CLINICAL STUDY REPORT SYNOPSIS: N01379

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 Study to Evaluate the Long-Term Safety and Efficacy of Brivaracetam, used as Adjunctive Treatment in Subjects Aged 16 Years or Older With Epilepsy

Study sites: A total of 167 sites in Austria, Belgium, Brazil, Bulgaria, Canada, Czech Republic, Estonia, Finland, France, Germany, Hong Kong, Hungary, India, Italy, Japan, Latvia, Lithuania, Mexico, Netherlands, Poland, Russian Federation, South Korea, Spain, Sweden, Taiwan, United Kingdom, and the US were initiated in the study.

Publication(s) (reference[s]): Toledo M, Whitesides J, Schiemann J, Johnson ME, Eckhardt K, McDonough B, et al. Safety, tolerability, and seizure control during long-term treatment with adjunctive brivaracetam for partial-onset seizures. Epilepsia. 2016;57:1139-51.

Study period: Approximately 7 years, 11 months **First study participant enrolled:** 10 May 2011 **Last study participant completed:** 18 Apr 2019	**Phase of development:** Phase 3

Objectives: The primary objective of N01379 was to evaluate the long-term safety and tolerability of brivaracetam (BRV) at individualized doses up to a maximum of 200mg/day in epilepsy study participants (also referred to as participant).

The secondary objective of N01379 was to evaluate the maintenance of efficacy of BRV over time.

The exploratory objectives were to explore the effects of BRV on study participants' Health-related Quality of Life (HRQoL), direct medical resource use, any change in socioprofessional status, and to assess the role of gene variants of synaptic vesicle 2 (SV2) in affecting response to BRV (as part of a deoxyribonucleic acid [DNA] analysis at the program level).

Methodology: N01379 was an open-label, long-term follow up (LTFU), multicenter, noncomparative, and single-arm study to evaluate long-term safety and efficacy of BRV used as adjunctive treatment at a flexible dose up to a maximum of 200mg/day in study participants aged 16 years of age or older diagnosed with epilepsy. The study participant population was adults (≥16 years of age) with refractory partial onset seizures (POS) whether or not secondarily generalized from N01358 and study participants with localization related or generalized epilepsy from N01258. For each study participant, the study lasted from study

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entry until either regulatory approval of BRV had been granted by any Health Authority in an indication of adjunctive treatment of POS; until the Sponsor decided to close the study; until study participants 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.

The following study periods were defined:

- Evaluation Period (Visit 1 until the Last Evaluation Period Visit or Early Discontinuation Visit [EDV]): Study participants who enrolled in N01379 immediately entered the Evaluation Period.
- Down-Titration Period (up to 4 weeks)
  - If the study participant was discontinuing study drug, the Investigator first planned an EDV followed by the progressive down-titration of study drug.
  - During the Down-Titration Period, the BRV dose may have been decreased in steps of a maximum of 50mg/day on a weekly basis. A last down-titration step at 20mg/day for 1 week should have been included prior to the Post-Treatment Period.
- Post-Treatment Period (2 to 4 weeks): After completion of the Down-Titration Period, or for those study participants who for extenuating circumstances did not complete a Down-Titration Period, the study participant was required to enter a Post-Treatment Period for a minimum of 2 weeks and a maximum of 4 weeks, followed by a Final Visit (FV).
- The end of the study was defined as the date of the last visit of the last study participant in the study.

For study participants who transitioned to another BRV study, a managed access program or similar type of program, or converted to commercial BRV if, when, and where available, the Down-Titration Period and FV were not applicable.

An abbreviated CSR based on a clinical cutoff date of 17 Jan 2014 was previously submitted for N01379 for the purpose of providing supportive information for the BRV POS adjunctive therapy New Drug Application (NDA)/Marketing Authorization Application (MAA). The current report is the final CSR based on the completed study and addendum (N01379 CSR Appendix 13).

Number of study participants (planned and analyzed): The Safety Analysis Set (N=766 study participants) consisted of all study participants who took at least 1 dose of study drug. Efficacy Populations consisted of all participants who took at least 1 dose of study drug

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and had at least 1 seizure DRC day during the Evaluation Period. Separate Efficacy Populations were defined for participants with focal epilepsy from N01358 and N01258 and participants with generalized epilepsy from N01258 (N=749 and 12 study participants, respectively).

