CLINICAL STUDY REPORT SYNOPSIS: N01199

Name of company: UCB Biosciences, Inc.	**Individual study table referring to part of the dossier:** Not applicable	*(For National Authority Use Only)*
Name of finished product: Not applicable	**Volume**: Not applicable	
Name of active ingredient: Brivaracetam	**Page:** Not applicable	

Title of study: An Open-Label, Multicenter, Follow-Up Trial to Evaluate the Long-Term Safety and Efficacy of Brivaracetam Used as Adjunctive Treatment at a Flexible Dose Up to a Maximum of 200 mg/day in Subjects Aged 16 Years or Older Suffering From Epilepsy

Study sites: A total of 99 sites in Australia, Brazil, Canada, India, Mexico, and the United States 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 11 years and 7 months **First subject enrolled:** 23 Jan 2006 **Last subject completed:** 18 Sep 2017	**Phase of development:** Phase 3

Objectives: The primary objective of N01199 was to evaluate the long-term safety and tolerability of brivaracetam (BRV) at individualized doses with a maximum of 200mg/day. N01199 started with a maximum dose of BRV 100mg/day; however, the protocol was amended to allow for a maximum dose of BRV 150mg/day (Protocol Amendment 2, 02 Mar 2007) and subsequently for a maximum dose of BRV 200mg/day (Protocol Amendment 6, 26 Jun 2011) in subjects with epilepsy.

The secondary objective of N01199 was to evaluate the maintenance of efficacy over time of BRV (for partial onset seizure [POS]/primary generalized seizure [PGS] subjects).

The exploratory objectives were to explore the effects of BRV on the subject's Health-Related Quality of Life, anxiety, and depression for the first 2 years, to explore medical resource use and indirect cost parameters for the first 2 years, to obtain a description of the subject's self-reported health status for the first 2 years, and to explore any change in the subject's socioprofessional status for the first 2 years.

Methodology: N01199 was a Phase 3, therapeutic, multicenter, noncomparative, open-label, single-arm, long-term follow-up (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. This study ran for the duration of the clinical development period of BRV, and continued until a marketing authorization was granted by any Health Authority in an indication of the adjunctive treatment in adults with refractory POS, whether or not secondarily

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generalized, until the Sponsor closed the study, until subjects transitioned to another BRV study, until a managed access program, named patient 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.

Subjects from the double-blind, placebo-controlled study, N01193, entered N01199 at a dose of BRV 20mg/day. Subjects from the double-blind, placebo-controlled study N01252 entered N01199 at a dose of BRV 50mg/day. Subjects from the double-blind, placebo-controlled study N01253 entered N01199 at a dose of BRV 50mg/day or 20mg/day. The starting doses for subjects from the double-blind, placebo-controlled, flexible-dose study N01254 were based on the blinded dose levels achieved during the Maintenance Period of N01254, but were not to exceed BRV 100mg/day; thus, starting doses for subjects from N01254 were BRV 20mg/day, 50mg/day, or 100mg/day, with most subjects entering N01199 at a dose of BRV 100mg/day.

Subjects who enrolled in the study directly entered the Evaluation Period. The dose of BRV could have been adjusted based on the individual subject's seizure control and tolerability. Brivaracetam dose increases could have been made in increments of a maximum of 50mg/day on a weekly basis up to a maximum of 200mg/day. The daily dose should have been administered in 2 equal intakes (morning and evening), taken with or without food.

Number of subjects (planned and analyzed): No sample size calculation was done. Sample size was dependent upon recruitment into and completion of preceding studies. A total of 668 subjects were enrolled into N01199.

Diagnosis and main criteria for inclusion: This study enrolled male and female subjects with epilepsy aged 16 years or older who participated in previous studies N01193, N01252, N01253, or N01254. N01199 gave subjects for whom the Investigator believed a reasonable benefit from the long-term administration of BRV may have been expected the opportunity to continue to receive the study drug. 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. Subjects with severe medical, neurological, and psychiatric disorders, or laboratory values which may have had an impact on the safety of the subject, as determined by the Investigator, were excluded.

