

CLINICAL STUDY REPORT SYNOPSIS: N01315

Name of company: UCB Biosciences, Inc.	Individual study table referring to part of the dossier: Not applicable	<i>(For National Authority Use Only)</i>
Name of finished product: Not applicable	Volume: Not applicable	
Name of active ingredient: Brivaracetam	Page: Not applicable	
Title of study: An Open-Label, Multinational, Multicenter, Follow-Up Study to Evaluate the Long-Term Safety and Efficacy of Brivaracetam, used at a Flexible Dose up to a Maximum of 200mg/Day, in Subjects Aged 16 Years or Older Suffering from Epilepsy		
Study sites: A total of 141 sites in Australia, Belgium, Canada, Czech Republic, France, Germany, Hungary, Italy, Spain, Sweden, and the US were initiated in the study.		
Publication(s) (reference[s]): None.		
Study period: This study is complete. Study duration from the first subject enrolled to the final subject completed was 8 years, 4 months.		Phase of development: Phase 3
First subject enrolled: 19 Nov 2008		
Last subject completed: 20 Mar 2017		
<p>Objectives: The primary objective was to evaluate the long-term safety and tolerability of brivaracetam (BRV) at individualized doses with a maximum of 200mg/day in subjects suffering from epilepsy. N01315 started with a maximum dose of BRV 150mg/day; however, the maximum dose was increased to BRV 200mg/day to align with the more recent long-term follow-up (LTFU) studies (Protocol Amendment 2 [02 Aug 2011]).</p> <p>The secondary objective of N01315 was to evaluate the maintenance of efficacy over time of BRV.</p> <p>The exploratory objectives were to explore impact on health-related quality of life, anxiety, and depression, to obtain a description of patient's self-reported health status, and to collect data on medical resources used and on indirect cost parameters.</p>		
<p>Methodology: N01315 was a Phase 3, multinational, multicenter, noncomparative, open-label, single-arm, LTFU study to evaluate long-term safety and efficacy of BRV used at individualized doses with a maximum of 200mg/day in subjects aged 16 years or older diagnosed with epilepsy. For each subject, this study ran throughout the duration of the clinical development period of BRV and continued until a marketing authorization was granted by a health authority in an indication for the adjunctive treatment in adults with refractory partial onset seizures (POS), whether or not secondarily generalized, until the Sponsor decided to close the study, until subjects transition to another BRV study, until a managed access program, named patient</p>		

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program, compassionate use program, or similar type of access program was established as allowed per country-specific requirement in addition to legal and regulatory guidelines, or until BRV development was stopped by the Sponsor.

Subjects who enrolled in the study entered an Evaluation Period at a recommended starting dose of 100mg/day. The dose of BRV could have then been adjusted based on the individual subject's seizure control and tolerability. Dose increases could have been made in increments of a maximum 50mg/day on a weekly basis and up to a maximum dose of 200mg/day; dose decreases could have been made in steps of maximum 50mg/day on a weekly basis with a last down-titration step at 20mg/day for 1 week. Subjects who completed the Down-Titration Period or subjects who discontinued during the Evaluation Period without entering the Down-Titration Period entered a Study Drug-Free Period for a minimum of 2 weeks and a maximum of 4 weeks. The maximum allowable daily dose for this study was increased from 150mg/day to 200mg/day based on integrated amendment 2 to the protocol. The daily dose should have been administered in 2 equal intakes (morning and evening), taken with or without food.

Subjects entering N01315 on BRV monotherapy could have converted to adjunctive BRV treatment during the N01315 study. In this case, as well as for subjects entering N01315 taking BRV and a concomitant anti-epileptic drug (AED), the Investigator may have adapted the concomitant AED drug/dosage for safety or efficacy reasons. In case of excellent efficacy and tolerability of BRV, withdrawal of concomitant AED(s) resulting in monotherapy with BRV may have been reattempted by the Investigator.

