CLINICAL STUDY REPORT SYNOPSIS: N01372

Name of company: UCB Pharma	**Individual study table referring to part of the dossier:** Not applicable	*(For National Authority Use Only)*
Name of finished product: Briviact®	**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

Investigator(s): This was a multicenter study in which 12 Investigators (at 10 sites) enrolled 26 subjects.

Study site(s): The study was conducted at 10 sites located in 4 countries in North America and Europe (United States, France, Germany, and Spain).

Publication(s) (reference[s]): none

Study period: 2 years and 10 months **First subject enrolled:** 17 Oct 2013 **Last subject completed:** 09 Aug 2016	**Phase of development:** Phase 3b

Objective(s): The primary objective was to evaluate the long-term safety and tolerability of brivaracetam (BRV) at individualized doses up to a maximum of 200mg/day as adjunctive treatment in adult subjects with epilepsy.

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

Exploratory objectives included the following:

- To explore the effects of BRV on subjects' Health-Related Quality of Life
- To explore direct medical resource use for subjects entering N01372 from a study where pharmacoeconomic data were collected.

Only subjects from N01395 enrolled in this study, and hospitalizations and healthcare provider consultations not foreseen per the protocol were not planned to be collected for these subjects. Therefore, only medical procedures were analyzed for this objective.

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Methodology: N01372 was a Phase 3b, open-label, long-term follow-up (LTFU), multicenter, noncomparative, single-arm study. The subject population was adults (≥16 years of age) with epilepsy. Subjects under 18 years of age were included only where legally permitted and ethically accepted. Following completion of the Treatment Period of N01395, subjects for whom the Investigator believed a reasonable benefit from the long-term administration of BRV may have been expected had the ability to continue BRV treatment in order to enroll into N01372. Upon completion or early discontinuation from N01372, there was a Down-Titration Period (this did not apply if subjects continued on BRV after they completed this study), followed by a Post-Treatment Period (between 2 and 4 weeks) during which the subject did not receive study drug.

This LTFU 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 for the adjunctive treatment in adults (≥16 years) with epilepsy, until the Sponsor decided to close the study, or until BRV development was stopped by the Sponsor.

In this LTFU study, subjects started on the individual BRV dose that they had reached at the completion of N01395. The BRV dose was adjusted based on the individual subject's seizure control and tolerability (ie, dose reductions to 150mg/day and, for some subjects, subsequently to 100mg/day or 50mg/day were permitted based on clinical response); however, the BRV dose was not to exceed 200mg/day during the study and was to always be administered as a symmetrical morning and evening dose.

Number of subjects (planned and analyzed): For this open-label LTFU study, no sample size calculation was performed. The sample size depended upon recruitment into and completion of the previous BRV Phase 3b studies. It was estimated that up to 650 subjects could have enrolled in this study, based on the assumption that ≥90% of enrolled subjects from previous studies with BRV as adjunctive treatment in epilepsy could have completed those studies and enrolled in the present study.

Only subjects from N01395 enrolled in the study. In total, 26 subjects enrolled in the study, including 19 subjects with focal epilepsy and 7 subjects with generalized epilepsy. All 26 subjects received at least 1 dose of BRV.

Diagnosis and main criteria for inclusion: This study enrolled male or female subjects (16 years of age or older) with well-characterized epilepsy according to the 1989 International League Against Epilepsy classification. Subjects must have completed the Treatment Period of an applicable previous BRV study and had access to the present study; the Investigator must have believed a reasonable benefit from the long-term administration of BRV may have been

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expected. Female subjects without childbearing potential were eligible, and female subjects with childbearing potential were eligible if they used a medically accepted contraceptive method. Subjects must have been considered reliable and capable of adhering to the protocol, visit schedule, or medicine intake according to the judgement of the Investigator.

Subjects with a lifetime history of suicide attempt or who had suicidal ideation in the past 6 months as indicated by a positive response to either Question 4 or Question 5 of the Columbia Suicide Severity Rating (C-SSRS) at the last visit of the previous study or at the Entry Visit of N01372 (if not completed at the last visit of the previous study) were excluded from the study.

Test product, dose(s) and mode of administration, batch number(s): Brivaracetam was administered [redacted] tablet formulations of BRV 10mg, 25mg, and 50mg. The BRV 10mg dose (20mg/day) was used only for down-titration.

