1. TITLE PAGE

Abbreviated Clinical Study Report

Title: K.E.E.P.E.R. (Keppra® Epilepsy Evaluation of Patient Time to Response)
A Phase IV, Open-Label, Multi-Center, Community-Based Trial Studying the Safety and Efficacy of Levetiracetam as Add-on Therapy in Adult Patients with Treatment-Resistant, Partial-Onset Epilepsy

Report Version: Final
Report Date: 14 May 2003
Study Number: N01030
Protocol Number: RPCE00A1201
Development Phase: Phase IV
Product: Levetiracetam (Keppra®)
Study Initiation: 24 March 2000 (First patient enrolled)
Study Completion: 30 July 2001 (Last patient completed)
Principal Investigator: Multicenter
Sponsor: UCB Pharma, Inc.
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SIGNATURE PAGE

PRINCIPAL OR COORDINATING INVESTIGATOR(S) SIGNATURE(S)

OR SPONSOR’S RESPONSIBLE MEDICAL OFFICER

STUDY TITLE: K.E.E.P.E.R. (Keppra® Epilepsy Evaluation of Patients Time to Response) A Phase IV, Open-Label, Multi-Center, Community-Based Trial Studying the Safety and Efficacy of Levetiracetam as Add-on Therapy in Adult Patients with Treatment-Resistant, Partial-Onset Epilepsy

I HAVE READ THIS REPORT AND CONFIRM THAT TO THE BEST OF MY KNOWLEDGE IT ACCURATELY DESCRIBES THE CONDUCT AND RESULTS OF THE STUDY

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<thead>
<tr>
<th>NAME(S)</th>
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<tr>
<td>INVESTIGATOR:</td>
<td>N/A</td>
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<td>CLINICAL RESEARCH PHYSICIAN:</td>
<td>Leslie Magnus, MD</td>
<td>1/3/04</td>
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<td>John Han, Ph.D.</td>
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<td>STATISTICIAN:</td>
<td>Marian DiGiandomenico, MS</td>
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<td>CTM:</td>
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<td>AFFILIATION:</td>
<td>UCB Pharma Inc.</td>
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2. SYNOPSIS

<table>
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<tr>
<th><strong>Title of the Study:</strong></th>
<th>K.E.E.P.E.R. (Keppra® Epilepsy Evaluation of Patient Time to Response)</th>
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<tbody>
<tr>
<td></td>
<td>A Phase IV, Open-Label, Multi-Center Community-Based Trial Studying the Safety and Efficacy of Levetiracetam as Add-on Therapy in Adult Patients with Treatment-Resistant, Partial-Onset Epilepsy</td>
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<td><strong>Principal Investigator(s):</strong></td>
<td>638 investigators participated in this study.</td>
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<td><strong>Study Center(s):</strong></td>
<td>This study was conducted at 638 sites in the United States.</td>
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<td><strong>Publication (ref.):</strong></td>
<td>None</td>
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<td><strong>Study Period:</strong></td>
<td>Study Period: First patient enrolled: 24 March 2000</td>
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<td>Last patient completed: 30 July 2001</td>
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<td><strong>Objectives:</strong></td>
<td>The primary goals of the study were to gather additional data on the safety and tolerability of the administration of levetiracetam as add-on therapy in patients with partial-onset seizures in community-based practices, and to measure the seizure reduction effect at the protocol-determined final doses (up to 3,000 mg/day). The secondary goals of the study were to assess the number of days since the last seizure at the final visit, to observe the percent reduction in the seizure frequency compared with baseline with percent reduction expressed as a categorical response to treatment (&gt;25% increase in seizures; 25% increase to &lt;25% decrease in seizures; 25% to &lt;50% decrease; 50% to &lt;75% decrease; 75% to &lt;100% decrease; or entirely seizure-free), and to tabulate the number of patients receiving each final dose.</td>
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Methodology: Study N01030 was an open-label multicenter study. Patients ≥16 years of age with partial-onset seizures were enrolled. At Visit 1, informed consent was obtained. Visit 1 also included: demographic and baseline information; a general medical and surgical history review, including the etiology (if known) and history of seizures; a complete listing of all antiepileptic drugs (AED) taken in the last three years; non-AED concomitant medications; physical and neurological examinations; measurement of vital signs; and the number(s) and type(s) of seizures experienced by the patient over the previous three months. The following were also performed at the investigator's discretion: clinical laboratory tests (complete blood count and chemistry, including assessment of AED blood level) if they had not been performed in the previous month; an electroencephalogram; Magnetic Resonance Imaging or Computerized Tomography Scan. A urine pregnancy test was performed on all women of childbearing potential.

Enrolled patients were given a Daily Record Card (DRC) with instructions on how to record seizures, adverse events, and concomitant medications. Each patient began treatment with levetiracetam at a total daily dose of 1,000 mg (administered as a divided dose of 500 mg twice daily [bid]). Four subsequent visits were planned for each patient during the 16-week treatment period (Visit 2 at Week 2, Visit 3 at Week 4, Visit 4 at Week 10, and Visit 5, the final visit, at Week 16). Based on the patient’s response to study medication, the investigator had the option of adjusting the patient's total daily dose at Visits 2 and 3, up to 3,000 mg (1,500 mg bid). The patient's dose was to remain stable after Visit 3 unless, in the investigator's opinion, a dosage modification was clinically necessary to achieve maximum benefit or for safety reasons. The DRC was collected at each visit and reviewed for seizure information such as frequency, types of seizures, and the number of days seizure-free since the previous visit. A new DRC was given to the patient at each visit. At the final visit (Visit 5/Week 16), in addition to the events scheduled for Visits 2 through 4 (assessment of adverse events, treatment compliance and both AED and non-AED concomitant medications), physical and neurological evaluations (including weight and vital signs) were to be performed. Prescriptions for levetiracetam were issued to patients who were to continue on levetiracetam, or for those not continuing on levetiracetam, the study medication dose was to be reduced gradually.

