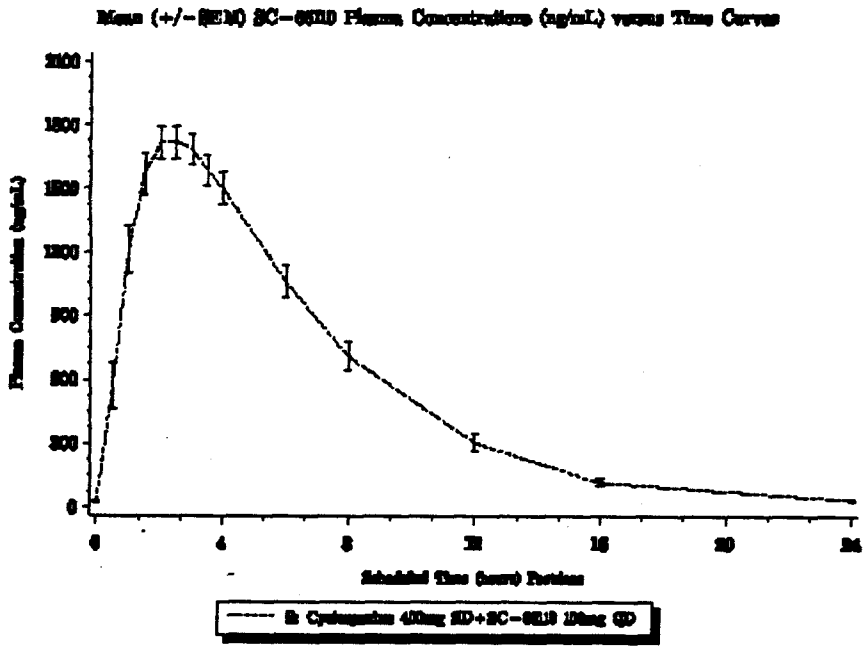
| Parameter | Least Squares Means | | Ratio of Means (Test/Ref) | 90% CI for Ratio of Means | p-value |
|---|---|---|---|---|---|
| | Cyclosporine 400 mg + Eplerenone 100 mg QD | Cyclosporine 400 mg + Placebo QD | | | |

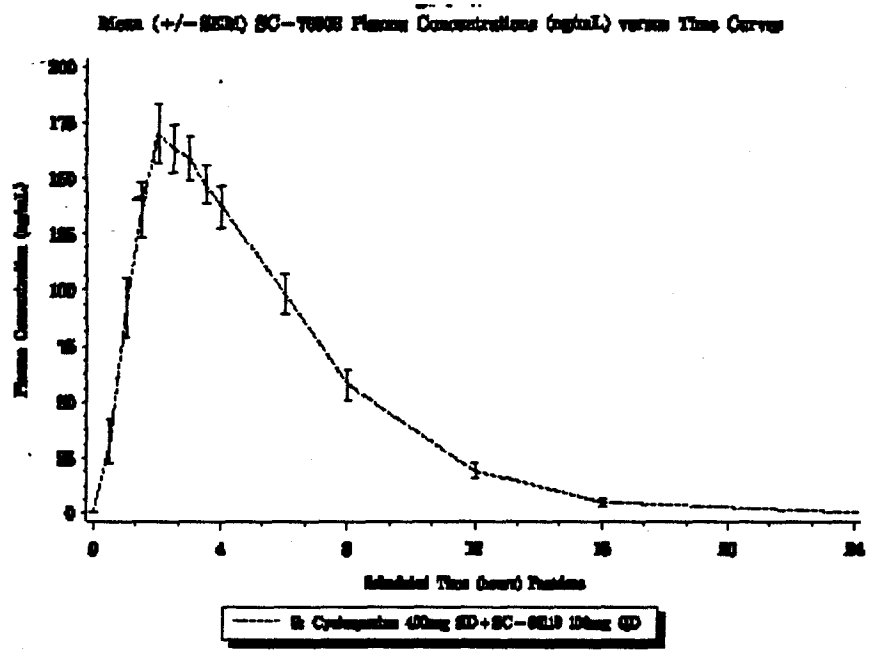
| | (Test) | (Reference) | | | |
|---|---|---|---|---|---|
| | N=20 | N=20 | | | |
| Cmax (ng/mL) | 1281.84 | 1345.76 | 0.95 | (0.907, 1.000) | 0.0994 |
| AUC(0-lqc) (hr*ng/mL) | 8689.14 | 8577.09 | 1.01 | (0.984, 1.043) | 0.4544 |
| AUC(0-inf) (hr*ng/mL) | 9045.44 | 8962.89 | 1.01 | (0.979, 1.040) | 0.6050 |
| CL/F (L/hr) | 44.22 | 44.63 | 0.99 | (0.961, 1.021) | 0.6050 |
| CL/F/WT (L/hr/70 kg) | 41.69 | 42.08 | 0.99 | (0.961, 1.021) | 0.6050 |
| Tmax (hr) | 1.43 | 1.38 | -- | -- | 0.6201 |
| T1/2 (hr) | 19.27 | 19.72 | -- | -- | 0.4091 |

***Effect of Cyclosporine on Eplerenone and SC-70303 Pharmacokinetics***

**Table 3: Mean Eplerenone and SC-70303 Pharmacokinetic Parameters**

| Parameter | Cyclosporine 400 mg SD + Eplerenone 100 mg QD | |
|---|---|---|
| | EPLERENONE | SC-70303 |
| | N=20 | N=20 |
| AUC(0-24) (hr*ng/mL) | 13382.35 | 1077.06 |
| Cmax (ng/mL) | 1849.50 | 175.53 |
| Tmax (hr) | 2.18 | 2.31 |
| T1/2 (hr) | 3.30 | 2.80 |
| Kel (1/hr) | 0.225 | 0.257 |
| CL/F (L/hr) | 8.03 | N/A |
| CL/F/WT (L/hr/70Kg) | 7.76 | N/A |
| AUMC(0-24) | 78874.69 | 5494.07 |
| MRT (hr) | 5.71 | 4.92 |
| XU(0-24) (mcg) | 1494.74 | 9859.57 |





Comparison of eplerenone pharmacokinetic parameter values from the present study to values obtained from other drug interaction studies where eplerenone was administered alone, indicates an absence of drug interaction on the pharmacokinetics of eplerenone following coadministration with cyclosporine.

