The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

**Study No:** PCR104074  
**Title:** A randomized, open, three-period crossover study to compare the pharmacokinetic profile of paroxetine after single dosing of each enteric-coated Geomatrix control releasetablet strength (12.5, 25, 37.5mg) in healthy Chinese subjects.

**Rationale:** Due to the possible involvement of local receptors (5-hydroxytryptamine [5-HT₃]) in mediating upper gastrointestinal (GI) side effects (notably nausea and vomiting) to paroxetine, a controlled release formulation of paroxetine (BRL 29060A) with altered absorption profiles could potentially reduce the incidence of these side effects, thereby improving subject compliance and maximising treatment benefit. This study was performed to characterise the pharmacokinetics of single doses of the enteric coated Geomatrix controlled release formulation in Healthy Chinese volunteers.

**Phase:** I  
**Study Period:** 16 March 2006 to 30 April 2006  
**Study Design:** Open, randomized, three-period crossover study design.  
**Centres:** 1 centre in China  
**Indication:** None  
**Treatment:** After screening, each eligible subject was allocated at random to one of six sequences: ABC, BAC, CBA, BCA, CAB and ACB (A=12.5mg, B=25mg and C=37.5 mg) according to a pre-determined randomization schedule. Subjects received randomly, on separate days, a single dose of paroxetine-CR tablet in the fasted state. The three dosing days were separated by a wash-out period of 10 days.

**Objectives:** To describe the relationship between dose and pharmacokinetic parameters of the paroxetine-CR tablet (12.5 to 37.5 mg) in healthy Chinese subjects.

**Criteria for evaluation** Pharmacokinetic parameters included Cmax, AUC(0-t), AUC(0-∞), T1/2 and Tmax. Safety endpoints included 12-lead ECG, vital signs, nurse records, spontaneous adverse event reports and laboratory results (hematology, urinalysis and blood chemistry).

**Statistical Methods:**
AUC(0-inf) and Cmax was dose-normalised to 12.5 mg ("reference" dose) and log-transformed (base e) prior to analysis, by analysis of variance (ANOVA) fitting terms for sequence, subject within sequence, period and dose. Point estimates and 90% confidence intervals for the difference between each dose and the reference dose were constructed using the residual variance from the ANOVA. The point and interval estimates on the log scale were back transformed to obtain estimates of the ratios of each dose relative to the reference dose. A similar analysis was carried out for e-transformed T1/2 to obtain 90% confidence intervals for the differences for each dose relative to the reference dose. Tmax was analysed non-parametrically using the Wilcoxon matched-pairs method for each comparison of interest. Point estimates and 90% confidence intervals were constructed for the median difference between each dose and the reference dose.

The safety analysis utilized the safety population data set. The safety and tolerability of protocol-specified treatments were assessed on by vital signs, clinical laboratory tests and clinical monitoring. Safety and tolerability data were summarized descriptively by regimen. No formal analysis was performed.

**Study Population:** All the subjects were Asian. The average age of subject was 24.63 years (range 19-45years). Body weight was > 50 kg and the average BMI was 20.82 (range 19-25). There were no baseline signs or symptoms at the baseline for all study subjects, and also no prior medications. There were no significant medical histories in the study subjects.

**Number of Subjects:**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Planned N</td>
<td>12</td>
</tr>
<tr>
<td>Dosed N</td>
<td>12</td>
</tr>
<tr>
<td>Completed n (%)</td>
<td>12(100)</td>
</tr>
</tbody>
</table>

**Total Number Subjects Withdrawn N (%):** 0
Withdrawn due to Adverse Events n (%): 0
Withdrawn due to Lack of Efficacy n (%): 0
Withdrawn for Other Reasons n (%)  0

Demographics
N (ITT) 12
Females: Males 4:8
Mean Age in Years (sd) 24.63 (3.90)
Mean Weight in Kg (sd) 59.5 (6.26)
Chinese n (%) 12 (100)