Number of patients (planned and analyzed): Planned enrollment was a maximum of 5,000 patients at 800 to 1,000 investigational sites. The actual number of patients enrolled in the study was 1,048; 1,030 patients were included in the intent-to-treat (ITT) analysis. The study was conducted at 638 sites in the United States; 326 sites enrolled one or more patients.

Test product, dose and mode of administration, batch number: Oral doses of levetiracetam 250 mg and 500 mg tablets (lot numbers 00A27 and 00G05 for 250 mg and lot numbers 00A20, 00C21, and 00F07 for 500 mg) were manufactured at UCB S.A. Pharma Sector, Braine l’Alleud, Belgium. Study medication was packaged at Simirex, Inc., Mount Laurel, New Jersey, USA.
**Duration of Treatment:** The treatment period of the study was 16 weeks, including four weeks of the Dose Adjustment Phase and 12 weeks of the Target Dose Period. After completion of the study, patients could continue to receive levetiracetam by conversion to prescription.

**Criteria for Evaluation:**

**Efficacy:** The primary efficacy variable was the percent reduction from baseline in partial-onset (type I) seizure frequency per week over the 16-week treatment period. The ITT population, used for efficacy analyses, consisted of patients with at least one measurement of seizure frequency as reported on the DRC. The percent reduction from baseline was defined as: (Seizure frequency per week during baseline) minus (seizure frequency per week during the treatment period) divided by (seizure frequency per week during baseline). The seizure frequency per week was derived from the historical seizure count for the baseline and from the seizure count information recorded on the case report form (CRF) for the treatment period. In both cases, it was defined as the number of seizures standardized to a seven-day period. The historical seizure count was defined as the number and type(s) of seizures reported by the patient at Visit 1 for the previous three months.

**Safety:** The ITT population was defined as all enrolled patients who received at least one dose of study medication. Safety assessments included reports of treatment-emergent adverse events, changes in vital signs (pulse, systolic and diastolic blood pressure and weight), and physical and neurological examination findings. Adverse events were summarized descriptively by body term and reported term.

**Statistical Methods:**
Due to the open nature of this study, efficacy and safety analyses were conducted primarily by descriptive methods on the ITT. The categorical variables (whether ordered or not), contained the numbers of observations and corresponding percentages, as well as distribution parameters of continuous variables consisting of the number of available observations, mean, standard deviation (SD), minimum, median and maximum; 25th and 75th percentiles could be added as needed.

**SUMMARY-CONCLUSIONS**

**Efficacy Results:** For the Overall Treatment Period, the median percent reduction from baseline in partial-onset (type I) seizure frequency per week over the 16 week treatment period was 62.3% for the 936 patients with seizure information. The responder rate (patients with ≥50% reduction from baseline in partial-onset seizure frequency per week) was 56.8% during the Dosage Adjustment Period, and 62.1% during the Evaluation Phase (Target Dose Period). The partial seizure responder rate (patients with a ≥ 50% reduction in their seizures) was 66.7% for the last six weeks of the study, and responder rate for the Overall Treatment Period was 57.9%. In addition, 170 (16.6%) patients in the ITT population who were not seizure-free at baseline had a 100% response rate throughout the entire treatment period. For patients assessed using the Investigator's Global Evaluation Scale, 35.5% (366) showed marked improvement, 25.0% (257) showed moderate improvement, and 10.9% (112) showed a slight improvement in the numbers of seizures. There was no change in seizure frequency for 17.4% (179) of patients.
Safety Results:
A total of 1,030 patients were included in the ITT population for the safety analysis. Safety endpoints for this study included the following: daily dosage of levetiracetam and extent of exposure; changes from screening in vital signs; possibly clinically significant abnormalities in vital signs; and physical and neurological abnormalities at the final visit. The most common treatment-emergent adverse events experienced by ≥5% of patients were somnolence, asthenia, dizziness, and headache. A total of 474 (46.0%) patients experienced at least one adverse event. Three hundred ninety-five (38.3%) patients experienced drug-related adverse events, and three (0.3%) experienced drug-related serious adverse events. There were 133 (12.9%) patients with adverse events which led to discontinuation from the study as reported on the study termination page of the Case Report Form (CRF). There were 26 (2.5%) patients with serious adverse events. Three patients died while participating in the study; all three deaths were considered to have an unlikely relationship to study medication. Following database lock on 14 February 2002 and statistical analysis, an additional 13 CRFs were submitted to UCB. This information was not entered into the database, however, the CRFs were reviewed. There were 10 males and 3 females. There were no SAEs or PTAEs reported on these CRFs. A separate group of six patients were reported to have completed the study on the study termination page; however on the AE page they were listed as having discontinued due to an AE. There were no deaths or serious adverse events reported in these additional CRFs.

CONCLUSIONS: In this open label community based study, Keppra® was well tolerated with the most common adverse events being somnolence, asthenia, dizziness, and headache. Only 12.9% of patients discontinued the study due to adverse events. Keppra® was effective with a partial seizure responder rate of 66.7% for the last six weeks of the study, and a 57.9% responder rate overall. As measured on the Investigator's Global Evaluation Scale, 71.4% of patients evaluated showed improvement with 35.5% showing marked improvement in numbers of seizures.