This reviewer noticed that the efficacy of the active treatments tended to be slightly better in the middle age group 35-44 years; however, the evidence was not strong. Similarly, the efficacy of Paxil CR tended to be slightly less in patients with Duration of Current Depressive Illness between 6 and 12 months.

In Study 487, there was a statistically significant interaction, treatment by the duration of current episode of depression, at Week 12 OC ($p=0.003$) but not at Week 12 LOCF ($p=0.2$). The sponsor stated, "... at week 12 OC there is a trend for placebo patients with long term depression to show a lower response to treatment than placebo patients with current episodes of depression which began relatively recently. In contrast, ... paroxetine CR patients with current episodes of depression of less than 6 months or greater than 2 years seem to respond less well than other groups of patients ..., notably the 13 to 18 month group."

This reviewer noted in relation to the former paragraph that in the ≤6 months group placebo (n=10) did better than Paxil CR (26 patients).

## IV. Overall Conclusion

The studies in this NDA have provided statistical evidence in favor of the efficacy of Paxil CR.

/S/ 6-2-98

Japobrata Choudhury, Ph.D.
Mathematical Statistician

Concur: Dr. Jin /S/ 6/16/98

Dr. Chi /S/ 6/18/98

CC:
Archival NDA 20-936

HFD-120/Dr. Leber
HFD-120/Dr. Laughren
HFD-120/Dr. Dubitsky
HFD-120/Mr. Purvis
HFD-120/Mr. David

HFD-344/Dr. Barton
HFD-710/Dr. Chi
HFD-710/Dr. Jin
HFD-710/Dr. Choudhury
HFD-710/Chron
J.Choudhury:x45582:DB I: 02-06-98

This review consists of 15 pages of text and 44 pages of Tables, Figures, etc.

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Table 0.1.1

## Table of Investigations

## Completed Controlled Release Paroxetine Clinical Trials Evaluating Depression

| Protocol No./ Country/ Centers/ Publications | Study Status | Study Design | Dosage Form Formulation Batch/Lot No. | Regimens[d], [e] (ITT Patients/Regimen) | Mean Age, Range (years) | Gender: M/F[b] Race: W/NonW[a] | Dosing Duration | Volume/Page for Full Report, CRTs, CRFs and Narratives[c] |
|---|---|---|---|---|---|---|---|---|
| 29060/448/ US/20 /None | Completed Final Report: 20 Oct '97 | Double-Blind Placebo-Controlled Flexible dose Trial with 1-week single-blind placebo run-in | Paroxetine-CR tablet (Crawley): U96179 (12.5 mg); U96146 (25 mg). Paroxetine IR tablet: U96038 (10 mg), U96059 (20 mg). All tablets were overencapsulated. | Paroxetine CR 25-62.5mg once daily (104)<br>Paroxetine IR 20-50 mg once daily (105)<br>Placebo (101) | 39.0<br>39.4<br>38.7<br>18-64 | 42M/62F;95W/ 9NonW<br>38M/67F;94W/11 NonW<br>34M/67F;86W/15 NonW | 12 weeks (daily dosing) | 1.026/000002 |
| 29060/449/ US /Canada/20 /None | Completed Final Report: 10 Oct '97 | Double-Blind Placebo-Controlled Flexible dose Trial with 1-week single-blind placebo run-in | Paroxetine-CR tablet (Crawley): U96179 (12.5 mg); U96146 (25 mg). Paroxetine IR tablet: U96038 (10 mg), U96059 (20 mg). All tablets were overencapsulated. | Paroxetine CR 25-62.5mg once daily (108)<br>Paroxetine IR 20-50 mg once daily (112)<br>Placebo (110) | 42.4<br>40.6<br>40.7<br>18-71 | 36M/72F;92W/16 NonW<br>29M/83F;94W/18 NonW<br>44M/66F;94W/16 NonW | 12 weeks (daily dosing) | 1.032/000002 |

[a] W = White, NonW = Nonwhite [b] M = Male, F= Female ; [c] CRT = Case Report Tabulation, CRF = Case Report Form; [d] CR -Controlled-release, IR-Immediate Release; [f] B = Black, W = White, O = Other; [g]EM-extensive metabolizer (an individual possessing CYP2D6), PM - poor metabolizer (an individual lacking CYP2D6)

• CRTs are located in ppcrt.pdf, CRFs are located in CRFTOC.PDF, narratives are listed in volume 1.039 pp.214-218

0.2.1a

## Table Number of Patients Exposed to Each Daily Dose of Study Drug by Visit

| | Paroxetine CR | | | | Paroxetine IR | | | | Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Dose Level | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 |
| Dose, mg/d | 25 | 37.5 | 50 | 62.5 | 20 | 30 | 40 | 50 | 0 | 0 | 0 | 0 |
| **Study 449** | | | | | | | | | | | | |
| | N=108 | | | | N=112 | | | | N=110 | | | |
| Week 1 | 64 | 44 | 0 | 0 | 68 | 44 | 0 | 0 | 55 | 55 | 0 | 0 |
| Week 2 | 33 | 45 | 26 | 0 | 33 | 42 | 27 | 0 | 24 | 41 | 39 | 0 |
| Week 3 | 25 | 26 | 41 | 11 | 24 | 32 | 29 | 14 | 16 | 32 | 31 | 23 |
| Week 4 | 20 | 22 | 24 | 31 | 21 | 24 | 27 | 24 | 14 | 22 | 24 | 37 |
| Week 6 | 18 | 20 | 20 | 36 | 16 | 23 | 21 | 30 | 11 | 19 | 17 | 47 |
| Week 8 | 17 | 20 | 19 | 33 | 14 | 23 | 20 | 27 | 11 | 13 | 15 | 50 |
| Week 12 | 18 | 16 | 23 | 26 | 14 | 19 | 18 | 25 | 11 | 14 | 13 | 43 |
| Week 12 Endpoint | 24 | 23 | 26 | 35 | 27 | 31 | 22 | 32 | 17 | 25 | 17 | 51 |
| **Study 448** | | | | | | | | | | | | |
| | N=104 | | | | N=105 | | | | N=101 | | | |
| Week 1 | 40 | 64 | 0 | 0 | 44 | 61 | 0 | 0 | 26 | 75 | 0 | 0 |
| Week 2 | 17 | 48 | 28 | 0 | 19 | 38 | 35 | 0 | 8 | 42 | 51 | 0 |
| Week 3 | 7 | 35 | 30 | 18 | 15 | 24 | 31 | 21 | 2 | 30 | 30 | 35 |
| Week 4 | 8 | 21 | 29 | 28 | 12 | 16 | 31 | 27 | 3 | 18 | 23 | 50 |
| Week 6 | 6 | 19 | 26 | 33 | 11 | 11 | 31 | 27 | 5 | 13 | 19 | 54 |
| Week 8 | 7 | 18 | 23 | 33 | 8 | 11 | 29 | 24 | 4 | 11 | 18 | 53 |
| Week 12 | 6 | 18 | 20 | 29 | 8 | 12 | 29 | 22 | 4 | 11 | 16 | 47 |
| Week 12 Endpoint | 21 | 23 | 26 | 34 | 22 | 17 | 37 | 29 | 7 | 16 | 23 | 55 |

Source: PAR-449 Data Source Table 13.11.1 and PAR-448 Data Source Table 13.11.1

0.2.1b

## Table Mean and Median Daily Dose of Active Medication by Week

| | Week | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | | 2 | | 3 | | 4 | | 6 | | 8 | | 12 | |
| | mg/day | | mg/day | | mg/day | | mg/day | | mg/day | | mg/day | | mg/day | |
| | Mn | Md | Mn | Md | Mn | Md | Mn | Md | Mn | Md | Mn | Md | Mn | Md |
| Study 449 | | | | | | | | | | | | | | |
| CR Paroxetine | 25.1 | 25 | 30.5 | 25 | 36.9 | 37.5 | 41.8 | 37.5 | 45.6 | 50 | 47.0 | 50 | 46.6 | 50 |
| IR Paroxetine | 20.0 | 20 | 24.4 | 20 | 30.2 | 30 | 33.7 | 30 | 35.2 | 40 | 36.5 | 40 | 37.0 | 40 |
| Study 448 | | | | | | | | | | | | | | |
| CR Paroxetine | 25.0 | 25 | 33.6 | 37.5 | 39.4 | 37.5 | 46.2 | 50 | 48.1 | 50 | 49.5 | 50 | 50.0 | 50 |
| IR Paroxetine | 20.0 | 20 | 27.0 | 30 | 31.6 | 30 | 36.6 | 40 | 38.0 | 40 | 38.6 | 40 | 39.5 | 40 |

Mn = Mean, Md = Median
Data Source: ISE Data Source Tables: 14.90.3b and 14.91.3b

1.1.1

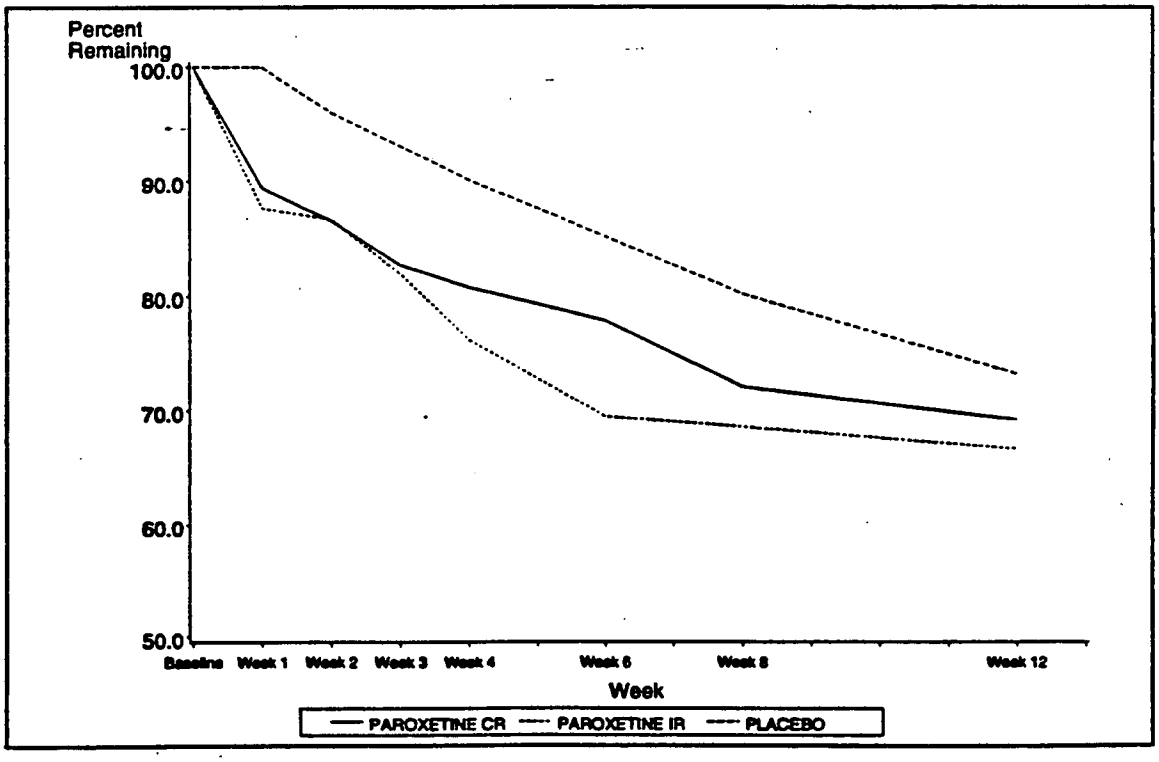
**Table Number of Patients Remaining at Each Visit for PAR-448**