Pharmacokinetics (PK), PK Endpoints:
Pharmacokinetic parameters of Single-dose of Paroxetine CR (Geometric Mean 95% CI-L&U, *except Median and range difference for Tmax)

<table>
<thead>
<tr>
<th></th>
<th>12.5mg</th>
<th>25mg</th>
<th>37.5mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1/2</td>
<td>12.5 (10.7, 14.6)</td>
<td>11.7 (10.1, 13.5)</td>
<td>13.4 (11.3, 15.9)</td>
</tr>
<tr>
<td>Tmax</td>
<td>9.0 (6.0, 10.0)</td>
<td>10.0 (6.0, 12.0)</td>
<td>10.0 (4.0, 12.0)</td>
</tr>
<tr>
<td>Cmax</td>
<td>1.36 (0.62, 3.00)</td>
<td>4.00 (2.10, 7.63)</td>
<td>11.22 (5.74, 21.93)</td>
</tr>
<tr>
<td>AUC0-96</td>
<td>25.96 (10.07, 66.91)</td>
<td>90.82 (41.01, 201.12)</td>
<td>235.69 (95.26, 583.07)</td>
</tr>
<tr>
<td>AUC0-inf</td>
<td>27.81 (11.22, 68.94)</td>
<td>92.79 (42.03, 204.83)</td>
<td>242.94 (99.92, 590.64)</td>
</tr>
</tbody>
</table>

1 Dose normalized to 12.5mg

Safety results:
Throughout the study, safety was assessed by spontaneous reporting of adverse experiences, by physician or nursing observation, and by direct questioning using a non-leading questionnaire before receiving study medication, at 12, 24, 48, 72 and 96 hours after study drug administration.
All subjects receiving at least one dose of paroxetine were included in clinical safety and tolerability evaluation.
A total of 8 AEs were reported in 7 subjects during the study. All AEs were mild in severity. No moderate or severe AEs occurred and there was no subject withdrawal due to AEs. The most commonly (5/8) reported AE was diarrhoea. 6 cases of AEs were suspected related to the investigational product. All AEs resolved by the end of the study.

<table>
<thead>
<tr>
<th>Adverse Events:</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (ITT)</td>
<td>12</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>No. subjects with AEs n (%)</td>
<td>4 (33.33%)</td>
<td>2 (16.67%)</td>
<td>2 (16.67%)</td>
</tr>
<tr>
<td>Most Frequent AEs</td>
<td>diarrhoea</td>
<td>Diarrhoea / dizziness</td>
<td>diarrhoea</td>
</tr>
</tbody>
</table>

No Serious Adverse Events occurred during the study.

Conclusions
The relationship between dose, Cmax and AUC for Paroxetine CR in healthy Chinese volunteers was not linear, and the within-subject variability was large (CVw was approximate 50%). These indicate that Paroxetine CR belongs to the high variant medication.
In the dose range of 12.5mg to 37.5mg, when dosing with 25mg and 37.5mg, dose normalized Cmax and AUC0-inf
increased non-proportionally compared with the referenced dose of 12.5mg. Saturable first-pass metabolism results in non-linear increases in paroxetine bioavailability with dose, but these are in accordance with expectations based on the known mechanisms of paroxetine clearance.

The average $C_{\text{max}}$ and $AUC_{0-\text{inf}}$ values for EMs are lower than for IMs at every dose. The average $C_{\text{max}}$ and $AUC_{0-\text{inf}}$ values following single doses of paroxetine in Chinese are a little higher than in Caucasians (in study 472). The possible reason of this result may be explained by that the mean CYP2D6 activity is lower in Asian than that in Caucasian populations.

Single doses of the paroxetine-CR tablet formulation at all dosage strengths (12.5, 25, 37.5mg) were generally safe and well tolerated in healthy Chinese volunteers. There were no serious adverse experiences or deaths reported during this study. The most frequent adverse event was diarrhoea. All probable and suspected drug related adverse events were mild and resolved at the end of study.

**Publications:** No Publications

Date updated: 20-Dec-2007