In contrast, coadministration of cyclosporine seemed to increase the concentrations of the open-ring form, SC-70303, by 100%, resulting in increases in Cmax and AUC of SC-70303 compared to previous studies. SC-70303 amount excreted in urine over 24 hours in the presence of cyclosporine was 9859.6 μg, which is about 6-fold higher than 1715.5 μg of SC-70303 excreted in the urine over 24 hours in the verapamil interaction study, and is about 2-fold higher than 5897.7 μg of SC-70303 excreted over 48 hours in the cisapride interaction study.

## CONCLUSIONS:

Coadministration of eplerenone 100 mg QD did not affect single-dose pharmacokinetics of cyclosporine 400 mg. Cyclosporine does not affect the steady-state pharmacokinetic parameters of eplerenone. However, the Cmax and AUC of SC-70303, the open-ring form of eplerenone increased 100%. Compared to other studies (verapamil interaction study) in the presence of cyclosporine and amount of SC-70303 excreted in the urine increased 6-fold..

**A SINGLE BLIND, RANDOMIZED, MULTIPLE DOSE, THREE-WAY CROSSOVER STUDY. TO ASSESS THE EFFECT OF EPLERENONE COADMINISTRATION ON THE STEADY-STATE PHARMACOKINETIC PROFILE OF SAQUINAVIR IN HEALTHY ADULT SUBJECTS**

**STUDY INVESTIGATORS AND SITE:**

Protocol Number: NE3-00-02-040

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## OBJECTIVES:

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

## FORMULATIONS:

Eplerenone – 100 mg tablets (lot number RCT 11465) by Searle.
Placebo –Tablets (lot number RCT 11464) by Searle.
Saquinavir - Fortovase® 200 mg softgel capsules, Lot number B1703.

## STUDY DESIGN:

This was a single-blind, randomized, multiple-dose, six-sequence, three-period, and three-treatment crossover design conducted in 24 healthy adult subjects, 12 M/12 F, age range 23-45 years. All subjects were randomized to any one of 6 sequences listed below.

| Treatment Sequence | Period | | |
|---|---|---|---|
| | 1 | 2 | 3 |
| | (Days 1-6) | (Days 12-17) | (Days 23-28) |
| I | A | B | C |
| II | B | C | A |
| III | C | A | B |
| IV | A | C | B |
| V | B | A | C |
| VI | C | B | A |

A = Eplerenone 100 mg tablet QD
B = Eplerenone placebo tablet QD + Saquinavir 1200 mg TID (QD on Days 6, 17 and 28)
C = Eplerenone 100 mg tablet QD + Saquinavir 1200 mg TID (QD on Days 6, 17 and 28)

Each subject was to receive 3 treatments in a crossover manner, with each treatment separated by a six-day washout period.

Subjects randomized to receive **Treatment A**: 100 mg QD eplerenone just after breakfast on Days 1-6, 12-17 or 23-28; **Treatment B:** Eplerenone placebo tablet QD and 1200 mg saquinavir (6 x 200 mg capsules) on Days 1-5, 12-16 or 23-27 at the following times: approximately 0700 just after breakfast; approximately 1500 (within two hours of lunch); approximately 2300 (within 30 minutes of an evening snack). In addition, on Days 6, 17 or 28, subjects were administered one eplerenone placebo capsule and 1200 mg saquinavir (6 x 200 mg capsules) at approximately 0700 just after breakfast; **Treatment C**: 100 mg QD eplerenone and 1200 mg saquinavir (6 x 200 mg capsules) on Days 1-5, 12-16 or 23-27 at the following times: in the morning at just after breakfast; at approximately 1500 h (within two hours of lunch); at approximately 2300 h (within 30 minutes of an evening snack). In addition, on Days 6, 17 or 28, subjects were administered 100 mg eplerenone and 1200 mg saquinavir (6 x 200 mg capsules) in the morning at approximately 0700 just after breakfast. Standard low-fat meals were served every day.

**ASSAY:**

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Sample Collection

Blood samples were drawn on the following days and times: Days 1, 12 and 23 at predose for analyses for saquinavir, eplerenone and SC-70303 predose plasma concentrations.

Days 3-5, 14-16 and 25-27 at predose (trough) for analysis for saquinavir and/or eplerenone and SC-70303 predose (trough) plasma concentrations, depending on the treatment being administered;

Days 6, 17 and 28 at approximately 30 minutes predose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16 and 24 hours postdose for analysis for saquinavir and/or eplerenone and SC-70303 plasma concentrations, depending on the treatment being administered.

Urine samples were collected and pooled from -12 hours to 0 hour predose on Days -1, 11 and 22 and on Days 6, 17 and 28 (0-24 hours postdose). Aliquots of pooled urine samples were analyzed for eplerenone, SC-70303 and/or saquinavir.

## RESULTS:

Saquinavir, a HIV protease inhibitor, is a substrate for the CYP3A4 isozyme. Eplerenone is also a substrate for CYP3A4, therefore this study assessed the interaction potential following coadministration of saquinavir and eplerenone.