| Study Phase | Paroxetine CR | | Paroxetine IR | | Placebo | | Total | |
|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % |
| Baseline | 104 | 100.0 | 105 | 100.0 | 101 | 100.0 | 310 | 100.0 |
| Week 1 | 93 | 89.4 | 92 | 87.6 | 101 | 100.0 | 286 | 92.3 |
| Week 2 | 90 | 86.5 | 91 | 86.7 | 97 | 96.0 | 278 | 89.7 |
| Week 3 | 86 | 82.7 | 86 | 81.9 | 94 | 93.1 | 266 | 85.8 |
| Week 4 | 84 | 80.8 | 80 | 76.2 | 91 | 90.1 | 255 | 82.3 |
| Week 6 | 81 | 77.9 | 73 | 69.5 | 86 | 85.1 | 240 | 77.4 |
| Week 8 | 75 | 72.1 | 72 | 68.6 | 81 | 80.2 | 228 | 73.5 |
| Week 12 | 72 | 69.2 | 70 | 66.7 | 74 | 73.3 | 216 | 69.7 |

Data Source: PAR-448, Data Source Table 13.3.2b
Patients 448.010.00494 and 448.021.00280 discontinued due to AE during treatment phase and were not included in Data Source Table 13.3.2b. See Errata Section 11 in Study 448 report.

1.1.1.

**Figure Percentage of Patients Remaining in Study 448 by Week**




Data Source: PAR-448 Data Source Table 13.3.2b.

Table 1.3.1(a)

Baseline and Change from Baseline in HAMD Total Score
Adjusting for the Effect of Centre Group Only
Statistical Analysis Presented at All Time Points
Intention to Treat Population

| | Treatment Groups | | | | | | | | Pairwise Comparisons | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Paroxetine CR | | | Paroxetine IR | | | Placebo | | | Paroxetine CR vs Placebo | | | Paroxetine IR vs Placebo | | |
| | Mean | (s.e.) | N | Mean | (s.e.) | N | Mean | (s.e.) | N | Mean | (95% C.I.) | p-value | Mean | (95% C.I.) | p-value |
| seline | 23.0 | (0.26) | 102 | 23.3 | (0.28) | 104 | 23.4 | (0.29) | 101 | | | | | | |
| ek 1 | -3.5 | (0.38) | 100 | -3.2 | (0.38) | 103 | -2.9 | (0.38) | 100 | -0.6 | ( -1.67, 0.45) | 0.256 | -0.3 | ( -1.37, 0.73) | 0.552 |
| ek 2 | -7.4 | (0.52) | 88 | -6.5 | (0.53) | 84 | -5.9 | (0.50) | 96 | -1.6 | ( -2.97, -0.16) | 0.029 | -0.7 | ( -2.08, 0.77) | 0.368 |
| ek 3 | -9.6 | (0.63) | 87 | -8.0 | (0.63) | 87 | -7.4 | (0.62) | 91 | -2.2 | ( -3.96, -0.49) | 0.012 | -0.6 | ( -2.32, 1.16) | 0.514 |
| ek 4 | -11.4 | (0.70) | 86 | -10.1 | (0.71) | 83 | -9.6 | (0.67) | 93 | -1.8 | ( -3.73, 0.07) | 0.059 | -0.6 | ( -2.50, 1.35) | 0.557 |
| ek 6 | -12.5 | (0.71) | 78 | -11.9 | (0.71) | 78 | -9.1 | (0.67) | 87 | -3.4 | ( -5.28, -1.42) | <0.001 | -2.8 | ( -4.68, -0.83) | 0.005 |
| ek 8 | -14.0 | (0.69) | 80 | -13.9 | (0.74) | 70 | -11.2 | (0.69) | 79 | -2.8 | ( -4.72, -0.86) | 0.005 | -2.7 | ( -4.67, -0.67) | 0.009 |
| ek 12 | -15.2 | (0.85) | 66 | -14.6 | (0.92) | 57 | -11.5 | (0.85) | 67 | -3.7 | ( -6.07, -1.32) | 0.002 | -3.1 | ( -5.56, -0.63) | 0.014 |
| End Point | -11.0 | (0.68) | 102 | -9.6 | (0.68) | 104 | -8.8 | (0.69) | 101 | -2.3 | ( -4.19, -0.39) | 0.018 | -0.9 | ( -2.74, 1.03) | 0.374 |
| 12 End Point | -12.6 | (0.78) | 102 | -11.2 | (0.78) | 104 | -9.9 | (0.79) | 101 | -2.7 | ( -4.89, -0.54) | 0.015 | -1.3 | ( -3.48, 0.85) | 0.233 |

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Note: Only patients with a baseline and at least one post baseline assessment

DISK$STATS4:[STATS_GROUP.SBBRL29060.448.CODE]LT14_1_NEW.SAS (25AUG97 15:12)

Table 1.3.1(b)

Baseline and Change from Baseline in HAMD Total Score
Excluding Centre Group 002/004
Adjusting for the Effect of Centre Group Only
Statistical Analysis Presented at All Time Points
Intention to Treat Population

| | Treatment Groups | | | | | | Pairwise Comparisons | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Paroxetine CR | | | Paroxetine IR | | | Placebo | | | Paroxetine CR vs Placebo | | | Paroxetine IR vs Placebo | | |
| | Mean | (s.e.) | N | Mean | (s.e.) | N | Mean | (s.e.) | N | Mean (95% C.I.) | p-value | | Mean (95% C.I.) | p-value | |
| seline | 22.9 | (0.26) | 94 | 23.3 | (0.28) | 96 | 23.2 | (0.29) | 93 | | | | | | |
| ek 1 | -3.7 | (0.41) | 92 | -3.5 | (0.41) | 95 | -3.0 | (0.41) | 92 | -0.6 ( -1.75, 0.53) | 0.292 | | -0.4 ( -1.56, 0.70) | 0.454 | |
| ek 2 | -7.2 | (0.55) | 80 | -6.6 | (0.55) | 77 | -6.2 | (0.52) | 89 | -1.0 ( -2.51, 0.43) | 0.165 | | -0.4 ( -1.86, 1.11) | 0.622 | |
| ek 3 | -9.3 | (0.66) | 79 | -7.6 | (0.66) | 79 | -7.7 | (0.64) | 84 | -1.6 ( -3.43, 0.18) | 0.078 | | 0.1 ( -1.69, 1.94) | 0.890 | |
| ek 4 | -11.0 | (0.73) | 78 | -9.7 | (0.75) | 75 | -9.7 | (0.69) | 86 | -1.3 ( -3.26, 0.70) | 0.205 | | 0.0 ( -1.98, 2.03) | 0.978 | |
| ek 6 | -11.9 | (0.72) | 71 | -11.5 | (0.73) | 70 | -9.4 | (0.68) | 79 | -2.6 ( -4.52, -0.60) | 0.011 | | -2.2 ( -4.12, -0.19) | 0.032 | |
| ek 8 | -13.5 | (0.71) | 72 | -13.6 | (0.76) | 62 | -11.5 | (0.69) | 74 | -2.0 ( -3.99, -0.10) | 0.040 | | -2.1 ( -4.12, -0.06) | 0.043 | |
| ek 12 | -14.5 | (0.84) | 58 | -14.4 | (0.91) | 50 | -12.5 | (0.82) | 61 | -2.0 ( -4.29, 0.38) | 0.100 | | -1.9 ( -4.29, 0.57) | 0.132 | |
| % End Point | -10.5 | (0.70) | 94 | -9.1 | (0.69) | 96 | -8.9 | (0.70) | 93 | -1.6 ( -3.54, 0.35) | 0.107 | | -0.2 ( -2.13, 1.73) | 0.838 | |
| k 12 End Point | -12.0 | (0.79) | 94 | -10.7 | (0.79) | 96 | -10.6 | (0.80) | 93 | -1.4 ( -3.62, 0.80) | 0.210 | | -0.2 ( -2.37, 2.02) | 0.874 | |





Note: Only patients with a baseline and at least one post baseline assessment

DISK$STATS4:[STATS_GROUP.SBBRL29060.448.CODE]LT14_1W_NEW.SAS (25AUG97 15:12)

Table 1.3.1 (a)

Baseline and Change from Baseline in HAMD Total Score
Adjusting for the Effect of Centre Group, Age, Sex, Baseline HAMD Total Score and Duration of Current Episode of Depression
Statistical Analysis Presented at all Time Points
Intention to Treat Population

| | Treatment Groups | | | | | | Pairwise Comparisons | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Paroxetine CR | | | Paroxetine IR | | | Placebo | | | Paroxetine CR vs Placebo | | | Paroxetine IR vs Placebo | | |
| | Mean | (s.e.) | N | Mean | (s.e.) | N | Mean | (s.e.) | N | Mean | (95% C.I.) | p-value | Mean | (95% C.I.) | p-value |
| eline | 23.0 | (0.26) | 102 | 23.3 | (0.28) | 104 | 23.4 | (0.29) | 101 | | | | | | |
| k 1 | -3.7 | (0.38) | 100 | -3.3 | (0.39) | 103 | -3.0 | (0.39) | 100 | -0.7 | ( -1.71, 0.38) | 0.212 | -0.3 | ( -1.38, 0.72) | 0.536 |
| k 2 | -7.5 | (0.52) | 88 | -6.5 | (0.54) | 84 | -5.9 | (0.50) | 96 | -1.6 | ( -3.02, -0.23) | 0.022 | -0.6 | ( -1.99, 0.86) | 0.434 |
| k 3 | -9.8 | (0.62) | 87 | -7.8 | (0.64) | 87 | -7.4 | (0.61) | 91 | -2.4 | ( -4.13, -0.76) | 0.005 | -0.4 | ( -2.13, 1.28) | 0.622 |
| k 4 | -11.4 | (0.70) | 86 | -9.8 | (0.73) | 83 | -9.5 | (0.68) | 93 | -1.9 | ( -3.79, -0.04) | 0.045 | -0.3 | ( -2.22, 1.62) | 0.757 |
| k 6 | -12.6 | (0.72) | 78 | -12.0 | (0.74) | 78 | -9.2 | (0.69) | 87 | -3.4 | ( -5.33, -1.47) | <0.001 | -2.8 | ( -4.75, -0.87) | 0.005 |
| k 8 | -14.2 | (0.69) | 80 | -14.0 | (0.76) | 70 | -11.1 | (0.69) | 79 | -3.1 | ( -4.98, -1.19) | 0.002 | -2.9 | ( -4.84, -0.86) | 0.005 |
| k 12 | -15.1 | (0.86) | 66 | -14.5 | (0.97) | 57 | -11.2 | (0.86) | 67 | -4.0 | ( -6.33, -1.59) | 0.001 | -3.3 | ( -5.78, -0.77) | 0.011 |
| End Point | -11.2 | (0.69) | 102 | -9.7 | (0.70) | 104 | -8.8 | (0.69) | 101 | -2.4 | ( -4.28, -0.52) | 0.013 | -0.9 | ( -2.78, 1.00) | 0.355 |
| 12 End Point | -12.7 | (0.80) | 102 | -11.1 | (0.81) | 104 | -9.9 | (0.80) | 101 | -2.8 | ( -4.94, -0.59) | 0.013 | -1.2 | ( -3.40, 0.97) | 0.275 |





