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.

<table>
<thead>
<tr>
<th>Study No.:</th>
<th>BRL29060A/799</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title:</td>
<td>Clinical Evaluation of BRL29060A (Paroxetine Hydrochloride Hydrate) in Posttraumatic Stress Disorder (PTSD) - A 52-Week, Non-Comparative, Uncontrolled Study for the Clinical Use Experience - &lt;Open-Label Study&gt;</td>
</tr>
<tr>
<td>Rationale:</td>
<td>This was a 52-week, non-comparative, uncontrolled study of paroxetine in Japanese PTSD patients to obtain clinical experience regarding efficacy and safety. In this study, subjects received paroxetine 20mg–40mg once daily after an evening meal.</td>
</tr>
<tr>
<td>Phase:</td>
<td>III</td>
</tr>
<tr>
<td>Study Period:</td>
<td>17 May 2002 - 19 November 2004</td>
</tr>
<tr>
<td>Study Design:</td>
<td>A 52-week, open-label study. This study was a study of non-comparative, uncontrolled design.</td>
</tr>
<tr>
<td>Centers:</td>
<td>11 centers in Japan</td>
</tr>
<tr>
<td>Indication:</td>
<td>Posttraumatic Stress Disorder (PTSD)</td>
</tr>
<tr>
<td>Treatment:</td>
<td>Posttraumatic Stress Disorder (PTSD)</td>
</tr>
</tbody>
</table>

Baseline Phase:
The one week prior to the first dose of the treatment phase medication was defined as the baseline phase. During this period, subjects were given placebo (Dose Level I) once daily after an evening meal to determine their eligibility to enter the treatment phase. If subjects had been treated with any prohibited concomitant medication, it was washed out during this period.

Treatment Phase:
Subjects took the treatment phase medication once daily after an evening meal. All subjects were maintained at Dose Level II (20 mg/day) for the first 2 weeks. If a sufficient clinical response (1. Very much improved” or 2. Much improved” based on the Clinical Global Impression (CGI) Global Improvement was achieved, the subject continued on the same dose level. When the clinical response was not sufficient but the investigational product was tolerated, the dose was to be increased to Dose Level III (30 mg/day) and then to Dose Level IV (40 mg/day) at intervals of at least 2 weeks, until a sufficient response was reached. Once a sufficient response was obtained, the treatment was maintained at that dose. The treatment phase was scheduled for a total of 52 weeks. In those subjects who received Dose Level III or IV, dosage reductions to the next lowest level (Dose Level II or III) consequent to an adverse event were permitted. Dosage adjustment was made at the discretion of the investigator or sub-investigator. The medication was dispensed at each clinic visit.

Taper Phase:
Subjects who were on Dose Level IV at the end of the treatment phase or at withdrawal entered a 2-week taper phase, and took Taper Medication I (30 mg/day) once daily after an evening meal for the first week and Taper Medication II (20 mg/day) for the second week. Subjects who were on Dose Level III at the end of the treatment phase or at withdrawal entered a 1-week taper phase and took Taper Medication II for 1 week. No taper phase was required for subjects finishing on Dose Level II.

Objectives: The objective was to obtain clinical experience regarding the efficacy and safety of paroxetine administered at 20mg–40mg once daily after an evening meal for 52 weeks in PTSD subjects.

Primary Outcome/Efficacy Variable:
Change from baseline in the Clinician-Administered Posttraumatic Stress Disorder Scale One Week Symptom Status Version (CAPS-SX) total score

Secondary Outcome/Efficacy Variable(s):
Proportion of responders based on the CGI Global Improvement
Change from baseline in the CAPS-SX re-experiencing cluster score
Change from baseline in the CAPS-SX avoidance/numbing cluster score
Change from baseline in the CAPS-SX hyperarousal cluster score
Change from baseline in the CGI Severity of Illness score

Statistical Methods:
Primary Efficacy Endpoints--Summary statistics for change from baseline in the CAPS-SX total score was presented and two-sided 95% confidence intervals constructed for the mean.
Secondary Efficacy Endpoints--Summary statistics for change from baseline in the CAPS-SX re-experiencing, avoidance/numbing and hyperarousal cluster scores were presented and two-sided 95% confidence intervals constructed for the mean. Two-sided 95% confidence intervals for the proportion of responders based on the CGI Global Improvement were presented. Summary statistics for change from baseline in the CGI Severity of Illness score was presented.

< Efficacy at Each Dose Level >
Efficacy variables were assessed at each dose level.

Handling of Missing Data--For primary analyses, missing data was estimated by the last observation carried forward method (LOCF).