Number of subjects (planned and analyzed): No sample size calculation was done. Sample size was dependent upon recruitment into and completion of preceding studies. It was estimated that approximately 300 to 600 subjects were to enter the study. However, the number of subjects entered was reduced due to the premature discontinuation of feeder studies N01276 and N01306. A total of 108 subjects were enrolled into N01315. The Safety Analysis Set consisted of all subjects who took at least 1 dose of BRV. The statistical summaries included all subjects who were dosed with BRV.

Diagnosis and main criteria for inclusion: This study enrolled male or female subjects with epilepsy aged 16 years or older who had participated in the core studies (N01276 and N01306, both conversion to monotherapy studies). N01315 gave subjects for whom the Investigator believed a reasonable potential benefit from the long-term administration of BRV was expected the opportunity to continue BRV treatment. Subjects with severe medical, neurological, and psychiatric disorders, including current suicidal ideation or behavior, or laboratory values which may have had an impact on the safety of the subject, as determined by the Investigator, were

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<p>excluded. Female subjects without childbearing potential were eligible. Female subjects with childbearing potential were eligible if they used a medically accepted contraceptive method for the duration of the study. The subject must have understood the consequences and potential risks of inadequately protected sexual activity, been educated about and understood the proper use of contraceptive methods, and undertook to inform the Investigator of any potential change in status.</p>		
<p>Test product, dose(s) and mode of administration, batch number(s): Oral tablets of BRV 10 and 25mg were used in this study. The recommended individual starting dose for each subject was 100mg/day. The doses administered in this study must have complied with doses that could have been administered with either BRV 10mg tablets, 25mg tablets, or a combination of these 2 strengths in a total daily dose that could have been administered in 2 equal doses. The maximum allowable daily dose of BRV was increased from 150mg/day to 200mg/day based on Protocol Amendment 2 (02 Aug 2011).</p> <p>Brivaracetam oral tablets were provided in the following strengths: 10 and 25mg. For the 10mg strength, batch numbers were as follows: BX1001843, BX1002989, BX1004257, BX1007320, BX1008825, BX1010469, BX1011638, BX1012799, BX1002165, BX1002947, BX1003801, BX1001604, and BX1003755. For the 25mg strength, batch numbers were as follows: BX1001842, BX1003004, BX1003763, BX1006478, BX1008226, BX1010470, BX1011639, BX1012800, and BX1003756.</p>		
<p>Duration of treatment: The study continued until a marketing authorization was granted by a health authority, until the Sponsor decided to close the study, or until BRV development was stopped by the Sponsor.</p>		
<p>Reference therapy, dose(s) and mode of administration, batch number(s): None.</p>		
<p>Criteria for evaluation:</p> <p>Safety: The safety variables of N01315 were as follows:</p> <ul style="list-style-type: none"> • Occurrence of a treatment-emergent adverse event (TEAE) • Withdrawal due to an adverse event (AE) • Occurrence of a serious AE (SAE) <p>Other safety variables include:</p> <ul style="list-style-type: none"> • Laboratory tests (blood chemistry, hematology, and urinalysis) 		