### *EFFECT OF EPLERENONE ON SAQUINAVIR PHARMACOKINETICS*

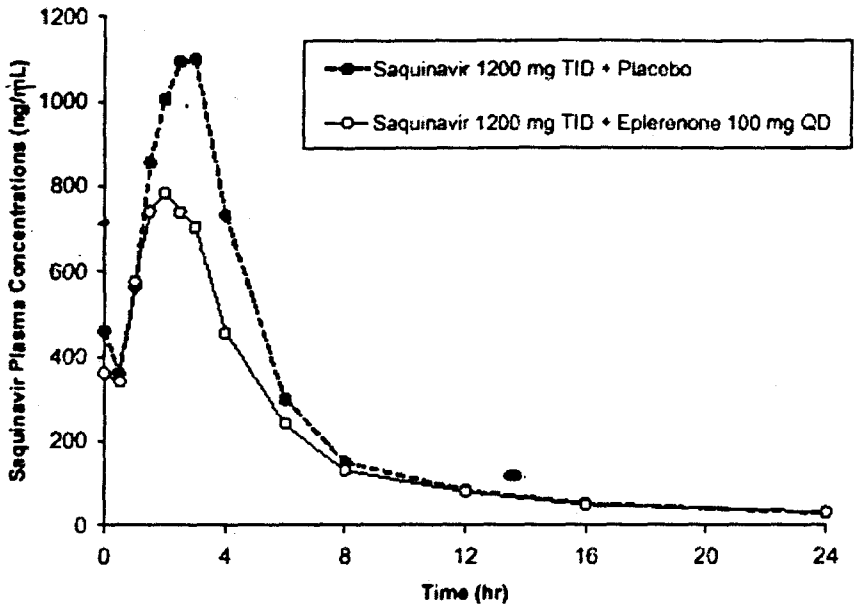
Mean pharmacokinetic parameters of 1200 mg TID saquinavir when administered alone and in the presence of 100 mg QD eplerenone along with the 90% confidence intervals for the ratios of the means are presented in the following table.

**Table 1: Ratios and 90% Confidence Intervals for Saquinavir Pharmacokinetic Parameters**

| Pharmacokinetic Parameter | Least Squares Means | | Ratio of Means Eplerenone /Placebo | 90% CI for Ratio of Mean | p-Value |
|---|---|---|---|---|---|
| | Eplerenone 100 mg QD + Saquinavir 1200 mg TID | Placebo + Saquinavir 1200 mg TID | | | |
| | N = 24 | N = 24 | | | |
| AUC(0-8) (hr*ng/mL) | 2608.46 | 3311.27 | 0.79 | (0.62 - 1.00) | 0.1030 |
| Cmax (ng/mL) | 750.30 | 1070.88 | 0.70 | (0.55 - 0.89) | 0.0178 |
| Cmin (ng/mL) | 204.64 | 236.97 | 0.86 | (0.62 - 1.20) | 0.4464 |
| CL/F (L/hr) | 460.04 | 362.40 | 1.27 | (1.00 - 1.62) | 0.1030 |
| CL/F/Wt (L/hr/70kg) | 471.88 | 371.72 | 1.27 | (1.00 - 1.62) | 0.1030 |
| Tmax (hr) | 1.96 | 2.33 | -- | -- | 0.0242 |
| T(1/2) (hr) | 9.77 | 9.01 | -- | -- | 0.2259 |

Coadministration of 100 mg QD eplerenone altered the pharmacokinetics of 1200 mg TID saquinavir significantly. Both peak steady-state exposure and total exposure of saquinavir decreased in the presence of eplerenone. Mean Cmax, AUC0-8, Cmin decreased by 30%, 21% and 14%, respectively. The mean apparent oral clearance of saquinavir adjusted for 70 kg body weight increased by 27% upon coadministration with eplerenone. Mean Tmax decreased by approximately 0.5 hour, while, mean saquinavir $T_{1/2}$ increased by approximately 1 hour in the presence of eplerenone.

**Mean Saquinavir Plasma Concentrations**




## *EFFECT OF SAQUINAVIR ON EPLERENONE AND SC-70303 PHARMACOKINETICS*

The following table lists the mean pharmacokinetic parameters of 100 mg QD eplerenone and SC-70303, the open-ring form of eplerenone, when administered alone and in the presence of 1200 mg TID saquinavir along with the 90% confidence intervals of the ratios of the means.