Study Population:

<table>
<thead>
<tr>
<th>Paroxetine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Subjects:</td>
</tr>
<tr>
<td>Planned, N</td>
</tr>
<tr>
<td>Entered, N</td>
</tr>
<tr>
<td>Completed, n (%)</td>
</tr>
<tr>
<td>Total Number Subjects Withdrawn, N (%)</td>
</tr>
<tr>
<td>Withdrawn due to Adverse Events n (%)</td>
</tr>
<tr>
<td>Withdrawn due to Lack of Efficacy n (%)</td>
</tr>
<tr>
<td>Withdrawn for other reasons n (%)</td>
</tr>
</tbody>
</table>

Demographics

Paroxetine
- N (FAS: Full Analysis Set): 49
- Females: Males = 43: 6
- Mean Age, years (SD): 34.5 (10.68)
- Japanese, n (%): 49 (100)

Primary Efficacy Results:

<table>
<thead>
<tr>
<th>(FAS-LOCF)</th>
<th>Paroxetine</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPS-SX Total Score</td>
<td>N</td>
</tr>
<tr>
<td>Baseline (SD)</td>
<td>49</td>
</tr>
<tr>
<td>Mean Change from baseline (SD) at Week4</td>
<td>49</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(-24.2, -14.1)</td>
</tr>
<tr>
<td>Mean Change from baseline (SD) at Week12</td>
<td>49</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(-28.7, -16.8)</td>
</tr>
<tr>
<td>Mean Change from baseline (SD) at Week24</td>
<td>49</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(-36.0, -22.2)</td>
</tr>
<tr>
<td>Mean Change from baseline (SD) at Week52</td>
<td>49</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(-39.3, -25.3)</td>
</tr>
</tbody>
</table>

Secondary Outcome Variable(s):

<table>
<thead>
<tr>
<th>(FAS-LOCF)</th>
<th>Paroxetine</th>
</tr>
</thead>
<tbody>
<tr>
<td>CGI Global Improvement Responder Analysis</td>
<td>N</td>
</tr>
<tr>
<td>Responders at Week4, n (%)</td>
<td>49</td>
</tr>
<tr>
<td>Responders at Week12, n (%)</td>
<td>49</td>
</tr>
<tr>
<td>Responders at Week24, n (%)</td>
<td>49</td>
</tr>
<tr>
<td>Responders at Week52, n (%)</td>
<td>49</td>
</tr>
<tr>
<td>CAPS-SX Re-experiencing cluster score (Cluster B)</td>
<td>N</td>
</tr>
</tbody>
</table>
### Baseline (SD)

| Mean Change from baseline (SD) at Week4 | 49 | 20.1 (7.76) |
| Mean Change from baseline (SD) at Week12 | 49 | -6.6 (7.74) |
| Mean Change from baseline (SD) at Week24 | 49 | -5.9 (9.15) |
| Mean Change from baseline (SD) at Week52 | 49 | -8.4 (9.52) |

### CAPS-SX Avoidance/Numbing cluster score (Cluster C)

| Mean Change from baseline (SD) at Week4 | 49 | -6.6 (7.74) |
| Mean Change from baseline (SD) at Week12 | 49 | -5.9 (9.15) |
| Mean Change from baseline (SD) at Week24 | 49 | -8.4 (9.16) |
| Mean Change from baseline (SD) at Week52 | 49 | -8.6 (9.16) |

### CAPS-SX Hyperarousal cluster score (Cluster D)

| Mean Change from baseline (SD) at Week4 | 49 | -7.8 (8.86) |
| Mean Change from baseline (SD) at Week12 | 49 | -11.1 (8.28) |
| Mean Change from baseline (SD) at Week24 | 49 | -12.4 (11.24) |
| Mean Change from baseline (SD) at Week52 | 49 | -14.4 (11.73) |

### CGI Severity of Illness score

| Mean Change from baseline (SD) at Week4 | 49 | -1.5 (1.14) |
| Mean Change from baseline (SD) at Week12 | 49 | -1.1 (0.97) |
| Mean Change from baseline (SD) at Week24 | 49 | -1.7 (1.21) |