Note: Only patients with a baseline and at least one post baseline assessment

DISK$STATS4:[STATS_GROUP.SBBRL29060.448.CODE]LT14_1_NEW.SAS (25AUG97 15:12)

**Comments to be sent to the sponsor:**

5. The two strengths (12.5 and 25 mg) of the CR products have been used in clinical efficacy studies.

6. Products manufactured at sites are not bioequivelant.

7. The sponsor is requested to adopt the following dissolution methods:

Apparatus: USP II (paddles) 150 rpm.

| Dissolution Media | Time | Limit (% dissolved) |
|---|---|---|
| Step 1: 0.1 M HCl (750 mL) for 2 hr | 2 hr | Not more than |
| Step 2: pH 7.5 Tris buffer containing 60 mmol Tris, 90 mmol NaCl (1000 mL) for 7 hr. | 1 hr<br>2 hr<br>4 hr<br>6 hr | |

at room temperature.

**RECOMMENDATION:**

The sponsor has performed adequate studies to describe the pharmacokinetic of CR formulation and also studied the effect of food.

. The product manufactured at were found to be bio-inequivalent to the product manufactured at . Hence, approval of site change application can not be justified. Please forward Comments 5-7 to the sponsor.

Rae Yuan, Ph.D. /S/

Team Leader: Chandra Sahajwalla /S/

Date of Signature: 9/30/98

Office of Clinical Pharmacology and Biopharmaceutics/Division I

CC list: HFD-120; CSO; HFD-860 (Yuan, Sahajwalla, Mehta); CDR (Barbara Murphy)

Attachment I

# Report Synopsis

## Title

A randomised, open, four-period crossover study to compare the pharmacokinetic profile of paroxetine after single doses of each enteric-coated Geomatrix controlled-release tablet strength (12.5, 25.

## Investigator(s) and Center(s)

## Study Dates

The first subject was included in the study on 6th February 1997 (first screening), the study lasted from 17th February 1997 (first medication) to 7th April 1997 (last medication) and was completed on 23rd April 1997 (follow-up).

## Objective(s)

To describe the relationship between dose and pharmacokinetic parameters of paroxetine over the complete range of proposed dosage strengths of the CR tablet formulation (12.5

## Study Design

A randomised, open, single dose, four-period crossover study. Each volunteer received randomly, on separate days, a single dose of each CR tablet (12.5, 25 . The four dosing days were separated by a wash-out period of at least 10 days. Volunteers fasted from 24.00 h in the evening before dosing until 4 hours postdose.

## Study Population

(18m 15F, age 18-49)

Twenty-three healthy young male or female volunteers were included to ensure at least 16 completers. Subjects had to be in good health and were not permitted to take any other prescribed medication; any exceptions had to be agreed by SB.

## Treatment and Administration

Subjects received enteric-coated Geomatrix controlled-release (CR) tablets containing 12.5, 25, of paroxetine. To each subject, single doses of each CR tablet were administered orally on separate days (separated by a wash-out of at least 10 days). Subjects attended the research unit from the evening before each dosing day and remained in the unit until the 24 hours postdose pharmacokinetic sample had been taken. Subjects were required to fast from food and fluids from 24.00 h in the evening prior to dosing until lunch 4-5 hours postdose.

Batch numbers for the tablets containing 12.5, 25 ; of paroxetine were M96285, M96179, M96335 and M96338, respectively.

For brevity, throughout this report, the term 'paroxetine-CR' is used when referring to the enteric-coated Geomatrix controlled-release tablet formulation of paroxetine examined in this study.

## Evaluation Criteria

### Safety Parameters

For safety and tolerability vital signs, adverse experiences and clinical laboratory data were assessed.

Vital signs, i.e. supine and standing blood pressure and pulse, and 12-lead ECG were recorded at prestudy and follow-up.

Adverse experiences were monitored at prestudy, baseline (predose) and at 12, 24, 48, 72, 96 and 120 hours postdose and at follow-up. In addition, all spontaneously reported adverse experiences were recorded.

Blood samples for haematology, clinical chemistry and urinalysis were performed at prestudy and follow-up.

### Pharmacokinetic Parameters

On each dosing occasion, blood samples (approximately 5 mL) were collected into EDTA tubes, predose and at 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 18, 24, 32, 48, 72, 96 and 120 hours after dosing. Paroxetine plasma concentrations were quantitated using a method based on liquid-liquid extraction followed by . The paroxetine plasma concentration versus time data were subjected to non-compartmental pharmacokinetic analysis to obtain Cmax, Tmax, AUC(0-inf) and T1/2.

**Table 11 Summary of Pharmacokinetic Parameters**

| Pharmacokinetic Parameter | Dose | |
|---|---|---|
| | 12.5 mg | 25 mg |
| Cmax * (ng/mL) | 2.14 / 1.20 | 5.55 / 3.20 |
| Tmax ** (h) | 6.0 | 8.0 |
| AUC(0-inf) * (ng.h/mL) | 121 / 22.6 | |
| Half-life*** (h) | 16.0 | |

* arithmetic mean/geometric mean (range) ** median (range) *** arithmetic mean (range)

**Table 10.14**

**Times to maximum observed plasma concentrations of paroxetine (Tmax, hour) in healthy subjects after single oral administration of paroxetine-CR (12.5, 25**

| Subject No. | Regimen A 12.5 mg | Regimen B 25 mg |
|---|---|---|
| 001 | | |
| 002 | | |
| 003 | | |
| 004 | | |
| 005 | | |
| 006 | | |
| 007 | | |
| 008 | | |
| 009 | | |
| 010 | | |
| 011 | | |
| 012 | | |
| 013 | | |
| 014 | | |
| 015 | | |
| 016 | | |
| 017 | | |
| 018 | | |
| 019 | | |
| 020 | | |
| 021 | | |
| 022 | | |
| 023 | | |

**Table 10.15**

**Areas under the plasma concentration-time curves of paroxetine (AUC(0-inf), ng.h/mL) in healthy subjects after single oral administration of paroxetine-CR (12.5, 25**

| Subject No. | Regimen A 12.5 mg | Regimen B 25 mg |
|---|---|---|
| 001 | | |
| 002 | | |
| 003 | | |
| 004 | | |
| 005 | | |
| 006 | | |
| 007 | | |
| 008 | | |
| 009 | | |
| 010 | | |
| 011 | | |
| 012 | | |
| 013 | | |
| 014 | | |
| 015 | | |
| 016 | | |
| 017 | | |
| 018 | | |
| 019 | | |
| 020 | | |
| 021 | | |
| 022 | | |
| 023 | | |

* - AUC(0-t) value (terminal phase could not be delineated) - not included in summary statistics

ND - not determined (no/too few concentrations to permit AUC calculation)

Values in brackets indicates extrapolated area, AUC(t-inf), as % of AUC(0-inf)

**Figure 11.1**

**Mean (±SD) plasma concentrations of paroxetine in healthy subjects after single oral administration of paroxetine-CR (12.5, 25**

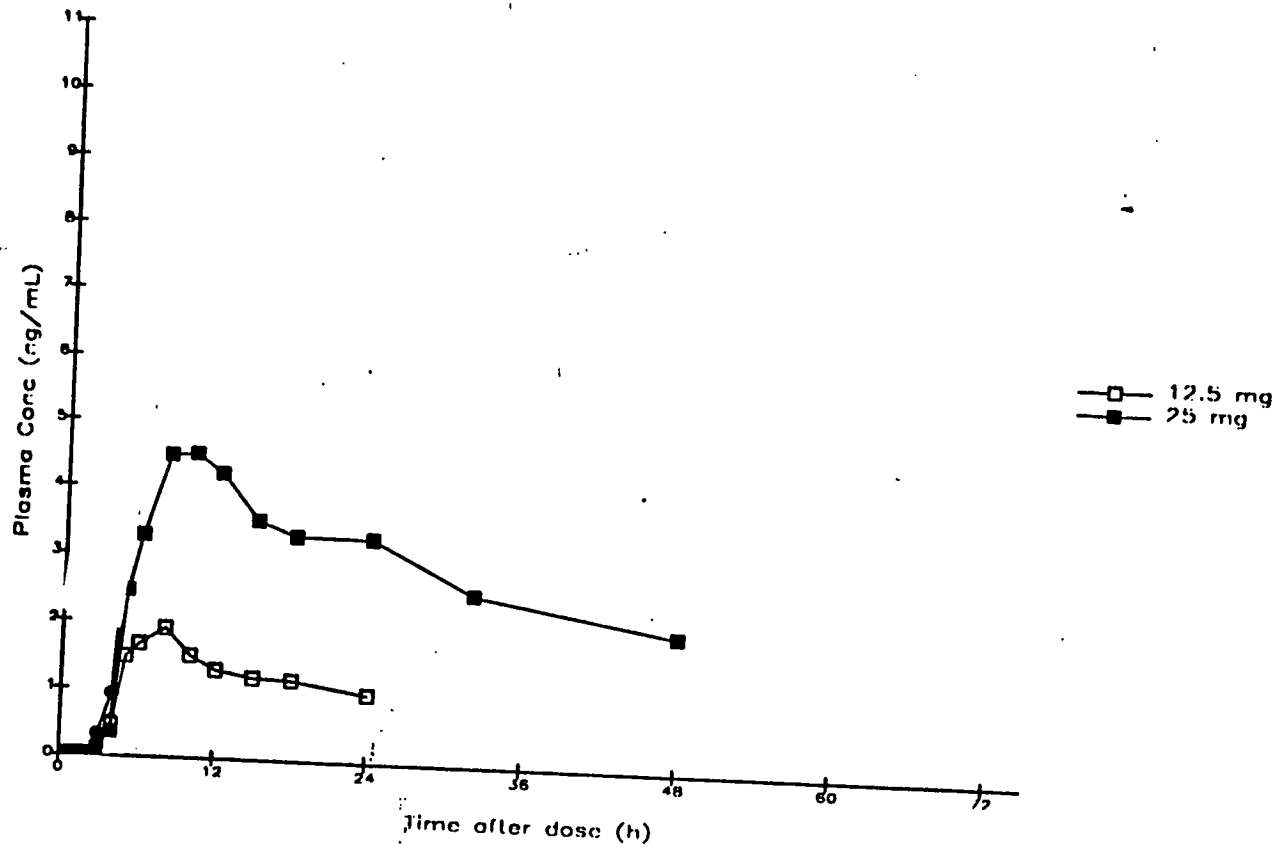

Figure B.9

Plasma concentrations of paroxetine (ng/mL) in Subject 009 after single oral administration of paroxetine-CR (12½, 25, 37½ and 50 mg)