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

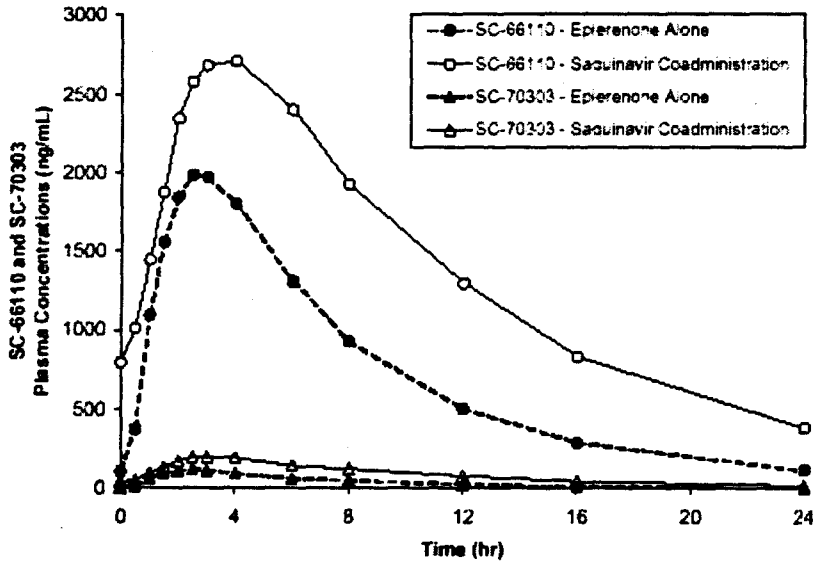
| Pharmacokinetic Parameter | Least Squares Means | | | | Ratio of Means Coadmin./ Eplerenone | 90% CI for Ratio of Mean | P-Value |
|---|---|---|---|---|---|---|---|
| | Eplerenone 100 mg QD + Saquinavir 1200 mg TID | | Eplerenone 100 mg QD | | | | |
| | N | Mean | N | Mean | | | |
| **Eplerenone** | | | | | | | |
| AUC(0-24) (hr*ng/mL) | 23 | 33662.57 | 24 | 16247.96 | 2.07 | (1.90 - 2.26) | 0.0001 |
| Cmax (ng/mL) | 23 | 2994.13 | 24 | 2136.88 | 1.40 | (1.33 - 1.47) | 0.0001 |
| Cmin (ng/mL) | 23 | 720.79 | 24 | 67.89 | 10.62 | (7.80 - 14.4) | 0.0001 |
| CL/F (L/hr) | 23 | 2.97 | 24 | 6.15 | 0.48 | (0.44 - 0.53) | 0.0001 |
| CL/F/Wt (L/hr/70kg) | 23 | 3.05 | 24 | 6.31 | 0.48 | (0.44 - 0.53) | 0.0001 |
| XU(0-24) (mg) | 23 | 6.77 | 24 | 3.32 | 2.04 | (1.83 - 2.28) | 0.0001 |
| Tmax (hr) | 23 | 3.10 | 24 | 2.60 | -- | -- | 0.0097 |
| T1/2 (hr) | 23 | 6.49 | 24 | 4.87 | -- | -- | 0.0001 |
| **SC-70303** | | | | | | | |
| AUC(0-24) (hr*ng/mL) | 23 | 1939.60 | 24 | 755.52 | 2.57 | (2.29 - 2.88) | 0.0001 |
| Cmax (ng/mL) | 23 | 215.60 | 24 | 121.97 | 1.77 | (1.59 - 1.97) | 0.0001 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| XU(0-24) (mg) | 23 | 16.09 | 24 | 8.13 | 1.98 | (1.75 - 2.24) | 0.0001 |
| Tmax (hr) | 23 | 2.90 | 24 | 2.63 | -- | -- | 0.0603 |
| T(1/2) (hr) | 23 | 5.50 | 24 | 4.10 | -- | -- | 0.0001 |

In the presence of saquinavir, mean steady-state Cmax and AUC of eplerenone increased by 40% and 107%, respectively. Mean Cmin increased approximately 11-fold in the presence of saquinavir. Mean apparent oral clearance of eplerenone adjusted for 70 kg body weight decreased by 52% upon coadministration with saquinavir. Mean Tmax increased by approximately 0.5 hour, while, mean eplerenone $T_{1/2}$ increased by approximately 1.5 hour in the presence of saquinavir. The amount of eplerenone excreted in urine increased by 104% in the presence of saquinavir indicating an increase in bioavailability of eplerenone.

In the presence of saquinavir, mean steady-state Cmax and AUC of SC-70303, the open-ring form of eplerenone, increased by 177% and 157%, respectively. Mean Tmax was unchanged, mean SC-70303 $T_{1/2}$ increased by approximately 1.5 hour in the presence of saquinavir. As seen with eplerenone, the amount of SC-70303 excreted in urine increased by 98% in the presence of saquinavir.

**Mean Eplerenone and SC-70303 Plasma Concentrations**




## CONCLUSIONS:

Coadministration of 100 mg QD eplerenone altered the pharmacokinetics of 1200 mg TID saquinavir moderately; mean Cmax, AUC, Cmin of saquinavir decreased by 30%, 21% and 14%, respectively.

Coadministration of saquinavir 1200 mg TID significantly decreased CYP3A4-mediated metabolism of eplerenone. Following coadministration with saquinavir, mean AUC and $C_{max}$ of eplerenone increased by 107% and 40%, respectively, while mean AUC and $C_{max}$ of SC-70303 increased by 157% and 77%, respectively. Saquinavir increased bioavailability of eplerenone by decreasing first-pass metabolism as reflected by the 104% increase in eplerenone excretion in urine in the presence of saquinavir.

**COMMENTS:**

1. The magnitude of increase in eplerenone Cmax and AUC with coadministration of saquinavir should be reported in the label.
2. Eplerenone dose should be reduced to 50 mg QD when coadministered with saquinavir.



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**THE EVALUATION OF THE EFFECT OF EPLERENONE ON THE STEADY-STATE PHARMACOKINETIC PROFILE OF ERYTHROMYCIN IN HEALTHY ADULT SUBJECTS**

**STUDY INVESTIGATORS AND SITE:**

Protocol Number: NE3-00-02-042

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**OBJECTIVES:**

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

**FORMULATIONS:**

Eplerenone – 100 mg tablets (lot number RCT 11569) by Searle.
Erythromycin - Ery-Tab (erythromycin delayed-release) 500 mg tablets by Abbott Lot number 59427AF21

**STUDY DESIGN:**

This was an open-label, randomized, multiple-dose, six-sequence, three-period and three-treatment crossover design study conducted in 24 healthy adult subjects, 18 M/6 F, age range: 21-44 years. All subjects were randomized to sequences presented in the following table:

| Treatment Sequence | Period | | |
|---|---|---|---|
| | 1 (Days 1-7) | 2 (Days 9-15) | 3 (Days 17-23) |
| I | A | B | C |
| II | B | C | A |
| III | C | A | B |
| IV | A | C | B |
| V | B | A | C |
| VI | C | B | A |

A = Eplerenone 100 mg QD
B = Erythromycin 500 mg BID
C = Erythromycin 500 mg BID + Eplerenone 100 mg QD

Subjects were randomized to **Treatment A:** received 100 mg QD eplerenone alone for 7 consecutive days, **Treatment B**: 500 mg BID erythromycin 7 consecutive days and **Treatment C:** 500 mg BID erythromycin + 100 mg QD eplerenone 7 consecutive days.