### Sub-group analysis:

#### CGI Severity of illness (Baseline) Dose at endpoint

<p>| Sub-group analysis: | Mean Change from baseline (SD) in CAPS-SX Total score at Week52 by dose level at endpoint and by baseline CGI Severity of Illness grouping (FAS-LOCF) |</p>
<table>
<thead>
<tr>
<th>CGI Severity of illness (Baseline)</th>
<th>Dose at endpoint</th>
<th>N</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (SD)</td>
<td>20mg/day, n (%)</td>
<td>15</td>
<td>13 (86.7)</td>
</tr>
<tr>
<td></td>
<td>30mg/day, n (%)</td>
<td>4</td>
<td>2 (50.0)</td>
</tr>
<tr>
<td></td>
<td>40mg/day, n (%)</td>
<td>7</td>
<td>2 (28.6)</td>
</tr>
<tr>
<td></td>
<td>Sub Total, n (%)</td>
<td>26</td>
<td>17 (65.4)</td>
</tr>
<tr>
<td>Moderately ill or more</td>
<td>20mg/day, n (%)</td>
<td>6</td>
<td>4 (66.7)</td>
</tr>
<tr>
<td></td>
<td>30mg/day, n (%)</td>
<td>5</td>
<td>4 (80.0)</td>
</tr>
<tr>
<td></td>
<td>40mg/day, n (%)</td>
<td>12</td>
<td>8 (66.7)</td>
</tr>
<tr>
<td></td>
<td>Sub Total, n (%)</td>
<td>23</td>
<td>16 (69.6)</td>
</tr>
</tbody>
</table>

### Sub-group analysis: CGI Global Improvement Responders

<table>
<thead>
<tr>
<th>CGI Global Improvement Responders (Very much improved and Much improved) at Week52 by dose level at endpoint and by baseline CGI Severity of Illness grouping (FAS-LOCF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CGI Severity of illness (Baseline)</td>
</tr>
<tr>
<td>-----------------------------------</td>
</tr>
<tr>
<td>Moderately ill or less</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Markedly ill or more</td>
</tr>
<tr>
<td></td>
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<td></td>
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<tr>
<td></td>
</tr>
</tbody>
</table>

### Safety Results:

#### Most Frequent Adverse Events – On-Therapy

<table>
<thead>
<tr>
<th>Most Frequent Adverse Events – On-Therapy</th>
<th>Paroxetine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with any AE(s), n(%)</td>
<td>48 (92.3)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>29 (55.8)</td>
</tr>
<tr>
<td>Symptom</td>
<td>n (%)</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>-------</td>
</tr>
<tr>
<td>Nausea</td>
<td>27 (51.9)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>19 (36.5)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10 (19.2)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>10 (19.2)</td>
</tr>
<tr>
<td>Headache</td>
<td>9 (17.3)</td>
</tr>
<tr>
<td>Post-traumatic stress disorder (Exacerbation of PTSD)</td>
<td>7 (13.5)</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>6 (11.5)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>6 (11.5)</td>
</tr>
<tr>
<td>Malaise</td>
<td>6 (11.5)</td>
</tr>
<tr>
<td>Hepatic function abnormal</td>
<td>6 (11.5)</td>
</tr>
</tbody>
</table>

### Serious Adverse Events - On-Therapy

<table>
<thead>
<tr>
<th>Event</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paroxetine</td>
<td></td>
</tr>
<tr>
<td>Subjects with non-fatal SAEs, n (%) [related]</td>
<td>9 (17.3) [0]</td>
</tr>
<tr>
<td>Non-accidental overdose</td>
<td>2 (3.8) [0]</td>
</tr>
<tr>
<td>Post-traumatic stress disorder (Exacerbation of PTSD)</td>
<td>2 (3.8) [0]</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>1 (1.9) [0]</td>
</tr>
<tr>
<td>Aggression</td>
<td>1 (1.9) [0]</td>
</tr>
<tr>
<td>Depression</td>
<td>1 (1.9) [0]</td>
</tr>
<tr>
<td>Dissociation</td>
<td>1 (1.9) [0]</td>
</tr>
<tr>
<td>Impulsive behaviour</td>
<td>1 (1.9) [0]</td>
</tr>
<tr>
<td>Mania</td>
<td>1 (1.9) [0]</td>
</tr>
<tr>
<td>Abortion induced*</td>
<td>1 (2.2) [0]</td>
</tr>
</tbody>
</table>

*: Percentage corrected for gender

### Conclusion:
See publication below.

### Publications:
Yoshiharu Kim, MD, PhD; Nozomu Asukai, MD, PhD; Takako Konishi, MD, PhD; Hiroshi Kato, MD, PhD; Hideto Hirosune, MD; Masaharu Maeda, MD, PhD; Hirotaka Inoue, PhD; Hiroyasu Narita, PhD; and Masaru Iwasaki, MD, PhD. Clinical evaluation of paroxetine in post-traumatic stress disorder (PTSD): 52-week, non-comparative open-label study for clinical use experience. Psychiatry and Clinical Neurosciences 2008; 62: 646–652.

Date Updated: 04-Feb-2009