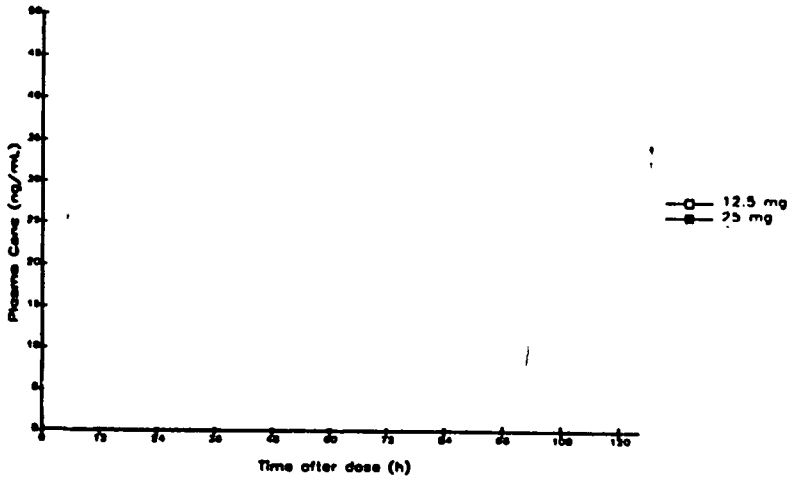


Figure B.10

Plasma concentrations of paroxetine (ng/mL) in Subject 010 after single oral administration of paroxetine-CR (12½, 25, 37½ and 50 mg)

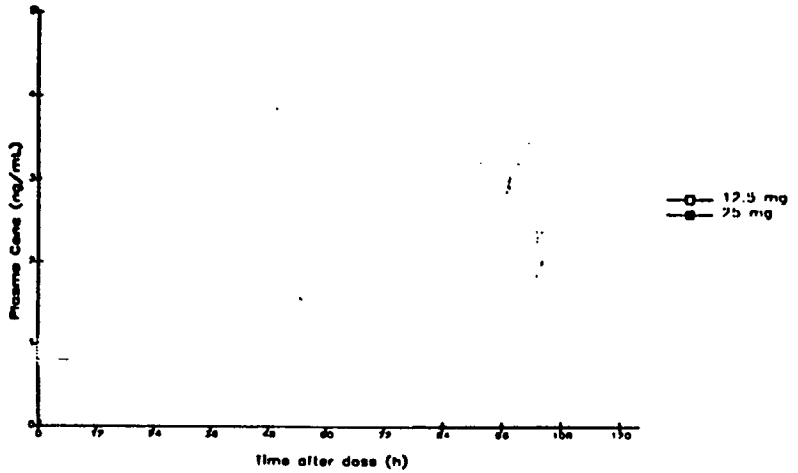


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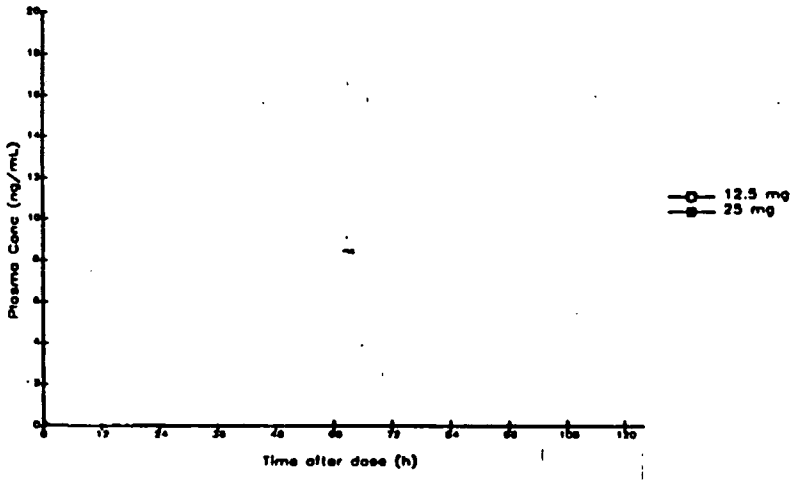
Figure B.11

Plasma concentrations of paroxetine (ng/mL) in Subject 011 after single oral administration of paroxetine-CR (12½, 25, 37½ and 50 mg)

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Attachment IV

# Report Synopsis

## Title

A steady state study to assess the pharmacokinetic profile of paroxetine after repeated daily dosing of the controlled release paroxetine tablet (25 mg) when given fasted and when given immediately after a standard FDA high-fat breakfast

## Investigator(s) and Center(s)

## Study Dates

This study was conducted from 11 July 1997 to 1 September 1997. The first dose of study medication was administered on 18 July 1997 and the last dose was administered on 21 August 1997.

## Objective(s)

1. To assess the pharmacokinetic profile of the controlled release paroxetine tablet formulation (25 mg) when administered immediately after a single standard FDA high fat breakfast (Day 15) relative to the steady state pharmacokinetic profile in the fasted state (Days 12 and 14).
2. To assess the steady-state pharmacokinetic profile of the controlled release paroxetine tablet formulation (25 mg) when administered, repeatedly, immediately after a standard FDA high fat breakfast (Days 19 and 21) relative to the steady state pharmacokinetic profile in the fasted-state (Days 12 and 14).

## Study Design

This study was an open, non-randomised, steady state study which was conducted at a single centre.

## Study Population

Twenty-four (24) healthy male and female volunteers were entered into this study to ensure the availability of at least 18 evaluable volunteers. Volunteers were aged between 23 and 50 years, inclusive and had been subjected to a comprehensive medical interview.

## Treatment and Administration

The enteric-coated, Geomatrix controlled release paroxetine tablet (25 mg) manufactured at Crawley was administered to healthy volunteers once daily over a period of 21 days. For the first 14 days the study medication was administered to subjects in the fasted state. For the last 7 days

study medication was administered to subjects immediately after a standard FDA high fat breakfast. For brevity, throughout this report, the term 'paroxetine-CR' is used when referring to the enteric-coated Geomatrix controlled-release tablet formulation of paroxetine.

# Evaluation Criteria

## Safety Parameters

Clinical safety was evaluated by measurement of clinical chemistry, haematology and urinalysis parameters prestudy and at the follow-up examination. Supine blood pressure and pulse rate were recorded prestudy and at the follow-up examination. A 12-lead ECG was recorded prestudy and at the follow-up examination. Adverse experiences (AEs) were elicited by direct questioning of each subject using a non-leading prompt at predose on days 1, 5, 12 and 19 and at the follow-up examination. They were also collected from spontaneous reports.

## Pharmacokinetic Parameters

On Days 12, 14, 15, 19 and 21, blood samples (5 mL, into EDTA) were collected predose and at 2, 4, 6, 8, 10, 12, 15, 18, 21 and 24 hours after dosing. Additional blood samples were collected predose on Days 10, 11, 17 and 18 for assessment of steady state conditions. Paroxetine plasma concentrations were quantitated using a method based on followed by . The paroxetine plasma concentration versus time data were subjected to non-compartmental pharmacokinetic analysis to obtain Cmax, Tmax, AUCτ and Cmin. The degree of fluctuation (DF) was calculated as (Cmax–Cmin)/(AUCτ/24).

# Statistical Methods

Two separate analyses were conducted for each pharmacokinetic parameter: the first day of dosing in the fed state (Day 15) and repeated dosing in the fed state (Days 19 and 21) were each compared with repeated dosing in the fasted state (Days 12 and 14). AUCτ, Cmax, Cmin and DF were log-transformed (base e) and analysed by analysis of variance, fitting terms for subject, regimen, and their interaction. Point estimates and 90% confidence intervals were calculated for the ratio 'fed:fasted', using the subject by regimen (interaction) mean square as the error term. Tmax was analysed non-parametrically using the Wilcoxon matched pairs method for each comparison of interest. The arithmetic means of the replicate fasted (Days 12 and 14) and replicate fed (Days 19 and 21) Tmax values were calculated for each subject prior to the analyses. The median difference 'fed – fasted' was estimated for Tmax, together with a distribution-free 95% confidence interval

## Subject Disposition and Key Demographic Data

24 healthy subjects (20 males and 4 females) were enrolled for this study.

| Parameter | Age (years) | Weight (kg) | Height (cm) |
|---|---|---|---|
| n | 24 | 24 | 24 |
| Mean | 32 | 80.3 | 181 |
| SD | 6.6 | 9.71 | 9.0 |
| Range | 23-50 | 58.0-95.0 | 163-195 |

Race: White 100%

## Safety Results

**Adverse experiences:** There were no deaths or serious non-fatal adverse experiences in this study. Fifty-two (51) adverse experiences which were treatment emergent (i.e. not present prior to the first dose), were reported by 19 different subjects following administration of paroxetine-CRg (25 mg, Crawley) in the fasted state. Eight (8) AEs were reported by 5 different subjects following administration of paroxetine-CR (25 mg, Crawley) in the fed state (i.e.immediately after a standard FDA high fat breakfast). More than 60 % of the AEs were reported within 3 days after the first dosing with paroxetine-CR and were characteristic of adverse experiences commonly seen following dosing with paroxetine-CR. These effects diminished with continued dosing so that the apparent reduction of AEs when dosed with food is likely to be due to the characteristic reduction in AEs with continued dosing of paroxetine-CR and not due to dosing in the fed state. In the majority of cases the relation of the AEs to the study drug was considered as 'probable' or 'suspected' and relatively few cases were judged as 'unrelated' or 'unlikely' to be related to the study drug. Generally, the intensity of AEs was 'mild'. All signs and symptoms had resolved by the end of the study.