On Days 1-6, 9-14, and 17-22, subjects were administered their eplerenone and/or erythromycin doses in the morning within 30 minutes after breakfast. On the same study days, subjects randomized to treatments B or C were administered an additional dose of erythromycin 12 hours later, without regard to meals. On study Days 7, 15 and 23, subjects received the morning dose following an overnight fast. On the same study days, subjects randomized to treatments B or C were administered an additional dose of erythromycin 12 hours later, without regard to meals. All meals were standard low-fat diet.

**ASSAY:**

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Sample Collection

Blood samples for plasma erythromycin, eplerenone, SC-71597 and SC-70303 were drawn on Days 1, 4-6, 12-14, 20-22 at predose for trough concentration measurements. Relative to dosing on Days 7, 15 and 23, blood samples were drawn at predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 14, 16, 20, 24, 36 and 48 hours postdose.

**RESULTS:**

Erythromycin, a broad-spectrum macrolide antibiotic, is a substrate and a potent inhibitor of, CYP3A4. Eplerenone (SC-66110) is a substrate of CYP3A4, therefore this study was designed to assess the impact of coadministration of the pharmacokinetic parameters of eplerenone and erythromycin.

***Effect of Eplerenone on Erythromycin Pharmacokinetics***

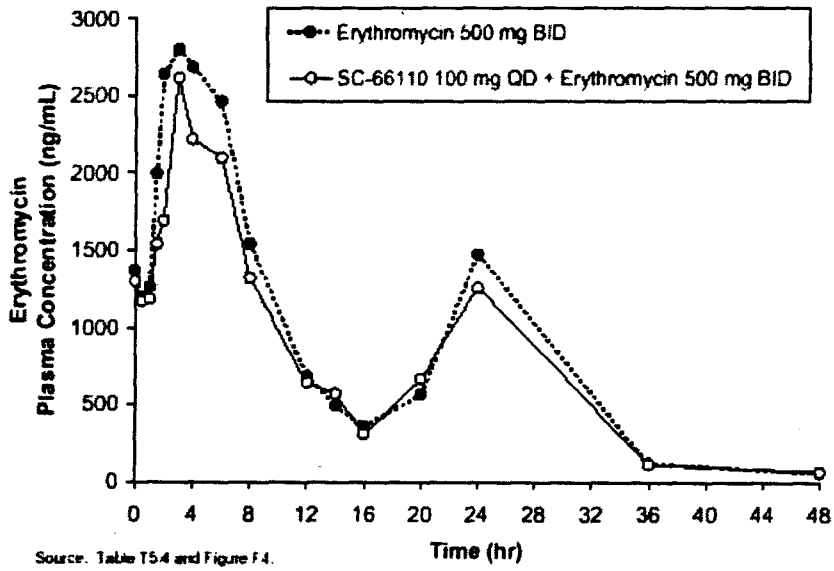
Steady-state pharmacokinetic parameters of 500-mg BID erythromycin when administered alone and with 100 mg QD eplerenone are listed in the following table.

**Table 1: Ratios and 90% Confidence Intervals for Saquinavir Pharmacokinetic Parameters**

| Pharmacokinetic Parameter | Erythromycin 500 mg BID | | | Eplerenone 100 mg QD + Erythromycin 500 mg BID | | |
|---|---|---|---|---|---|---|
| | N | Mean | (%CV) | N | Mean | (%CV) |
| **Erythromycin** | | | | | | |
| AUC(0-12) (hr*ng/mL) | 23 | 22304.93 | ( 45%) | 23 | 18725.17 | ( 43%) |
| Cmax (ng/mL) | 24 | 3469.17 | ( 49%) | 24 | 2942.50 | ( 67%) |
| Tmax (hr) | 24 | 3.75 | ( 47%) | 24 | 4.39 | ( 53%) |
| Cmin (ng/mL) | 23 | 1366.05 | ( 98%) | 23 | 1300.10 | ( 68%) |
| CL/F (L/hr) | 23 | 28.79 | ( 66%) | 23 | 32.07 | ( 45%) |
| CL/F/WT (L/hr/70kg) | 23 | 26.73 | ( 55%) | 23 | 30.42 | ( 44%) |

Coadministration of eplerenone decreased steady-state erythromycin Cmax and AUC by 20% and 15%, respectively. Mean erythromycin apparent oral clearance adjusted for 70 kg body weight increased by 18% in the presence of eplerenone.

**Mean Erythromycin Plasma Concentrations**




Source: Table T5.4 and Figure F4.