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<ul style="list-style-type: none"> • Vital signs (systolic blood pressure, diastolic blood pressure, pulse rate) and body weight • Electrocardiogram (ECG) • Physical and neurological examination • Change in Hospital Anxiety and Depression Scale (HADS) scores from the Baseline of the previous study to each assessment for the first 2 years and to the final Evaluation Period assessment during the first 2 years 		
<p>Efficacy:</p> <p>The secondary efficacy variable of N01315 was as follows:</p> <ul style="list-style-type: none"> • Percentage of subjects on continuous BRV monotherapy for at least 3 months, at least 6 months, and at least 12 months of the Evaluation Period. <p>Other efficacy variables included:</p> <ul style="list-style-type: none"> • Partial onset seizure (Type I) frequency per 28 days during the Evaluation Period • Percent reduction in POS (Type I) frequency per 28 days from Baseline of the previous study to the Evaluation Period • Percentage of subjects continuously seizure-free for all seizure types (I+II+III) for at least 6 months and at least 12 months during the Evaluation Period • Change in Patient-Weighted Quality of Life in Epilepsy Questionnaire (QOLIE-31-P) scores from Baseline of the previous study to each assessment for the first 2 years and to the last Evaluation Period assessment during the first 2 years • EuroQoL-5 Dimensions (EQ-5D) questionnaire response for each assessment for the first 2 years for the Evaluation Period and for the last assessment during the first 2 years of the Evaluation Period 		
<p>Pharmacokinetics: Plasma samples to analyze BRV and concomitant AED plasma concentrations were no longer obtained, as directed by the integrated Protocol Amendment 2. No summaries of BRV or concomitant AED plasma levels were provided; plasma levels were only provided in subject data listings.</p>		
<p>Statistical methods: The Safety Analysis Set consisted of all subjects who took at least 1 dose of study drug. Summaries of demographics and Baseline characteristics, medical history, AEDs,</p>		

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non-AEDs, HADS, direct and indirect cost parameters, socioprofessional data, study drug exposure, and safety outcomes were provided for the Safety Analysis Set.

The Efficacy Analysis Set consisted of all subjects who took at least 1 dose of study drug and had at least 1 seizure daily record card day during the Evaluation Period.

Summaries of seizure outcomes, epilepsy history, QOLIE-31-P, and EQ-5D were provided for the Efficacy Analysis Set.

Descriptive statistics, such as the mean, standard deviation (SD), median, 25th percentile, 75th percentile, minimum value, and maximum value for quantitative variables, and counts and percentages for categorical variables, were provided.

Overall subject disposition was summarized for all enrolled subjects (ie, all subjects who signed informed consent), the Safety Analysis Set, and by geographic region for the Safety Analysis Set. Demographic variables collected at the time of entry into the core study were summarized for the Safety Analysis Set and by geographic region for the Safety Analysis Set.

The number and percentage of subjects exposed to BRV were summarized overall and by the modal dose category. The number and percentage of subjects in each exposure duration cohort (≥ 3 , ≥ 6 , ≥ 12 months, and so forth) were summarized. The number and percentage of subjects within each modal dose category were summarized for each exposure duration cohort. Percentages were relative to the total number of subjects in each exposure duration cohort.

Summaries of safety were provided for all subjects in the Safety Analysis Set and also by geographic region.

The cumulative proportion of subjects able to achieve BRV monotherapy for 3, 6, and 12 months during the Evaluation Period was summarized. Brivaracetam monotherapy was defined as continuous treatment with BRV only (ie, no treatment with another AED). Use of rescue AED medications for a duration of no more than 2 consecutive days did not disqualify a subject from being defined as on continuous monotherapy provided the use of rescue AED medication did not exceed more than 1 time per week.

The numbers and percentages of subjects who were seizure free for all seizure types for any continuous 6-month interval, 12-month interval, 18-month interval, and so forth were summarized overall for the period of time that subjects were being treated with BRV and by exposure duration cohort. Percent reduction from Baseline for POS frequency was summarized with quantitative descriptive statistics for the On-Treatment Period and by 3-month time intervals over the On-Treatment Period. The summary over the On-Treatment Period included all subjects in the Efficacy Analysis Set. Similar summaries were provided for the full cohort interval and by 3-month time intervals for each exposure duration cohort. Percent reduction from