| Adverse Experience Occuring in Two or More Subjects | Number of Subjects | |
|---|---|---|
| | Regimen A | Regimen B |
| **Dizziness** | 3 | 1 |
| **Headache** | 4 | 1 |
| **Diarrhea** | 8 | 1 |
| **Vomiting** | 1 | 1 |
| **Vision Abnormal** | 0 | 1 |
| **Nausea** | 4 | 1 |
| **Fatigue** | 12 | 1 |
| **Infection viral** | 0 | 1 |
| **Anorexia** | 3 | 0 |
| **Constipation** | 3 | 0 |
| **Insomnia** | 2 | 0 |
| **Mouth dry** | 2 | 0 |
| **Ejaculation disorder** | 2 | 0 |
| **Number of Subjects with AES** | 19 | 5 |
| **Number of Subjects Exposed** | 24 | 22 |

Regimen key: A: Paroxetine-CR tablet (25 mg, Crawley,), fasted; B: Paroxetine-CR tablet (25 mg, Crawley), fed

**Vital Signs and ECG:** None of the subjects had vital signs of potential clinical concern or abnormal findings in ECG intervals or morphology at the prestudy medical examination and at the

follow-up examination.
**Safety Laboratory:** Laboratory values of potential clinical concern were seen in three (3) subjects. Subject no. 010 had elevated total bilirubin at the prestudy examination (1.84 mg/dL, reference range: 0 - 1 mg/dL), which were in the normal range at a repeat examination. The same subject had elevated total bilirubin levels at the follow-up examination (1.62 mg/dL), which decreased within 22 days to 1.27 mg/dL. Subject no. 23 had elevated total bilirubin values at the follow-up examination (1.53 mg/dL) which decreased to normal values (0.77 mg/dL) within one day. Subject 024 had elevated glucose values (144.6 mg/dL, reference range: 70 - 100 mg/dL) at the follow-up visit because he was not fasted. The glucose values of this subject were normal at a repeat examination (89.2 mg/dL). The laboratory findings were not associated with clinical symptoms, and in the view of the Principal Investigator these observations were not related to the study drug and not clinically relevant.

## Pharmacokinetics

Twenty-one of the 24 subjects completed both study treatment periods (14 days fasted and seven days fed administration) and provided fully-evaluable plasma concentration profiles on each of the five sampling occasions. One subject (023) withdrew during the third week of the study and only provided profiles for Days 12 and 14 (repeated fasted administration) and Day 15 (first dose in the fed state).
In all evaluable subjects, paroxetine was quantifiable throughout the 24 hour dosing interval on all sampling occasions. Predose plasma concentrations recorded on the last five days of dosing in each dietary state show random small fluctuations but no systematic changes with time over either period (Days 10 - 14 or 17 - 21), or between the two periods. This suggests not only that steady state had been reached when formal pharmacokinetic analysis was first conducted on Day 12, but also that there was no marked change to this established steady state after switching from fasted to fed administration. The steady state pharmacokinetic parameters (arithmetic means and between-subject coefficients of variation) are summarized in the Table below:

| Steady state Parameter | (n = 22) | FASTED | | FED | | |
|---|---|---|---|---|---|---|
| | | Day 12 | Day 14 | Day 15 | Day 19 * | Day 21 * |
| Cmax (ng/mL) | mean [CVb%] | 29.2 [84%] | 30.6 [71%] | 27.6 [67%] | 29.2 [65%] | 28.9 [78%] |
| Tmax (h) | median (range) | 10.0 | 10.0 | 12.0 | 10.0 | 10.0 |
| AUCτ (ng.h/mL) | mean [CVb%] | 491 [91%] | 550 [80%] | 505 [73%] | 526 [80%] | 529 [84%] |
| Cmin (ng/mL) | mean [CVb%] | 14.8 [119%] | 16.7 [98%] | 15.3 [101%] | 16.5 [111%] | 16.4 [99%] |
| DF | mean [CVb%] | 0.79 [46%] | 0.70 [42%] | 0.65 [44%] | 0.72 [55%] | 0.64 [30%] |

* n = 21

For all pharmacokinetic parameters, the similarity of mean values on each day of sampling is clearly evident. Between-subject variability also remains relatively constant throughout the study. The results of the comparison between the first day of dosing in the fed state (Day 15) and repeated dosing in the fasted state (Days 12 and 14) are summarized in the Table overleaf:

| Parameter | Comparison | Ratio (a) | 90% CI |
|---|---|---|---|
| Cmax | Fed (first day) : Fasted | 0.95 | (0.87, 1.04) |
| AUCτ | Fed (first day) : Fasted | 1.01 | (0.92, 1.11) |
| Cmin | Fed (first day) : Fasted | 1.00 | (0.89, 1.12) |
| DF | Fed (first day) : Fasted | 0.87 | (0.78, 0.97) |
| **Parameter** | **Comparison** | **Difference (b)** | **95% CI** |
| Tmax | Fed (first day) – Fasted | 1.75 | (–1.00, 4.00) |

N = 22 (all subjects with complete data on days 12, 14 and 15)
(a) Ratio of the adjusted geometric means from ANOVA
(b) Median difference (based on mean of 2 fasted administrations)
Fasted: Repeated dosing in the fasted state (Days 12 and 14)
Fed (first day): Dosing after the first high-fat breakfast (Day 15)

The point estimates of the geometric mean ratios for Cmax, AUCτ and Cmin all lie close to unity, and the 90% confidence intervals all lie within the standard bioequivalence range of 0.80 to 1.25. The ratio and confidence interval for DF, being slightly lower, indicate a marginally smaller daily range in plasma concentrations on the first day of dosing in the fed state (Day 15) compared to repeated administration in the fasted state. Tmax was slightly delayed (by 1.75 hours, on average) but the 95% confidence interval indicates that the true median difference is unlikely to exceed 4 hours. The results of the comparison between repeated dosing in the fed and fasted states (Days 19 and 21, and Days 12 and 14, respectively) are summarized in the Table below:

| Parameter | Comparison | Ratio (a) | 90% CI |
|---|---|---|---|
| Cmax | Fed (repeat) : Fasted | 0.99 | (0.93, 1.06) |
| AUCτ | Fed (repeat) : Fasted | 1.02 | (0.96, 1.10) |
| Cmin | Fed (repeat) : Fasted | 1.06 | (0.97, 1.17) |
| DF | Fed (repeat) : Fasted | 0.91 | (0.82, 1.00) |
| **Parameter** | **Comparison** | **Difference (b)** | **95% CI** |
| Tmax | Fed (repeat) – Fasted | 0.00 | (–1.50, 1.75) |

N = 21 (all subjects with complete data on days 12 and 14, 19 and 21)
(a) Ratio of the adjusted geometric means from ANOVA
(b) Median difference (based on means of 2 fed and fasted administrations)
Fasted: Repeated dosing in the fasted state (Days 12 and 14)
Fed (repeat): Repeated dosing after high-fat breakfasts (Days 19 and 21)

The point estimates for Cmax, AUCτ, Cmin and DF all lie close to unity and the 90% confidence intervals all lie within the standard bioequivalence range of 0.80 to 1.25. Median Tmax was unaltered, and the 95% confidence interval indicates that the true median difference is likely to be less than 2 hours. Within-subject coefficients of variation for Cmax and AUCτ were low: 23-24% in the fasted state and lower still (9-16%) in the fed state.

## Conclusion

- The results of this study indicate that, during repeated daily dosing of paroxetine-CR, the bioavailability and pharmacokinetics of paroxetine-CR are unaffected when administered with a high-fat meal compared to dosing in the fasted state.
- No changes in ECG, vital signs or safety laboratory data that were of clinical importance were observed with paroxetine-CR dosed in the fasted or in the fed state.

The within-subject coefficients of variation (CVw) for each repeat dosing regimen (fasted and fed) are given in the Table below:

**Table 13: Within-subject coefficients of variation by regimen**

| Parameter | Fasted CVw Days 12 and 14 | Fed CVw Days 19 and 21 |
|---|---|---|
| Cmax | 23.8% | 15.6% |
| AUCτ | 22.8% | 9.2% |
| Cmin | 26.7% | 14.6% |
| DF | 30.5% | 25.7% |

N = 21 (all subjects with complete data on days 12 and 14, 19 and 21)
Source: Statistical derivation given in full in Tables C.11 to C.18

As noted above, the within-subject coefficients of variation for all parameters (notably Cmax, AUCτ and Cmin) were lower in the fed state.

# 7 Discussion

## 7.1 Safety

Fifty-two (51) AEs were reported in 19 different subjects following administration of paroxetine-CR in the fasted state compared to eight (8) AEs reported in five (5) subjects following administration of paroxetine-CR in the fed state (i.e. immediately after a standard FDA high-fat breakfast). More than 60 % of the AEs were reported within 3 days after the first dosing with paroxetine-CR and the incidence and nature of the reported AEs was similar to those observed in previous studies. These effects diminished with continued dosing so that the apparent reduction of AEs when dosed with food is likely to be due to the characteristic reduction in AEs with continued dosing of paroxetine-CR and not due to dosing in the fed state.

Evaluation of vital signs, ECG and laboratory parameters gave no indication of any drug related effect.

**Figure 11.2**

**Maximum observed plasma concentrations of paroxetine (Cmax, ng/mL) in healthy subjects after repeated once daily oral administration of paroxetine-CR (25 mg) for 14 days in the fasted state and for 7 days following a standard FDA high-fat breakfast, by subject and by day**