**Table 2: Ratios and 90% Confidence Intervals for Erythromycin Pharmacokinetic Parameters**

| Pharmacokinetic Parameter | Least Squares Means | | | | Ratio Coadmin./ Erythromycin | 90% Confidence Interval | p-value |
|---|---|---|---|---|---|---|---|
| | Eplerenone 100 mg QD + Erythromycin 500 mg BID | | Erythromycin 500 mg BID | | | | |
| | N | LS Mean | N | LS Mean | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| AUC(0-12) (hr*ng/mL) | 23 | 17064.586 | 23 | 20048.308 | 0.851 | (0.762, 0.951) | 0.021 |
| Cmax (ng/mL) | 24 | 2501.190 | 24 | 3113.616 | 0.803 | (0.716, 0.902) | 0.004 |
| CL/F (L/hr) | 23 | 29.300 | 23 | 24.940 | 1.175 | (1.051, 1.313) | 0.021 |
| CL/F/WT (L/hr/70kg) | 23 | 28.162 | 23 | 23.971 | 1.175 | (1.051, 1.313) | 0.021 |
| Tmax (hr) | 24 | 4.385 | 24 | 3.750 | -- | -- | 0.178 |

***Effect of Erythromycin on Eplerenone Pharmacokinetics***

Steady-state pharmacokinetic parameters of eplerenone, SC-70303 and SC-71597 when administered as 100 mg eplerenone alone and with 500 mg BID erythromycin are listed in the following table.

**Table 3: Arithmetic Mean (%CV) Eplerenone, SC-70303 and SC-71597 Pharmacokinetic Parameters**

| Pharmacokinetic Parameter | Eplerenone 100 mg QD | | | Eplerenone 100 mg QD + Erythromycin 500 mg BID | | |
|---|---|---|---|---|---|---|
| | N | Mean | (%CV) | N | Mean | (%CV) |
| **EPLERENONE** | | | | | | |
| AUC(0-24) (hr*ng/mL) | 24 | 9161.61 | ( 50%) | 24 | 24800.15 | ( 28%) |
| Cmax (ng/mL) | 24 | 1543.00 | ( 32%) | 24 | 2483.12 | ( 30%) |
| Tmax (hr) | 24 | 1.96 | ( 44%) | 24 | 1.61 | ( 38%) |
| Cmin (ng/mL) | 24 | 31.15 | (136%) | 24 | 325.63 | ( 49%) |
| T(1/2) (hr) | 23 | 4.40 | ( 49%) | 24 | 6.63 | ( 18%) |
| CL/F (L/hr) | 24 | 13.03 | ( 40%) | 24 | 4.35 | ( 29%) |
| CL/F/WT (L/hr/70kg) | 24 | 12.68 | ( 44%) | 24 | 4.17 | ( 29%) |
| XU(0-24) (µg) | 24 | 1616.82 | ( 65%) | 24 | 5193.35 | ( 69%) |
| **SC-70303** | | | | | | |
| AUC(0-24) (hr*ng/mL) | 24 | 425.67 | ( 39%) | 24 | 1681.74 | ( 27%) |
| Cmax (ng/mL) | 24 | 90.35 | ( 38%) | 24 | 178.44 | ( 29%) |
| Tmax (hr) | 24 | 1.63 | ( 54%) | 24 | 1.52 | ( 50%) |
| Cmin (ng/mL) | 24 | 0.00 | ( NAP) | 24 | 17.35 | ( 51%) |
| T(1/2) (hr) | 23 | 3.25 | ( 24%) | 23 | 7.17 | ( 28%) |
| XU(0-24) (:g) | 24 | 5007.74 | ( 38%) | 24 | 17225.93 | ( 34%) |
| **SC-71597** | | | | | | |
| AUC(0-24) (hr*ng/mL) | 24 | 5237.13 | ( 32%) | 24 | 5647.03 | ( 31%) |
| Cmax (ng/mL) | 24 | 579.80 | ( 25%) | 24 | 375.88 | ( 33%) |
| Tmax (hr) | 24 | 3.17 | ( 39%) | 24 | 2.89 | ( 78%) |
| Cmin (ng/mL) | 24 | 39.85 | ( 85%) | 24 | 136.23 | ( 27%) |
| T(1/2) (hr) | 24 | 5.02 | ( 27%) | 24 | 8.68 | ( 19%) |
| XU(0-24) (µg) | 24 | 22804.41 | ( 22%) | 23 | 22406.57 | ( 21%) |

Coadministration of 500 mg BID erythromycin significantly altered the pharmacokinetics of 100 mg QD eplerenone. Mean eplerenone $AUC_{0-24}$ increased by 187% and eplerenone Cmax increased by 61% indicating reduced metabolism of eplerenone. Eplerenone apparent oral clearance adjusted for 70 kg body weight decreased by 66% in the presence of erythromycin. Mean $T_{1/2}$ of eplerenone increased by approximately 2 hours in the presence of erythromycin indicating decreased rate of elimination of eplerenone. Urinary excretion of unchanged eplerenone increased by 234% in the presence of erythromycin

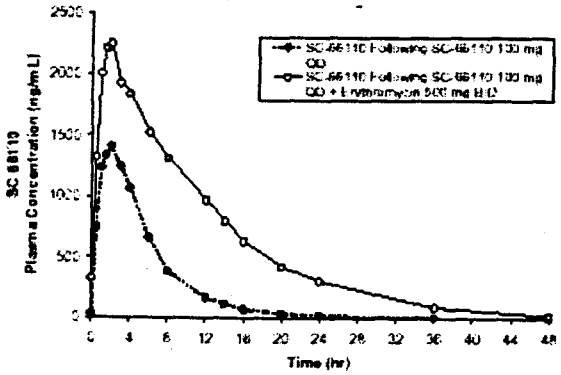
indicating increased bioavailability of eplerenone. Administration of eplerenone alone was better tolerated than following coadministration with erythromycin.