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Test product, doses and mode of administration, batch numbers: In N01199, subjects coming from previous BRV studies had the opportunity to access BRV treatment at a flexible dose up to a maximum of 200mg/day in twice daily administration. The individual starting dose for each subject was the dose defined/reached at the end of their respective previous study.

Oral tablets of BRV 2.5mg (prior to Protocol Amendment 6 [26 Jun 2011]), 10mg, and 25mg (following Protocol Amendment 6 [26 Jun 2011]) were used in this study.

- For the 2.5mg strength, the batch numbers were as follows: BX1002652, BX1002811, and BX1003507.
- For the 10mg strength, the batch numbers were as follows: BX1002649, BX1002943, BX1003437, BX1003707, BX1003740, BX1004110, BX1004578, BX1004579, BX1006236, BX1008186, BX1010218, BX1011526, BX1012676, BX1013840, BX1002651, BX1003436, BX1004577, and BX1006216.
- For the 25mg strength, the batch numbers were as follows: BX1002645, BX1002985, BX1002986, BX1003410, BX1003772, BX1003771, BX1005426, BX1005427, BX1008187, BX1010219, BX1011527, BX1012677, BX1013841, BX1013842, BX1002647, BX1003200, and BX1005425.

Duration of treatment: 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 any Health Authority in an indication of the adjunctive treatment in adults with refractory POS, whether or not secondarily generalized, until the Sponsor closed the study, until subjects transitioned to another BRV study, until a managed access program, named patient 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.

Reference therapy, dose(s) and mode of administration, batch number(s): None.

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Criteria for evaluation:

Safety: The safety variables of N01199 were as follows:

- Occurrence of a treatment-emergent adverse event (TEAE)
- Withdrawal due to an adverse event (AE)
- Occurrence of a serious AE (SAE)

Other safety variables included:

- Laboratory tests (blood chemistry, hematology, and urinalysis)
- 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 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

Efficacy:

The secondary efficacy variables were as follows:

- POS (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
- Responder rate for POS (type I) frequency over the Evaluation Period. A responder was defined as a subject with a ≥50% reduction in seizure frequency from the Baseline Period of the previous study

Other efficacy variables included:

For subjects with POS epilepsy:

- 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.

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For subjects with generalized epilepsy:

- Generalized (type II) seizure days per 28 days during the Evaluation Period.
- Percent reduction in generalized (type II) seizure days per 28 days from Baseline of the previous study to the Evaluation Period.
- Responder rate for generalized (type II) seizure days over the Evaluation Period. A responder was defined as a subject with a ≥50% reduction in seizure days from the Baseline Period of the previous study.
- 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.

The following were evaluated separately for subjects with POS epilepsy and subjects with generalized epilepsy:

- Change in Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (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 Questionnaire (EQ-5D) 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.

Pharmacokinetics: Plasma samples for BRV and concomitant AED plasma concentrations were not obtained following Protocol Amendment 6 (26 Jun 2011). Plasma levels were only provided in subject data listings.

Pharmacoeconomics: Due to the inconsistencies in data captured and collection forms across LTFU studies, pharmacoeconomic variables including direct costs, indirect costs, and socioprofessional data were provided in subject data listings only, and were not evaluated or descriptively summarized.

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, 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. Separate Efficacy

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Populations were defined for subjects with POS from N01193, N01252, N01253, and N01254 and subjects with generalized epilepsy from N01254.

Seizure outcomes were summarized for either the Efficacy Analysis Set for POS and the Efficacy Analysis Set for PGS. Summaries of epilepsy history, QOLIE-31-P, and EQ-5D were provided for the Efficacy Analysis Sets for both POS and PGS.

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.

An overall summary of disposition was provided for all enrolled subjects (ie, all subjects who signed the informed consent form) and for subjects in the Safety Analysis Set. Overall subject disposition was also summarized by geographic region and seizure type for the Safety Analysis Set.

Kaplan-Meier estimates of the percentage of subjects completing 3, 6, 12, 24, 36, and 48 months of treatment and through the end of study were provided. This analysis was based on the duration of exposure to BRV.