Diagnosis and main criteria for inclusion: This study enrolled male or female study participants with epilepsy aged 16 years or older who had completed the Treatment Period of N01358 or the Evaluation Period of N01258. N01379 gave study participants for whom the Investigator believed a reasonable potential benefit from the long-term administration of BRV was expected the opportunity to continue BRV treatment. Study participants 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 study participant, as determined by the Investigator, were excluded.

Test product, doses and mode of administration, batch numbers: [redacted] coated tablets of BRV 10mg, 25mg, and 50mg were used in this study. Study participants from N01358 and N01258 were started on a BRV dose of 150mg/day and 200mg/day, respectively, (2 equally divided doses administered twice daily) at study entry and were maintained at this dose for at least 2 weeks, unless the study participant was not able to tolerate treatment. The BRV dose could subsequently have been adjusted based on the individual study participant's seizure control and/or tolerability. However, the BRV dose should not have exceeded 200mg/day during the study.

- For the 10mg strength, batch numbers were as follows: 237129, 255837, 0000065256, BX1006335, BX1008881, BX1011133, BX1012319, BX1012355, BX1012420, BX1012997, BX1013293, and BX1016660.
- For the 25mg strength, batch numbers were as follows: 233516, 255839, BX1005331, BX1006898, BX1007403, BX1009144, BX1009950, BX1011489, BX1011661, BX1012321, BX1012321 (PR:67875), BX1012421, and BX1013288.
- For the 50mg strength, batch numbers were as follows: 233190, 255842, BX1005332, BX1005333, BX1007406, BX1009145, BX1009951, BX1011490, BX1011662, BX1011663, BX1012141, BX1012322, BX1012422, and BX1013289.

Duration of treatment: The study was to continue until a marketing authorization was granted by a health authority, until the Sponsor decided to close 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

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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.

Criteria for evaluation:

Safety: The primary safety variables of N01379 were as follows:

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

Other safety variables included:

- Laboratory tests (blood chemistry, hematology, urinalysis, and endocrinology)
- Vital signs (systolic blood pressure, diastolic blood pressure, pulse rate) and body weight
- Electrocardiogram (ECG)
- Physical and neurological examinations
- 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 last Evaluation Period assessment during the first 2 years

Efficacy: The secondary efficacy variables of N01379 for participants with focal onset epilepsy:

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

No secondary efficacy variables were defined for study participants with generalized epilepsy.

The other efficacy variables of N01379 for participants with focal onset epilepsy:

- Percentage of participants 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 other efficacy variables of N01379 for participants with generalized epilepsy:

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- 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 study participant with a ≥50% reduction in seizure days from the Baseline Period of the previous study.
- Percentage of participants 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 other efficacy variable of N01379 was evaluated separately for participants with focal-onset epilepsy and participants with generalized epilepsy:

- 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.

Due to the inconsistencies in data captured and collection forms across LTFU studies, the following pharmacoeconomic variables were provided in participant data listings only, but were not evaluated or descriptively summarized:

- Direct costs (healthcare provider consultations not foreseen by the protocol, concurrent medical procedures, concomitant medications, hospitalizations, and ER visits) during the first 2 years of the Evaluation Period.
- Socioprofessional data for each assessment for the first 2 years and for the last assessment during the first 2 years of the Evaluation Period.

DNA analysis:

For study participants coming from N01358 who consented to DNA analysis, a blood sample for DNA analysis was collected at the entry visit (EV) in order to explore a possible correlation between the SV2 gene variations and the participant's response to BRV. Blood samples for DNA analysis were collected only in adults where ethically accepted and authorized by legal authorities. The DNA analysis has been performed on all samples collected in N01379 and the results will be reported separately at the program level.

Samples were split into 2 aliquots and were initially stored at the central biorepository and were then shipped to the genotyping facility for DNA extraction and genotyping. Remaining samples after analysis may be stored at -20°C for a period of up to 20 years where permitted by participant consent.

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Statistical methods: Descriptive statistics, such as the mean, standard deviation, median, minimum value, and maximum value for quantitative variables, and counts and percentages for categorical variables, were provided. In addition, for efficacy variables, the 25th percentile and 75th percentile were provided. No statistical hypothesis testing was performed for the primary or secondary safety variables, or for the efficacy variables assessed in this study.

Overall study participant disposition was summarized for all enrolled study participants (ie, all study participants who signed informed consent), the Safety Analysis Set, and by subgroups for geographic region and seizure type for the Safety Analysis Set.

Demographic variables collected at the time of entry into the core study were summarized for the Safety Analysis Set. This summary was presented overall and by subgroups for geographic region and indication.