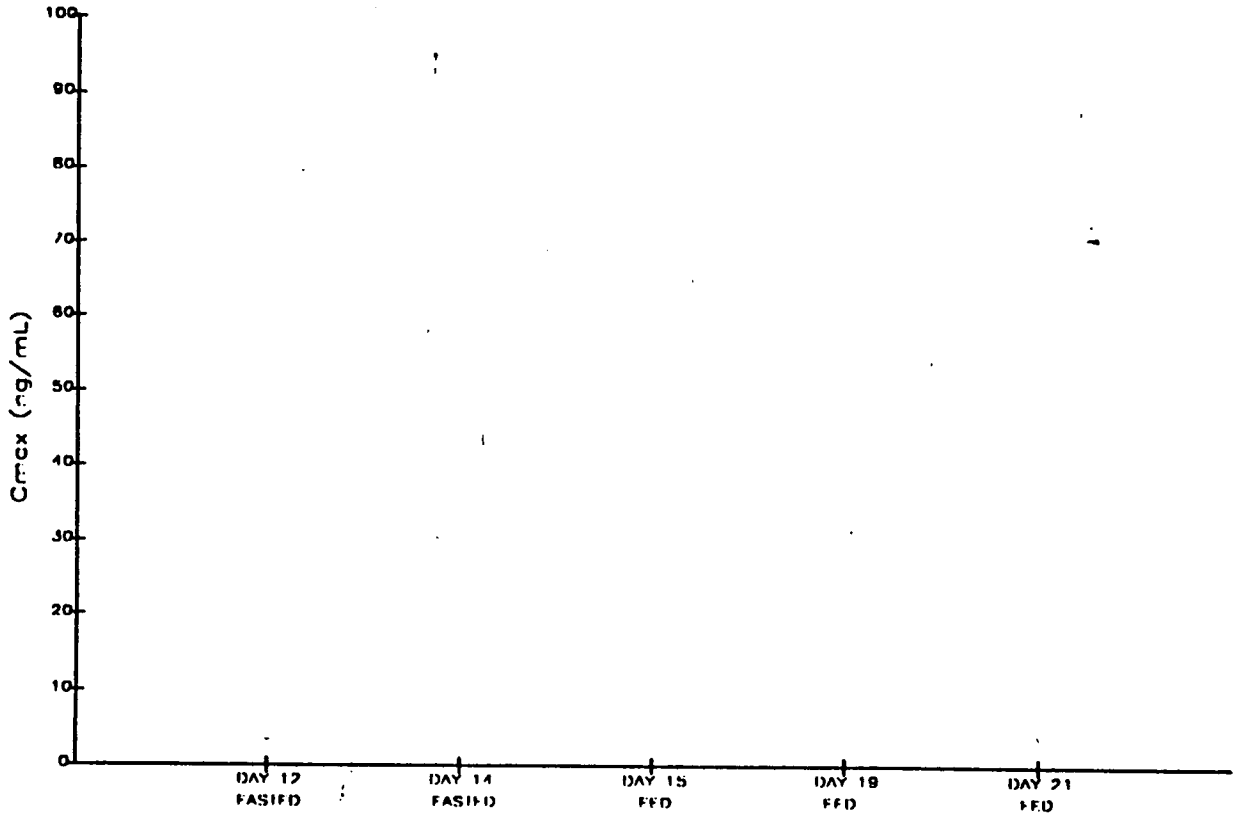


**Figure 11.3**

**Areas under the plasma concentration-time curves of paroxetine (AUCτ, ng.h/mL) in healthy subjects after repeated once daily oral administration of paroxetine-CR (25 mg) for 14 days in the fasted state and for 7 days following a standard FDA high-fat breakfast, by subject and by day**

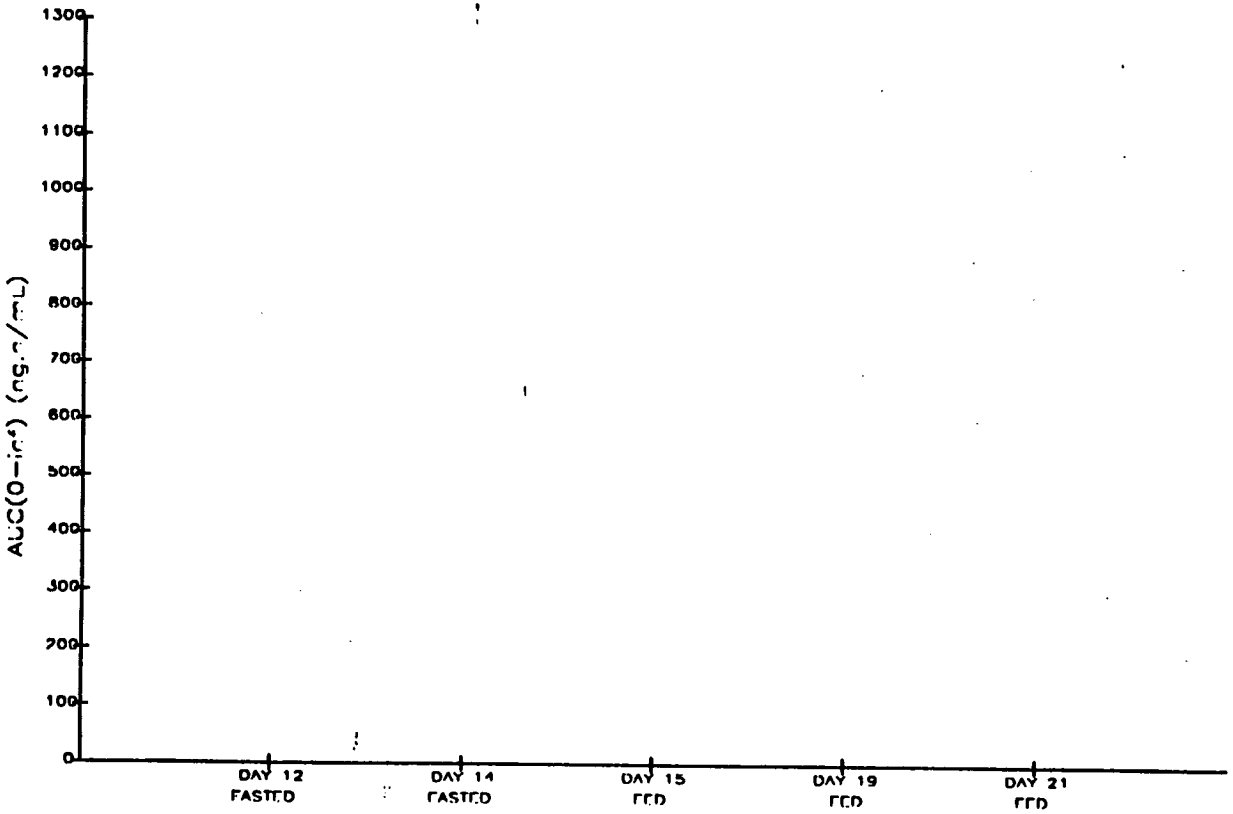


**Figure 11.4**

**Minimum observed plasma concentrations of paroxetine (Cmin, ng/mL) in healthy subjects after repeated once daily oral administration of paroxetine-CR (25 mg) for 14 days in the fasted state and for 7 days following a standard FDA high-fat breakfast, by subject and by day**

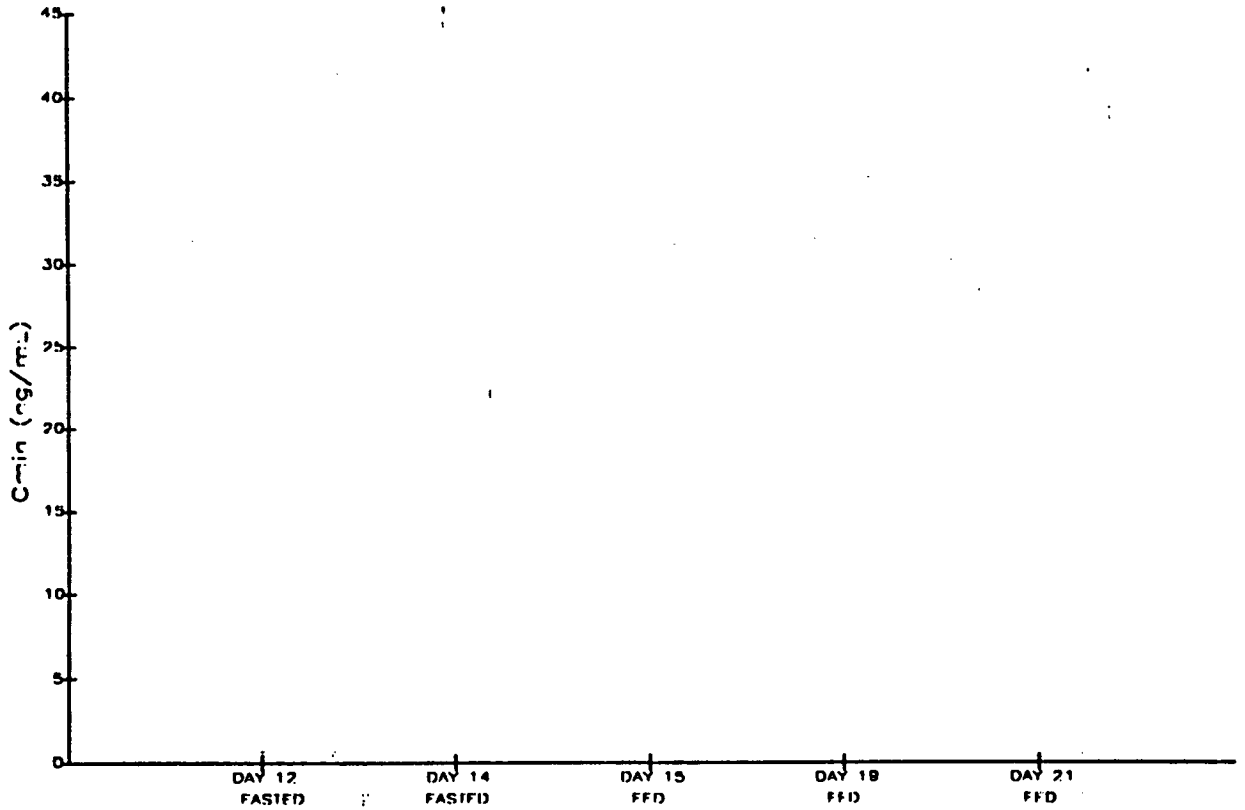
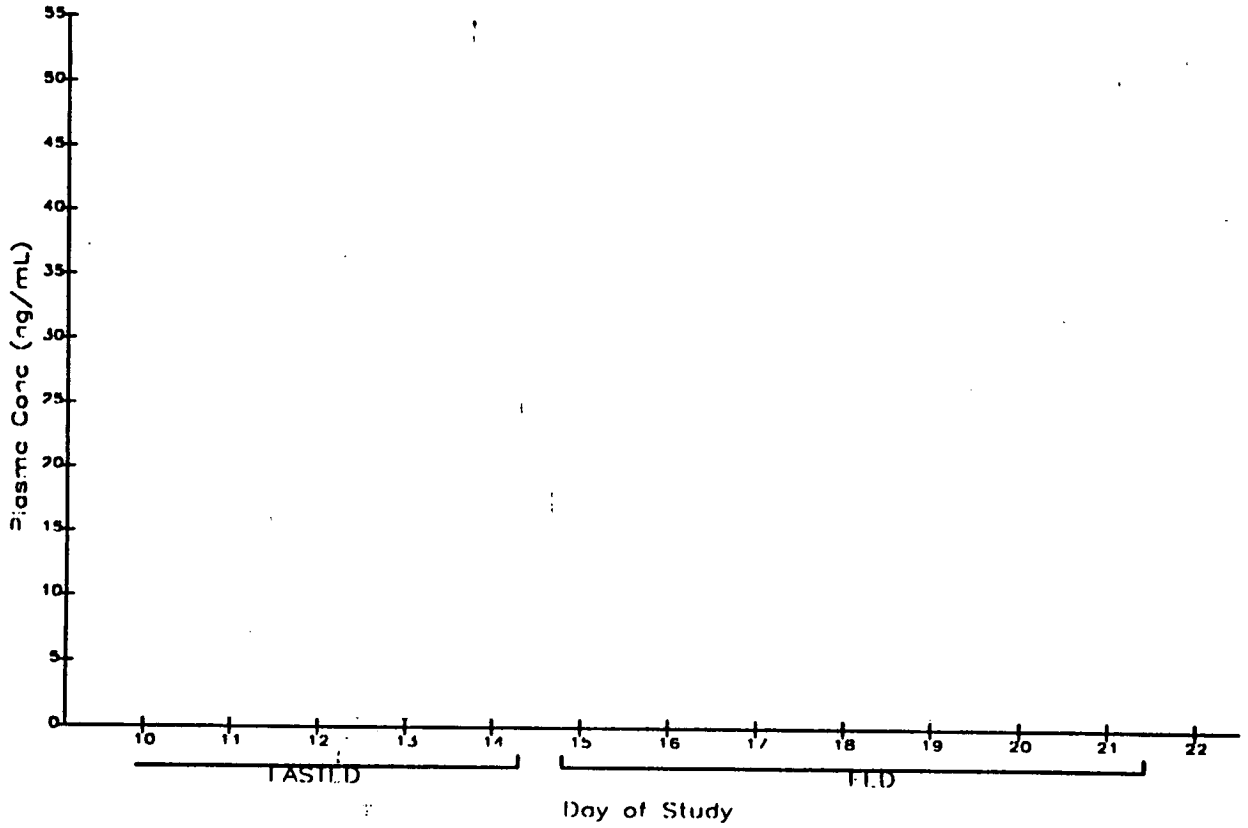