Demographic and baseline summaries were based on demographic and baseline data collected in the previous double-blind studies.

Summaries of safety were provided for all subjects in the Safety Analysis Set. A daily dose was calculated for each study day from the day of first dose of BRV to the day of last dose of BRV for the purposes of calculating modal dose. Daily dose was calculated as the sum of the morning and evening dose for each day. Modal daily dose was the most frequently taken daily dose during this period; however, in the event of a tie, the modal dose was set to the lower of the tied doses.

All summaries of efficacy data were descriptive; no statistical testing was performed.

Twenty-eight day adjusted seizure frequency for seizure types I, IA, IB, and IC, and for all seizure types (I+II+III) were calculated overall, within each 3-month time interval, and over each exposure duration cohort interval.

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 POS Efficacy Analysis Set. Similar summaries were provided for the full cohort interval and by 3-month time intervals for each exposure duration cohort.

Responders over the On Treatment Period were defined as subjects with a ≥50% reduction in 28-day adjusted POS frequency from Baseline to the On Treatment Period. A similar calculation

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applied to each 3-month time interval over the On Treatment Period and for the cohort interval for each exposure duration cohort.

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. The total number of seizure days for PGS was calculated overall, by 3 month time intervals, and over the cohort interval for each exposure duration cohort.

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, change from Baseline, and Last Value for the Efficacy Analysis Sets.

Qualitative EQ-5D items were summarized for Baseline and Last Value for the Efficacy Analysis Sets. Additionally these parameters were summarized for Baseline and by visit for each study visit cohort.

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.

Summary and conclusions:

Subject disposition: In N01199, 668 subjects were enrolled. A total of 667 of these subjects were included in the Safety Analysis Set. A total of 648 subjects were included in the POS Efficacy Analysis Set and 15 subjects were included in the PGS Efficacy Analysis Set.

Of the subjects enrolled, a total of 626 subjects (93.9%) completed at least 3 months of treatment, approximately one-third of subjects (34.0%) remained enrolled after 84 months, and 179 subjects (26.8%) were still enrolled after 96 months.

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

- All subjects in the Safety Analysis Set (667 subjects) received at least 1 dose of BRV for a total of 2965.1 subject-years of exposure. The most common modal dose of BRV was 150mg/day (228 subjects [34.2%]). No subjects received a modal dose of BRV >200mg/day. Approximately half of the subjects (328 subjects [49.2%]) had at least 48 months of exposure to BRV.
- A total of 608 subjects overall and 595 subjects with POS reported at least 1 TEAE (91.2% [6817 events] and 91.3% [6751 events]), respectively. In POS subjects, the most commonly reported TEAEs were headache (165 subjects [25.3%]) and dizziness (143 subjects [21.9%]). Other commonly reported TEAEs in POS subjects included nasopharyngitis (92 subjects [14.1%]), somnolence (88 subjects [13.5%]), influenza (84 subjects [12.9%]), convulsion (81 subjects [12.4%]), upper respiratory tract infection (75 subjects [11.5%]), depression (70 subjects [10.7%]), nausea (67 subjects [10.3%]), and back pain and pyrexia (65 subjects [10.0%] each).
- Overall, within TEAEs reported in ≥5% of subjects, the incidence of TEAEs was higher in months 1 to 3 (293 subjects [43.9%]) versus months 4 to 6 (158 subjects [25.3%]), as well as subsequent months (range: 0 to 20.6%).
- Overall, the incidence of TEAEs was similar between subjects who received placebo (77.8%) and BRV (79.0%) in previous studies, with the exceptions of dizziness, which had a higher incidence in subjects receiving placebo (27.2%) compared with BRV (19.6%), depression, which had a higher incidence in subjects receiving placebo (14.2%) compared with BRV (9.5%), and insomnia, which had a higher incidence in subjects receiving placebo (10.5%) compared with BRV (6.3%).
- The majority of subjects had TEAEs of a maximum intensity of mild to moderate. A total of 159 subjects (23.8%) and 267 subjects (40.0%) experienced TEAEs with a maximum intensity of mild or moderate severity, respectively. A total of 182 subjects (27.3%) reported TEAEs with a maximum intensity of severe. Treatment-emergent AEs with a maximum intensity of severe reported by ≥10 subjects were headache (22 subjects [3.3%]), dizziness (14 subjects [2.1%]), and convulsion (11 subjects [1.6%]).
- Treatment-emergent AEs considered drug-related by the Investigator reported by ≥5% of subjects included dizziness (82 subjects [12.3%]), somnolence (61 subjects [9.1%]),