Summaries of safety were provided for all study participants in the Safety Analysis Set and also by subgroups for geographic region and indication.

In general, all study outcomes based on seizure frequency were summarized for the Efficacy Analysis Set for POS and all study outcomes based on seizure days were summarized for the Efficacy Analysis Set for primary generalized seizures. For the analyses of maintenance of efficacy, cohorts were defined by 3-month time intervals; which were based on a 30-day month (eg, Months 1 to 3 corresponded to Days 1 to 90) and were defined relative to the first dose of BRV. A study participant was included in summaries by efficacy time intervals if the participant was receiving BRV for at least the full duration of the 3-month interval based on their duration of exposure to BRV.

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 by dividing the total number of seizures for each seizure type by the number of days for which the diary was completed overall, within each 3-month interval, and within each exposure duration cohort interval, and multiplying the resulting value by 28.

Percent reduction from Baseline for POS frequency was summarized with quantitative descriptive statistics for the On Treatment Period (ie, the overall duration of exposure) and by 3-month time intervals over the On Treatment Period. The summary over the On Treatment Period included all study participants 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. Percent reduction from Baseline for POS frequency was summarized in the same manner by geographic region.

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Responders over the On Treatment Period were defined as study participants with ≥50% reduction in 28-day adjusted POS frequency from Baseline to the On Treatment Period. A similar calculation applied to each 3-month time interval over the On Treatment Period and for the cohort interval for each exposure duration cohort.

The number and percentage of responders for POS frequency were summarized 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 study participants in the POS Efficacy Analysis Set. Similar summaries were provided over the full cohort interval and by 3-month time intervals for each exposure duration cohort. Responder rates for POS frequency were summarized in the same manner by geographic region.

The numbers and percentages of study participants 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 study participants were being treated with BRV and by exposure duration cohort. The overall summary presented the number and percentage of study participants who reported no seizures for the specified duration of seizure freedom and the seizure diary was completed for at least 90% of days within the seizure-free interval. Study participants whose duration of BRV treatment was less than the specified duration of seizure freedom were considered failures for seizure freedom. Summaries by exposure duration cohort presented the number and percentage of study participants who reported no seizures for the specified duration of seizure freedom at any time during the cohort interval (eg, through the end of Month 6 for the 6-month cohort) and the seizure diary was completed for at least 90% of days within the seizure-free interval. Percentages were relative to the number of study participants within each exposure duration cohort.

Summary and conclusions:

Study participant disposition: In N01379, a total of 767 participants were enrolled in the study; 766 participants were included in the Safety Analysis Set, 749 participants were included in the POS Efficacy Analysis Set, and 12 participants were included in the Primary Generalized Seizure (PGS) Efficacy Analysis Set. Overall, most common reason for discontinuation was lack of efficacy (164 participants [21.4%]), followed by AEs (96 participants [12.5%]) and participant choice (89 participants [11.6%]).

Safety results: The safety results are summarized as follows:

- All participants in the Safety Analysis Set (766 participants) received at least 1 dose of BRV for a total of 1932.9 participant-years of exposure. The most common modal dose of BRV was 200mg/day (494 participants [64.5%]). Twenty-two participants received a total

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daily dose of BRV >200mg/day during the Treatment Period; 2 of these 22 participants reported 5 TEAEs assessed as drug-related by the Investigator while on a total daily dose of BRV >200mg/day. Three hundred twenty-three participants (42.2%) in the Safety Analysis Set had at least 36 months of exposure to BRV.