**Figure 11.6**

**Predose plasma concentrations of paroxetine in healthy subjects after repeated once daily oral administration of paroxetine-CR (25 mg) for 14 days in the fasted state and for 7 days following a standard FDA high-fat breakfast, by subject and by day**



# Report Synopsis Attachment V

## Title

A single dose two-period crossover study to demonstrate bioequivalence between the controlled release paroxetine tablet (25 mg) manufactured at

## Investigator(s) and Center(s)

## Publication

No publications as of July 1997

## Study Dates

The first subject was enrolled on the 11th March 1997, the first dose was administered on the 7th April 1997, the last dose was administered on the 28th April 1997 and the last study visit was on the 5th June 1997.

## Objective(s)

To demonstrate bioequivalence between the controlled-release paroxetine tablets (25 mg) manufactured at

## Study Design

This study was conducted to an open, randomised, two-period crossover study design. Each subject received randomly, on two separate days, a single 25 mg controlled release paroxetine tablet manufactured at and a 25 mg controlled-

release paroxetine tablet manufactured at A period of at least 10 days separated the two doses. Subjects were dosed in the fasted state.

## Study Population

49 healthy young male and female subjects were entered into this study to ensure 40 evaluable subjects. Subjects were aged between 18 and 55 years, inclusive, and all passed a comprehensive medical interview. (38 M + 11 F)

## Treatment and Administration

Two formulations of controlled release paroxetine tablets (25 mg dose), one manufactured at and the other manufactured at . Single doses of each formulation were administered orally on separate days (at least 10 days between) to each subject.

For brevity, throughout this report, the term 'paroxetine-CR' is used when referring to the enteric-coated Geomatrix controlled release tablet formulations of paroxetine examined in this study.

Batch Numbers : M96175 (ex. ) and M97052 (ex. )

## Evaluation Criteria

### Safety Parameters

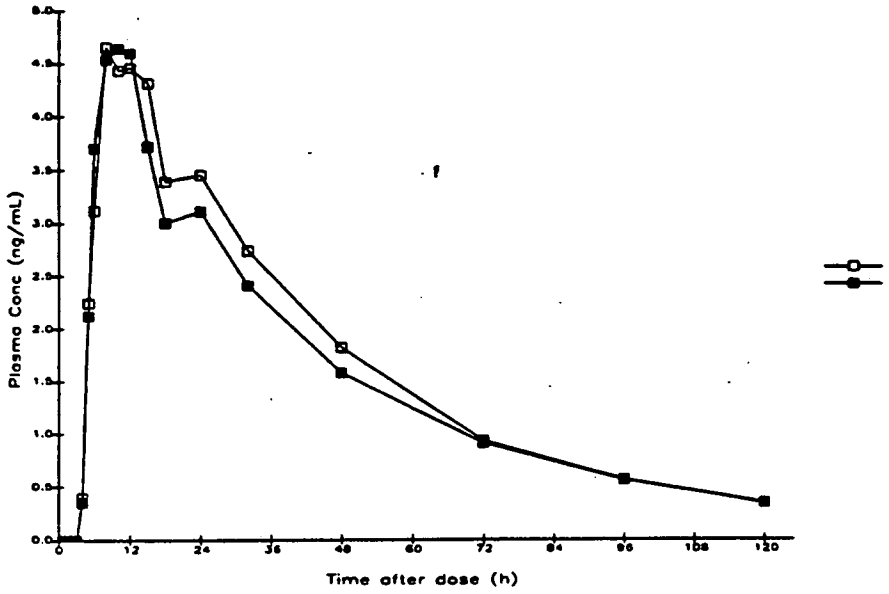
Blood samples for haematology, clinical chemistry and urinalysis were performed at pre-study and follow-up.

Adverse event forms were completed, pre-dose (baseline) and at 12, 24, 48, 72, 96 and 120 hours post-dose (and at follow-up).

### Pharmacokinetic Parameters

On each dosing occasion, blood samples (approx. 5 mL) were collected into EDTA tubes, pre-dose and at 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 18, 24, 32, 48, 72, 96 and 120 hours after dosing. Paroxetine plasma concentrations were quantitated using a method based on followed by . The paroxetine plasma concentration versus time data were

**Figure 1. Mean plasma concentrations of paroxetine in healthy subjects after single oral administration of paroxetine-CR (25 mg tablet and 25 mg tablet)**




Pharmacokinetic data are tabulated in Appendix A, Tables A1-A4 and summarized below in Table 1.

**Table 1 Summary of pharmacokinetic parameters Cmax, AUC(0-inf) and Tmax of paroxetine in healthy subjects after single oral administration of paroxetine-CR (25 mg tablet and 25 mg tablet)**

| Pharmacokinetic Parameter | | Cmax (ng/mL) (n = 47) | AUC(0-inf) (ng.h/mL) (n = 45) | Tmax (h) (n = 47) |
|---|---|---|---|---|
| (25 mg) | Mean (range) | 5.7 | 222 | 8.0 * |
| (25 mg) | Mean (range) | 5.4 | 205 | 8.0 * |

* median

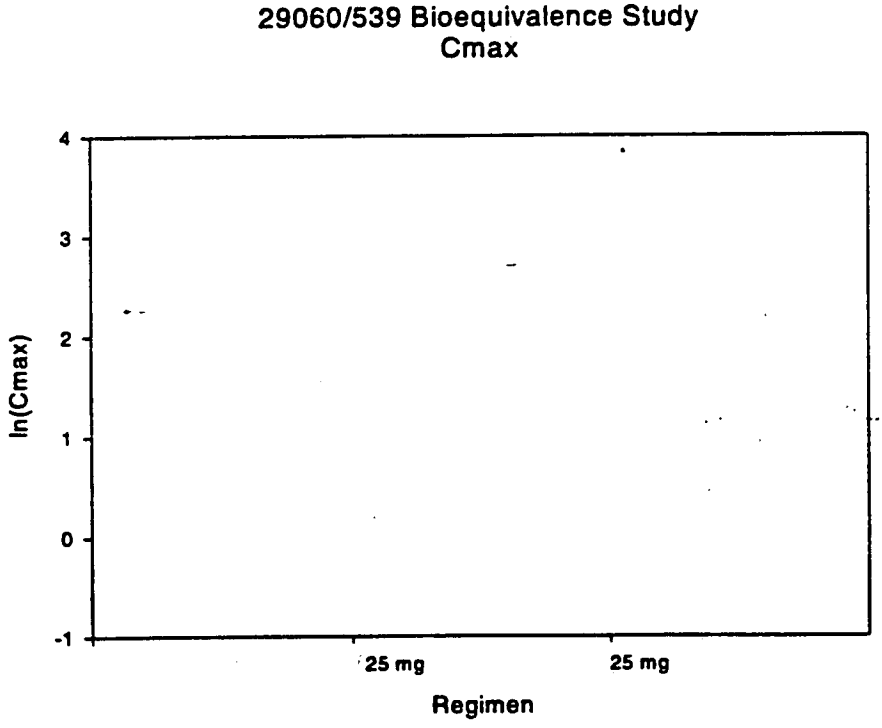
Point estimates for the ratio of the formulation relative to the formulation are provided below. Details of the analysis can be found in Appendix A, Table A5-A6.

**Table 2 Assessment of Bioequivalence based on current guidelines: Point estimates and 90% Confidence Intervals.**

| | N | Ratio | 90% C.I. | $CV_W$% |
|---|---|---|---|---|
| AUC(0-inf) (ng.h/mL) | 45 | 1.10 | (0.94, 1.29) | 46.9 |
| Cmax(ng/mL) | 47 | 1.05 | (0.92, 1.21) | 41.4 |

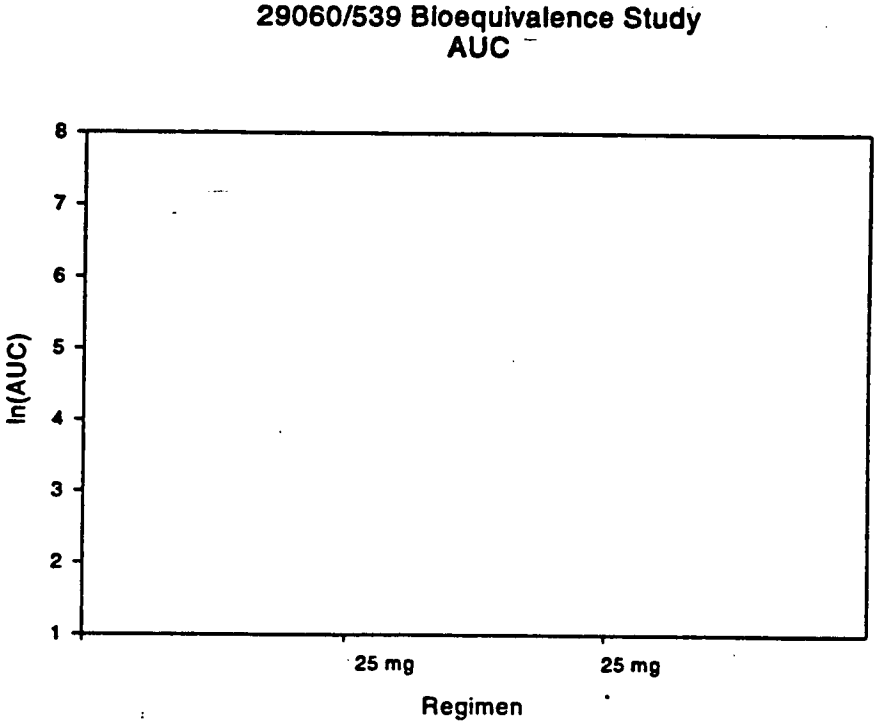
These results are presented pictorially in Figures 2 and 3 allowing the assessment of individual ratios.