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<p>Baseline for POS frequency was summarized in the same manner by geographic region. Observed values for QOLIE-31-P total score and subscale scores for Seizure Worry, Daily Activities/Social Function, Energy/Fatigue, Emotional Well-Being, Cognitive Function, Medication Effects, Overall Quality of Life, and Health Status were summarized for Baseline and Last Value for the Efficacy Analysis Set.</p> <p>Qualitative EuroQoL-5 Dimensions (EQ-5D) items were summarized for Baseline and Last Value for the Efficacy Analysis Set. Additionally these parameters were summarized for Baseline and by visit for each study visit cohort.</p> <p>Direct cost parameters, number of school or working days lost, and socioprofessional data were not summarized, but are provided in subject data listings. All summaries of efficacy data were descriptive; no statistical testing was performed.</p>		
<p>Summary and conclusions:</p> <p>Subject disposition: In N01315, 108 subjects were enrolled. All 108 enrolled subjects were included in the Safety Analysis Set.</p>		

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Safety results: At individualized doses up to a maximum of 200mg/day, BRV was well tolerated when administered as treatment in adult subjects with epilepsy.

- All subjects in the Safety Analysis Set (108 subjects) received at least 1 dose of BRV for a total of 360.7 subject-years of exposure. Approximately half of the subjects (58 subjects; 53.7%) received a modal dose of ≥ 100 mg/day to < 150 mg/day. Three subjects received a total daily dose of BRV > 200 mg/day (2 subjects received a dose > 200 mg/day for 1 day and 1 subject received a dose > 200 mg/day for 97 days); no TEAEs were reported during the time which the subject received this dose. In addition, approximately one-half of the subjects (56 subjects [51.9%]) had ≥ 24 months of exposure to BRV.
- A total of 98 subjects reported at least 1 TEAE (90.7%; 1108 events) and the most commonly reported TEAEs ($\geq 10\%$ by PT) included nasopharyngitis and convulsion (19 subjects [17.6%], each), depression (18 subjects [16.7%]), fatigue (17 subjects [15.7%]), and fall, headache, anxiety, and insomnia (15 subjects [13.9%], each), dizziness (14 subjects [13.0%]), back pain and rash (13 subjects [12.0%], each), diarrhea (12 subjects [11.1%]), and contusion (11 subjects [10.2%]).
- A total of 17 subjects (15.7%) and 56 subjects (51.9%) experienced TEAEs of maximum intensity considered to be mild or moderate, respectively. A total of 25 subjects (23.1%) reported TEAEs that were considered to be severe. Severe TEAEs reported by ≥ 2 subjects were convulsion and grand mal convulsion (3 subjects [2.8%], each), and angina pectoris, nasopharyngitis, and status epilepticus (2 subjects [1.9%], each). Seventeen of the 25 subjects reported severe TEAEs that were assessed by the Investigators as drug-related.
- Drug-related TEAEs reported by $\geq 5\%$ of subjects included depression (9 subjects [8.3%]) and fatigue and convulsion (6 subjects [5.6%], each). All other drug-related TEAEs were reported by $< 5\%$ of subjects each.
- A total of 26 subjects (24.1%) reported at least 1 treatment-emergent SAE:
 - One subject (Subject ██████████) died. This subject experienced a SUDEP 467 days after the first dose of BRV in this study. The subject was not taking study drug at the time of the SUDEP. The SAE was considered not related to study drug by the Investigator.
 - The most common treatment-emergent SAEs reported were convulsion (5 subjects [4.6%]), angina pectoris (3 subjects [2.8%]), atrial fibrillation, cholelithiasis, contusion, and grand mal convulsion (2 subjects [1.9%], each).