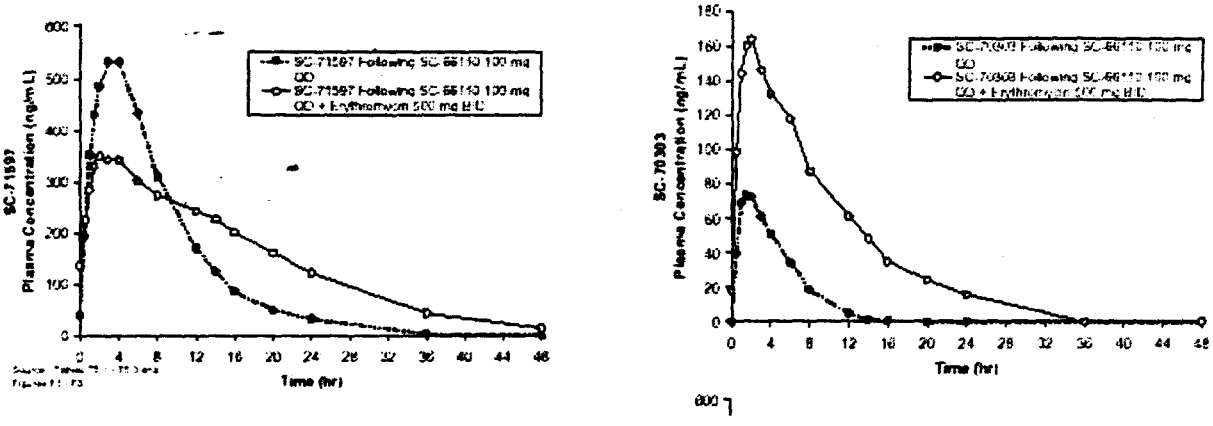
Following coadministration with erythromycin, a larger increase in peak exposure and total exposure was observed with SC-70303, open-ring form of eplerenone, compared to eplerenone. Mean SC-70303 $AUC_{0-24}$ increased 4-fold and Cmax increased 2-fold in the presence of erythromycin. Mean $T_{1/2}$ of SC-70303 increased by 4 hours, however, it is not known if this increase is a result of decreased rate of elimination of SC-70303 or slower rate of formation of SC-70303. Urinary excretion of SC-70303 increased by 354% in the presence of erythromycin.

**Table 4: Ratios and 90% Confidence Intervals for Eplerenone, SC-70303 and SC-71597 Pharmacokinetic Parameters**

| Pharmacokinetic Parameter | Least Squares Means | | Ratio Coadmin./ Eplerenone | 90% Confidence Interval | p-value |
|---|---|---|---|---|---|
| | Eplerenone 100 mg + Erythromycin 500 mg BID | Eplerenone 100 mg Alone | | | |
| | N = 24 | N = 24 | | | |
| **EPLERENONE** | | | | | |
| AUC(0-24) (hr*ng/mL) | 23874.111 | 8333.270 | 2.865 | (2.558, 3.209) | <0.001 |
| Cmax (ng/mL) | 2382.460 | 1479.522 | 1.610 | (1.462, 1.774) | <0.001 |
| CL/F (L/hr) | 4.189 | 12.000 | 0.349 | (0.312, 0.391) | <0.001 |
| CL/F/WT (L/hr/70kg) | 4.002 | 11.465 | 0.349 | (0.312, 0.391) | <0.001 |
| XU(0-24) (µg) | 4361.123 | 1306.747 | 3.337 | (2.797, 3.982) | <0.001 |
| Tmax (hr) | 1.610 | 1.960 | -- | -- | 0.082 |
| T(1/2) (hr) | 6.625 | 4.417 | -- | -- | <0.001 |
| **SC-70303** | | | | | |
| AUC(0-24) (hr*ng/mL) | 1617.980 | 395.920 | 4.087 | (3.525, 4.737) | <0.001 |
| Cmax (ng/mL) | 171.315 | 85.063 | 2.014 | (1.782, 2.276) | <0.001 |
| XU(0-24) (µg) | 16361.546 | 4613.916 | 3.546 | (3.106, 4.049) | <0.001 |
| Tmax (hr) | 1.524 | 1.627 | -- | -- | 0.641 |
| T(1/2) (hr) | 7.121 | 3.165 | -- | -- | <0.001 |
| **SC-71597** | | | | | |
| AUC(0-24) (hr*ng/mL) | 5392.788 | 5048.689 | 1.068 | (0.979, 1.165) | 0.206 |
| Cmax (ng/mL) | 355.598 | 563.998 | 0.630 | (0.570, 0.697) | <0.001 |
| XU(0-24) (µg) | 23685.521 | 22112.581 | 1.071 | (0.982, 1.168) | 0.186 |
| Tmax (hr) | 2.888 | 3.167 | -- | -- | 0.592 |
| T(1/2) (hr) | 8.677 | 5.017 | -- | -- | <0.001 |

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





Following coadministration with erythromycin, peak exposure (Cmax) of SC-7197 decreased by 37% while there was no change in total exposure or urinary excretion of SC-71597. Mean $T_{1/2}$ of SC-71597 increased by approximately 4 hours in the presence of erythromycin. It is not know if the increased T1/2 is due to decreased rate of elimination of SC-71597 or if the increase reflects a change in some other process. The magnitude of increase in T1/2 is similar to that seen with SC-70303.