- Treatment-emergent AEs were most commonly reported overall in the system organ classes (SOCs) of Nervous system disorders (252 participants [32.9%]) and Infections and infestations (190 participants [24.8%]). The most common TEAEs (by PT) overall were headache (104 participants [13.6%]) and dizziness (100 participants [13.1%]).
- A total of 150 participants (63.3%) and 288 participants (54.4%) who received placebo and BRV, respectively, in previous studies reported at least 1 TEAE in N01379. In general, the incidence of TEAEs was similar between participants who received placebo and BRV in previous studies, with the exception of dizziness, which had a higher incidence in participants receiving placebo (19.0%) compared with BRV (10.4%) in previous studies.
- Overall, within TEAEs reported in ≥5% of participants, the incidence of TEAEs was higher in months 1 to 3 (231 participants [30.2%]) versus months 4 to 6 (79 participants [11.3%]), as well as subsequent months (range: 0 to 11.8%).
- The majority of TEAEs overall reported had a maximum intensity of mild or moderate; 217 participants (28.3%) and 309 participants (40.3%) reported TEAEs considered to be mild or moderate, respectively, in intensity by the Investigator. A total of 117 participants (15.3%) reported 192 TEAEs with a maximum intensity of severe. Severe TEAEs reported by ≥1.0% of participants were convulsion (9 participants [1.2%]) and status epilepticus (10 participants [1.3%]).
- Treatment emergent AEs considered drug-related by the Investigator reported by ≥5% of participants included somnolence (49 participants [6.4%]) and dizziness (41 participants [5.4%]). All other TEAEs considered drug-related by the Investigator were reported by <5% of participants.
- Five deaths were reported: Four participants died from one fatal SAE each. For the last participant, 2 fatal SAEs and 3 nonserious AEs (reported with the outcome fatal) were reported. All 5 deaths occurred in participants with POS and occurred during the Post-Treatment Period; all 6 SAEs were assessed as not related to study drug by the Investigator, the three nonserious AEs of simple partial seizures, somnolence and weight decreased were considered related by the Investigator.
- A total of 140 participants (18.3%) reported at least 1 treatment-emergent SAE. The treatment-emergent SAEs reported by >2 participants were convulsion (15 participants

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[2.0%]), status epilepticus (11 participants [1.4%]), epilepsy and suicide attempt (7 participants [0.9%] each), pneumonia (5 participants [0.7%]), seizure cluster (4 participants [0.5%]), and toxicity to various agents (reported as carbamazepine and tegretol toxicity) and hyponatremia (3 participants [0.4%] each).

- A total of 91 participants (11.9%) reported TEAEs leading to discontinuation of study drug. The most common TEAEs (by PT) leading to discontinuation of study drug reported by ≥5 participants were convulsion (12 participants [1.6%]); somnolence and pregnancy (8 participants [1.0%] each), and suicide attempt (6 participants [0.8%]).
- No clinically relevant findings were observed for any mean changes from Baseline in hematology, blood chemistry, urinalysis parameters, endocrinology, vital signs, body weight, or ECGs.
- No meaningful interpretation could be drawn from the PGS Safety Population due to the low number of participants. Nonetheless, there were no safety concerns in these 13 participants.

Efficacy results: Overall, at individualized doses up to a maximum of 200mg/day, administration of BRV resulted in the following based on the data available for the 749 participants included in the POS Efficacy Analysis Set:

- Participants on treatment reported a median POS frequency of 4.2 seizures per 28-day period, compared with Baseline median and mean POS frequency of 9.7 seizures and 25.8 seizures, respectively. Mean and median POS frequency values decreased by exposure duration cohort from Baseline to the 36-month cohort.
- Participants on treatment reported a median percent reduction in POS frequency from Baseline of 52.0% per 28-day period. Participants who remained in the study and on BRV treatment reported increasing median percent reductions from Baseline at each efficacy time interval assessed through 36 months (reduction range: 51.9% to 65.6%).
- Of the participants with POS on BRV treatment, 51.7% were 50% responders. For the participants with POS who remained in the study and on BRV treatment, the percentage of 50% responders increased consistently at each efficacy time interval assessed through 36 months.
- Of the participants with POS on BRV treatment, 26.0% were seizure free for any continuous 6 month period of treatment.
- As anticipated in an LTFU of approximately 8 years, with increasing exposure duration, participants experienced an increase in continuous seizure freedom over time. However,

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with increasing exposure duration cohort, continuous seizure freedom for participants decreased over time.

- Overall, QOLIE-31-P scores remained stable or were improving as early as 2 months and then remained stable through the Year 2 assessment (ie, 24 months).
- Overall, the number of participants with PGS enrolled in this study was small (13 participants); therefore, no meaningful conclusions can be drawn.

Conclusions: N01379 gave participants who participated in the core studies, N01358 or N01258, the opportunity to continue BRV treatment. The primary objective of N01379 was to evaluate the long-term safety and tolerability of BRV at individualized doses with a maximum of 200mg/day in participants with epilepsy.

- Participants in N01379 received BRV for a total of 1932.9 participant-years of exposure. The most common modal dose was 200mg/day.
- The safety profile of BRV demonstrated in N01379 is consistent with that observed in other BRV studies. Overall, BRV was well tolerated at individualized doses with a maximum of 200mg/day in participants 16 years of age or older with epilepsy and no new observations related to safety were made.
- In general, participants 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 at least the 36-month cohort. Within increasing exposure duration, participants experienced an increase in continuous seizure freedom over time.

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