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<ul style="list-style-type: none"> - The drug-related treatment-emergent SAEs by PT were convulsion (1 subject with a maximum intensity of moderate [0.9%], and 1 subject with a maximum intensity of severe [0.9%]), angina pectoris, pancreatitis acute, intentional overdose, suicide attempt, epileptic seizure, and grand mal convulsion (1 subject [0.9%], each). • No clinically relevant findings were observed for any changes from Baseline in hematology, blood chemistry, urinalysis parameters, vital signs, body weight, or ECGs. • The majority of subjects reported no abnormal physical or neurological examination findings. In addition, the majority of subjects had no findings in psychiatric or mental status reported during the study. 		
<p>Efficacy results: At individualized doses up to a maximum of 200mg/day, administration of BRV resulted in the following:</p> <ul style="list-style-type: none"> • Among all subjects, 6.5% had a continuous BRV monotherapy period of 3 to 6 months, 7.4% had a continuous BRV monotherapy period of 6 to 12 months and 12 to 18 months, 4.6% had a continuous BRV monotherapy period of 18 to 24 months, and 13% had a continuous BRV monotherapy period of ≥ 24 months. • During the Evaluation Period, subjects reported an overall median and mean POS frequency of 3.3 seizures and 5.0 seizures, respectively, per 28-day period compared with Baseline median and mean POS frequency of 6.3 seizures and 8.7 seizures, respectively. Mean and median POS frequency values decreased by exposure duration cohort from Baseline to the 12-month cohort and then generally remained stable through the 90-month cohort. • Overall, during the Evaluation Period, subjects reported a median reduction in POS frequency from Baseline of 56.8% per 28-day period. The mean (SD) reduction in POS frequency during the Evaluation Period was 37.5% (62.7) per 28-day period. Subjects who remained in the study and on BRV treatment reported increasing median percent reductions by exposure duration cohort from Baseline for each efficacy time interval assessed through the 12-month cohort and then remained stable through the 90-month cohort. • As anticipated in an LTFU study of 8 years, more subjects remained seizure free for a specific time with increasing exposure duration. With increasing exposure duration and within each exposure duration cohort, continuous seizure freedom for subjects decreased over time. • Overall, QOLIE-31-P total and subscale scores remained stable from Baseline to the Last 		

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<p>Value recorded. The largest overall increase in subscale scores was reported for Seizure Worry, where the overall mean (SD) change from Baseline to Last Value recorded was 8.3 (23.5), followed by Cognitive Function (4.0 [21.9]), indicating some improvement in these subscales.</p> <ul style="list-style-type: none"> The percentage of subjects reporting no problems with each of the EQ-5D categories (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) was similar from Baseline to the Last Value recorded. In general, increases (improvement) from Baseline in EQ-5D VAS scores were reported at each time point assessed for the 6-, 12-, 18-, and 24-month cohorts. 		
<p>Conclusions: N01315 provided LTFU continuation of treatment for subjects who participated in N01276 or N01306. The primary objective of N01315 was to evaluate the long-term safety and tolerability of BRV treatment at individualized doses with a maximum dose of 200mg/day in adult subjects with epilepsy. The secondary objective of N01315 was to evaluate the maintenance of efficacy over time of BRV.</p> <ul style="list-style-type: none"> Subjects in N01315 received BRV for a total of 360.7 subject-years of exposure. Most subjects received a modal dose of ≥ 100mg/day and < 200mg/day. Approximately one-half of the subjects (56 subjects [51.9%]) had ≥ 24 months of exposure to BRV. The safety profile of BRV demonstrated in N01315 is consistent with that observed in other BRV studies. Overall, BRV was well tolerated at individually optimized doses up to a maximum of 200mg/day given as either monotherapy or given with an adjunctive AED in adult subjects with epilepsy, and no new observations related to safety were made. In general, subjects who remained in the study and on BRV treatment reported improvements in POS frequency and increasing percent reductions in POS frequency by exposure duration cohort from Baseline for each efficacy time interval assessed through the 12-month cohort and then remained stable through the 90-month cohort. More subjects remained seizure free for a specific time with increasing exposure duration. With increasing exposure duration and within each exposure duration cohort, continuous seizure freedom for subjects decreased over time. The long-term efficacy data support that BRV, given as either monotherapy or with an adjunctive AED in adult subjects, is an effective long-term (>12 months) treatment for subjects with POS. 		
<p>Report date: 13 Nov 2017</p>		