***Effect of Erythromycin and Eplerenone Alone and in Combination on ECG Parameters***

Erythromycin when administered alone or in combination with eplerenone did not affect heart rate. Interestingly, in contrast with previous studies, no observable increase in heart rate was noted when eplerenone was administered alone. Erythromycin and eplerenone had no effect on the length of the PR and QRS intervals. When corrected for heart rate using either the Fridericia or Bazett method, the mean changes in QTc interval length indicated that neither erythromycin nor eplerenone had an effect. No subject had a QTc interval duration over 500 msec or a change from Baseline of equal to or greater than 60 msec. Using Fridericia's correction, a change from Baseline in QTc between 31 msec and 60 msec was noted in 1 subject while on eplerenone and in 2 subjects while on erythromycin, while no subject had a change in QTc interval between 31 msec to 60 msec when erythromycin and eplerenone were coadministered.

**Table 5: Mean (± SEM) Change From Baseline in ECG Parameters**

| Parameter | Erythromycin 500 mg BID Mean ± SEM | Eplerenone 100 mg QD Mean ± SEM | Erythromycin 500 mg BID + Eplerenone 100 mg QD Mean ± SEM | P-Value[a] |
|---|---|---|---|---|
| | N = 24 | N = 24 | N = 24 | |
| HR (bpm) | -1.52 ± 2.22 | -3.55 ± 1.69 [b] | 0.44 ± 1.90 | 0.0117 |
| PR (msec) | 1.47 ± 2.92 | 2.91 ± 3.03 | 2.88 ± 3.41 | NS |
| QRS (msec) | 1.53 ± 1.21 | 1.09 ±1.08 | 0.04 ± 1.45 | NS |
| QT (msec) | 2.05 ± 4.45 | 4.28 ± 3.10 | -3.31 ± 3.79 | 0.0257 |
| QTc[c] (msec) | -1.35 ± 2.53 | -3.02 ± 2.71 | -3.40 ± 2.55 | NS |
| QTc[d] (msec) | -2.97 ± 3.54 | -6.54 ± 3.77 | -3.28 ± 3.49 | NS |

| | | | | |
|---|---|---|---|---|
| MaxQTc[c] (msec) | 9.58 ± 3.00 [b] | 8.33 ± 3.44 [b] | 5.00 ± 2.73 | NS |
| MaxQTc[d] (msec) | 12.88 ± 3.82 [b] | 9.38 ± 4.13 [b] | 8.71 ± 3.73 | NS |

a – P-values < 0.05 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
NS – not statistically significant across treatments

## CONCLUSIONS:

Coadministration of 500 mg BID erythromycin significantly altered the pharmacokinetics of 100 mg QD eplerenone. Mean eplerenone $AUC_{0-24}$ increased by 187% and eplerenone Cmax increased by 61% indicating reduced metabolism of eplerenone. Eplerenone apparent oral clearance adjusted for 70 kg body weight decreased by 66% in the presence of erythromycin. Mean $T_{1/2}$ of eplerenone increased by approximately 2 hours in the presence of erythromycin indicating decreased rate of elimination of eplerenone. Urinary excretion of unchanged eplerenone increased by 234% in the presence of erythromycin indicating increased bioavailability of eplerenone. Administration of eplerenone alone was better tolerated than following coadministration with erythromycin.

Coadministration of eplerenone decreased steady-state erythromycin Cmax and AUC by 20% and 15%, respectively. Mean erythromycin apparent oral clearance adjusted for 70 kg body weight increased by 18% in the presence of eplerenone.

Erythromycin and eplerenone when administered alone or in combination with eplerenone did not affect hear rate, PR and QRS intervals. When corrected for heart rate using either the Fridericia or Bazett method, the mean changes in QTc interval length indicated that neither erythromycin nor eplerenone had an effect. No subject had a QTc interval duration over 500 msec or a change from Baseline of equal to or greater than 60 msec. Using Fridericia's correction, a change from Baseline in QTc between 31 msec and 60 msec was noted in 1 subject while on eplerenone and in 2 subjects while on erythromycin, while no subject had a change in QTc interval between 31 msec to 60 msec when erythromycin and eplereone were coadministered.

## COMMENTS:

1. The label should describe the increase in eplerenone peak and total exposure in the presence of erythromycin.
2. Eplerenone dose should be reduced to 50 mg QD when coadministered with erythromycin.

**THE EFFECT OF EPLERENONE ON THE PHARMACOKINETIC PROFILE OF ORAL CONTRACEPTIVES IN HEALTHY FEMALE SUBJECTS**

**STUDY INVESTIGATORS AND SITE:**

Protocol Number: NE3-00-02-044

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**OBJECTIVES:**

1. To examine the effect of multiple-dose eplerenone on the steady state pharmacokinetic profile of an oral contraceptive, norethindrone/ethinyl estradiol (Ortho-Novum 1/35®-28 day Regimen) in healthy adult female subjects.
2. To evaluate the safety and tolerability of coadministration of multiple-dose eplerenone with norethindrone/ethinyl estradiol (Ortho-Novum 1/35®-28-day Regimen).

**FORMULATIONS:**

Eplerenone – 100 mg tablets (lot number RCT 11408) by Searle.
Ortho-Novum 1/35®-28-day Regimen packages, Ortho-McNeil Pharmaceuticals, Lot number 29N215.

**STUDY DESIGN:**

This was a single-blind, multiple-dose, two-period study conducted in 24 nonsmoking, non-pregnant, healthy adult, female subjects, age range: 18-33 years with mean body weight of 66 kg. The following treatments were utilized in this study: **Treatment A** = Norethindrone/Ethinyl Estradiol (Ortho-Novum 1/35®-28-day Regimen) taken daily with eplerenone placebo QD for 28 days during Period 1. **Treatment B** = Norethindrone/Ethinyl Estradiol (Ortho-Novum 1/35®-28-day Regimen) taken daily with 100 mg QD eplerenone for 11 days during Period 2.

**ASSAY:**

C