**Figure 2. Individual subject data for Cmax**




Note : Above figure includes all available data

**Figure 3. Individual subject data for AUC(0-inf)**




Note : Above figure includes all available data

**Table 11 Comparisons between formulations for paroxetine pharmacokinetic parameters (excluding subject 004)**

| Parameter | n | Comparison | Ratio | 90% confidence interval |
|---|---|---|---|---|
| AUC(0-inf) | 44 | | 1.06 | (0.91, 1.22) |
| Cmax | 46 | | 1.02 | (0.90, 1.16) |
| Parameter | n | Comparison | Median difference | 95% confidence interval |
| Tmax | 46 | | –0.01 h | (–1.00, 0.98) |

Data Source : Appendix C, Tables C6-C8

## Table 10.10

**Maximum observed plasma concentrations of paroxetine (Cmax, ng/mL) in healthy subjects after single oral administration of paroxetine-CR (25 mg tablet and 25 mg tablet)**

| Subject No. | (25 mg) | (25 mg) | Ratio |
|---|---|---|---|
| 001 | | | 1.09 |
| 002 | | | 1.60 |
| 003 | | | 1.78 |
| 004 | | | 4.90 |
| 005 | | | - |
| 006 | | | 0.53 |
| 007 | | | 0.61 |
| 008 | | | 1.23 |
| 009 | | | 1.36 |
| 010 | | | 0.60 |
| 011 | | | 0.51 |
| 012 | | | 1.12 |
| 013 | | | 0.87 |
| 014 | | | 0.29 |
| 015 | | | 1.09 |
| 016 | | | 1.46 |
| 017 | | | 3.57 |
| 018 | | | 1.28 |
| 019 | | | 0.83 |
| 020 | | | 0.78 |
| 021 | | | 0.79 |
| 022 | | | 1.71 |
| 023 | | | 0.95 |
| 024 | | | 1.07 |
| 025 | | | 0.57 |

ND - not determined (subject withdrew from study)

* Cmax corrected for carry-over from previous period (see text)

**Table 10.10 (Contd)**

**Maximum observed plasma concentrations of paroxetine (Cmax, ng/mL) in healthy subjects after single oral administration of paroxetine-CR (25 mg tablet and 25 mg tablet)**

| Subject No. | (25 mg) | (25 mg) | Ratio |
|---|---|---|---|
| 026 | | | 1.44 |
| 027 | | | 1.33 |
| 028 | | | 1.68 |
| 029 | | | 1.46 |
| 030 | | | 1.70 |
| 031 | | | 0.66 |
| 032 | | | 0.77 |
| 033 | | | 1.24 |
| 034 | | | 0.64 |
| 036 | | | 0.92 |
| 037 | | | 1.20 |
| 038 | | | 0.50 |
| 039 | | | 2.13 |
| 040 | | | 0.99 |
| 041 | | | 0.96 |
| 042 | | | 1.90 |
| 043 | | | 2.31 |
| 044 | | | 1.60 |
| 045 | | | 1.09 |
| 046 | | | - |
| 047 | | | 0.34 |
| 048 | | | 0.47 |
| 049 | | | 1.07 |
| 050 | | | 0.97 |

ND - not determined (subject withdrew from study)

* Cmax corrected for carry-over from previous period (see text)

## Table 10.11

**Times to maximum observed plasma concentrations of paroxetine (Tmax, h) in healthy subjects after single oral administration of paroxetine-CR (25 mg tablet and 25 mg tablet)**

| Subject No. | (25 mg) | (25 mg) | Difference |
|---|---|---|---|
| 001 | | | 7.02 |
| 002 | | | -3.98 |
| 003 | | | -0.02 |
| 004 | | | -4.00 |
| 005 | | | - |
| 006 | | | -2.00 |
| 007 | | | -1.00 |
| 008 | | | 0.22 |
| 009 | | | 3.00 |
| 010 | | | 1.00 |
| 011 | | | -3.07 |
| 012 | | | 0.00 |
| 013 | | | 2.05 |
| 014 | | | 2.00 |
| 015 | | | -0.98 |
| 016 | | | -0.02 |
| 017 | | | 2.97 |
| 018 | | | 0.05 |
| 019 | | | 2.00 |
| 020 | | | -0.17 |
| 021 | | | -3.00 |
| 022 | | | 2.01 |
| 023 | | | 0.00 |
| 024 | | | 0.00 |
| 025 | | | 0.00 |

ND - not determined (subject withdrew from study)

## Table 10.11 (Contd)

**Times to maximum observed plasma concentrations of paroxetine (Tmax, h) in healthy subjects after single oral administration of paroxetine-CR (25 mg tablet and 25 mg tablet)**

| Subject No. | (25 mg) | (25 mg) | Difference |
|---|---|---|---|
| 026 | | | 0.03 |
| 027 | | | -7.00 |
| 028 | | | 0.00 |
| 029 | | | 6.00 |
| 030 | | | 0.00 |
| 031 | | | -4.00 |
| 032 | | | -1.98 |
| 033 | | | 7.00 |
| 034 | | | 4.07 |
| 036 | | | -2.09 |
| 037 | | | -4.00 |
| 038 | | | 0.00 |
| 039 | | | -4.00 |
| 040 | | | 5.12 |
| 041 | | | -2.00 |
| 042 | | | 0.02 |
| 043 | | | -3.02 |
| 044 | | | -3.00 |
| 045 | | | -7.00 |
| 046 | | | - |
| 047 | | | 1.95 |
| 048 | | | 3.02 |
| 049 | | | -1.97 |
| 050 | | | 2.02 |

ND - not determined (subject withdrew from study)

## Table 10.12

**Areas under the plasma concentration-time curves of paroxetine (AUC(0-inf), ng.h/mL) in healthy subjects after single oral administration of paroxetine-CR (25 mg tablet and 25 mg tablet)**

| Subject No. | (25 mg) | (25 mg) | Ratio |
|---|---|---|---|
| 001 | (8) | (6) | 1.36 |
| 002 | (7) | (6) | 1.06 |
| 003 | (3) | (5) | 1.23 |
| 004 | (15) | (28) | 7.39 |
| 005 | | (14) | - |
| 006 | (32) | (20) | 0.94 |
| 007 | (11) | (28) | 0.64 |
| 008 | (2) | (8) | 1.81 |
| 009 | (3) | (3) | 1.48 |
| 010 | (18) | (11) | 0.83 |
| 011 | (26) | (21) | 0.53 |
| 012 | (1) | (1) | 1.23 |
| 013 | (15) | (14) | 1.02 |
| 014 | (11) | (4) | 0.27 |
| 015 | (17) | | - |
| 016 | (5) | (16) | 1.02 |
| 017 | (2) | (15) | 4.32 |
| 018 | (1) | (1) | 1.33 |
| 019 | (20) | (6) | 1.22 |
| 020 | (1) | (1) | 1.07 |
| 021 | (22) | (7) | 0.71 |
| 022 | (13) | (5) | 3.36 |
| 023 | (30) | (10) | 1.01 |
| 024 | (7) | (15) | 1.44 |
| 025 | (6) | (7) | 0.68 |

ND - not determined (subject withdrew from study)
NE - not evaluable (AUC(0-inf) could not be determined because of low plasma concentrations and/or unsatisfactory terminal phase half-life delineation)
Values in brackets indicate extrapolated area beyond final concentration, AUC(t-inf), as a percentage of total area, AUC(0-t)
* AUC(0-inf) corrected for carry-over from previous period (see text)

**Table 10.12 (Contd)**

**Areas under the plasma concentration-time curves of paroxetine (AUC(0-inf), ng.h/mL) in healthy subjects after single oral administration of (25 mg tablet and 25 mg tablet)**

| Subject No. | (25 mg) | (25 mg) | Ratio |
|---|---|---|---|
| 026 | (9) | (20) | 1.64 |
| 027 | (3) | (5) | 1.48 |
| 028 | | | - |
| 029 | (9) | (23) | 2.70 |
| 030 | (18) | (12) | 0.92 |
| 031 | (15) | (8) | 0.50 |
| 032 | (30) | (21) | 0.91 |
| 033 | (9) | (13) | 1.15 |
| 034 | (2) | (3) | 0.85 |
| 036 | (12) | (9) | 1.11 |
| 037 | (3) | (2) | 0.77 |
| 038 | (22) | (33) | 0.43 |
| 039 | (14) | (14) | 1.98 |
| 040 | (10) | (8) | 0.96 |
| 041 | (9) | (9) | 0.79 |
| 042 | (9) | (12) | 3.04 |
| 043 | (21) | (12) | 1.34 |
| 044 | (12) | (41) | 1.00 |
| 045 | (1) | (1) | 1.08 |
| 046 | | | - |
| 047 | (18) | (2) | 0.37 |
| 048 | (4) | (1) | 0.42 |
| 049 | (10) | (9) | 1.05 |
| 050 | (7) | (7) | 1.41 |

ND - not determined (subject withdrew from study)
NE - not evaluable (AUC(0-inf) could not be determined because of low plasma concentrations and/or unsatisfactory terminal phase half-life delineation)
Values in brackets indicate extrapolated area beyond final concentration, AUC(t-inf), as a percentage of total area, AUC(0-t)
* AUC(0-inf) corrected for carry-over from previous period (see text)

ATTACHMENT VI. Formulation & Dissolution.

## Table 10.3.2: Unit Formula of Paroxetine CR Tablets

| Formula Code<br>Ingredients | 12.5 mg<br>DY<br>Quantity<br>(mg/tablet) | 25 mg<br>DT<br>Quantity<br>(mg/tablet) |
|---|---|---|
| Paroxetine Hydrochloride, hemihydrate | | |
| Lactose monohydrate | | |
| Hydroxypropylmethylcellulose | | |
| Polyvinylpyrrolidone | | |
| Magnesium Stearate | | |
| Colloidal Silicon Dioxide | | |
| Glyceryl Behenate | | |
| Red Ferric Oxide | | |
| Yellow Ferric Oxide | | |
| Methyacrylic Acid Copolymer Type C | | |
| Talc | | |
| Triethyl Citrate | | |

4 pages
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SECRET
(Exemp. 4)

20 pages

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