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headache (52 subjects [7.8%]), and depression (37 subjects [5.5%]). All other TEAEs considered drug-related by the Investigator were reported by <5% of subjects.

- A total of 152 subjects (22.8%) reported at least 1 treatment-emergent SAE. The treatment-emergent SAEs reported by >2 subjects were pneumonia (7 subjects [1.0%]); transient ischemic attack and toxicity to various agents (4 subjects [0.6%], each); myocardial infarction, unevaluable event, urinary tract infection, ankle fracture, craniocerebral injury, fall, uterine leiomyoma, cerebrovascular accident, and pneumonia aspiration (3 subjects [0.4%] each).
- Eighteen deaths were reported. One completed suicide and 1 SUDEP were considered by the Investigators as possibly related to BRV; all other fatal events were assessed as unlikely or not related.
- No clinically relevant findings were observed for any mean changes from Baseline in hematology, blood chemistry, urinalysis parameters, vital signs, body weight, or ECGs.
- No meaningful interpretation could be drawn from the PGS Safety Population due to the low number of subjects. Nonetheless, there were no safety concerns in these 15 subjects.

Efficacy results:

At individualized doses up to a maximum of 200mg/day, administration of BRV resulted in the following:

- During the Evaluation Period, subjects reported a median POS frequency of 4.2 seizures per 28-day period, compared with Baseline median and mean POS frequency of 9.2 seizures and 50.0 seizures, respectively. Mean and median POS frequency values decreased by exposure duration cohort from Baseline to the 36-month cohort and then generally remained stable through the 132-month cohort.
- During the Evaluation Period, subjects reported a median reduction in POS frequency from Baseline of 57.3% per 28-day period. For subjects who remained in the study and on BRV treatment, median percent reductions in POS frequency increased by exposure duration cohort from Baseline for each efficacy time interval through the 36-month cohort, and then remained stable through the 132-month cohort.
- The 50% responder rate for POS frequency during the Evaluation Period for subjects with POS was 55.6% (360 subjects). The 50% responder rate was generally increasing through the 30-month cohort, and then remained consistent across exposure duration cohort through the 90-month cohort.

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- As anticipated in an LTFU of 11 years, with increasing exposure duration, subjects experienced an increase in continuous seizure freedom over time.
- Overall, QOLIE-31-P scores remained stable or were improving as early as 2 months and then remained stable throughout the remainder of the study.
- 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 generally stable from Baseline to the Last Value recorded.
- Overall, the number of subjects with PGS enrolled in this study was small (15 subjects); therefore, no meaningful conclusions can be drawn.

N01199 provided LTFU continuation of treatment for subjects had completed N01193, N01252, N01253, or N01254. The primary objective of N01199 was to evaluate the long-term safety and tolerability of BRV treatment at individualized doses with a maximum dose of 200mg/day in subjects ≥16 years of age with epilepsy. The secondary objective of N01199 was to evaluate the maintenance of efficacy over time of BRV.

- Subject retention was high, with a total of 26.8% of subjects remaining in the study after 8 years; 16 subjects remained in the study for 11 years.
- Subjects in N01199 received BRV for a total of 2965.1 subject-years of exposure. The most common modal dose of BRV was 150mg/day.
- The safety profile of BRV demonstrated in N01199 is consistent with that observed in other BRV studies. Overall, BRV appeared to be generally [redacted] and well-tolerated at individually optimized doses up to a maximum of 200mg/day, and no unexpected 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 36-month cohort and then remained stable through the 132-month cohort. Within increasing exposure duration, subjects experienced an increase in continuous seizure freedom over time.

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