Batch numbers for BRV included:

- BRV 10mg: BX1008089, BX1011038, BX1012475
- BRV 25mg: BX1008090, BX1011039, BX1012476, BX1011990
- BRV 50mg: BX1008091, BX1010204, BX1012477, BX1011525

At study entry, subjects started on the individualized BRV dose that they had reached at the completion of N01395.

Dose adjustments of study drug were allowed at any time based on the clinical judgment of the Investigator. The BRV dose could have been increased or decreased in increments of 50mg/day based on the individual subject's seizure control and/or tolerability; however, the BRV dose was not to exceed 200mg/day during the study and was to always be administered as a symmetrical morning and evening dose.

Duration of treatment: For each subject, the study lasted from study entry until either regulatory approval of BRV had been granted by any health authority in an indication for the adjunctive treatment of epilepsy, until the Sponsor decided to close the study, or until BRV development was stopped by the Sponsor.

The study was divided into 3 periods: Evaluation Period, Down-Titration Period, and Post-Treatment Period. Subjects who enrolled in N01372 immediately entered the Evaluation Period. Upon completion or early discontinuation from N01372, there was a Down-Titration Period (up to 4 weeks; this did not apply if subjects continued on BRV after they completed this study), followed by a Post-Treatment Period (between 2 and 4 weeks) during which the subject did not receive study drug. The end of the study was defined as the date of the last visit of the

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last subject in the study.

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

Criteria for evaluation:

Safety: The primary safety variables in this study were the following:

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

Other safety variables in this study were the following:

- Laboratory tests (hematology, blood chemistry, urinalysis)
- Vital signs (systolic blood pressure, diastolic blood pressure, pulse rate) and body weight
- Electrocardiogram (ECG)
- Physical and neurological examinations

Efficacy:

The secondary efficacy variables in this study were the following:

For subjects with focal epilepsy:

- Partial-onset seizure (POS) (Type I) frequency per 28 days during the Evaluation Period.
- Percent reduction in POS (Type I) frequency per 28 days from Baseline of N01395 to the Evaluation Period.
- Responder rate in 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 N01395.

No secondary efficacy variables were defined for subjects with generalized epilepsy.

Other efficacy variables in this study were the following:

For subjects with focal epilepsy:

- Percentage of subjects continuously seizure free for all seizure types (I+II+III) for ≥6 months and ≥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 N01395 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 N01395
- Percentage of subjects continuously seizure free for all seizure types (I+II+III) for ≥6 months and ≥12 months during the Evaluation Period.

The following was evaluated separately for subjects with focal 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.

Pharmacoeconomics: Pharmacoeconomic variables included the following:

- Number of concurrent medical procedures

Pharmacokinetics/pharmacodynamics: None.

Statistical methods: The Safety Set (SS) consisted of all subjects who took ≥1 dose of study drug. Summaries of demographics and Baseline characteristics, medical history, non-epileptic drugs, direct cost parameters, study drug exposure, and safety outcomes were provided for the SS.

The Efficacy Analysis Set (EAS) consisted of subjects who took ≥1 dose of study drug and had ≥1 seizure daily record card (DRC) day during the Evaluation Period. Summaries of seizure outcomes, epilepsy history, anti-epileptic drugs (AEDs), and QOLIE-31-P were provided for the EAS.

All summaries were descriptive; no statistical hypothesis testing was planned. Statistical analyses and generation of tables, figures, subject data listings, and statistical output were carried out using SAS® version 9.1 or higher.

Continuous data were summarized using descriptive statistics, such as the mean, standard deviation (SD), median, minimum value, and maximum value. Categorical data were

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summarized using counts and percentages. Denominators for percentages were generally based on the set of subjects with ≥1 assessment at the time point or ≥1 assessment during the time interval being summarized. Select summaries were provided by seizure type (focal epilepsy, generalized epilepsy) and geographic region (as requested by the Food and Drug Administration and the Committee for Medicinal Products for Human Use). Subject data listings presented source data and key derived variables for statistical analyses.

Efficacy and safety outcomes were not assessed for individual Investigator sites due to the low expected number for enrollment within each Investigator site.

Summary and conclusions:

Subject disposition: A total of 26 subjects enrolled in the study, including 19 subjects with focal epilepsy and 7 subjects with generalized epilepsy. A total of 13 subjects (50.0%) completed the study, including 11 subjects (57.9%) with focal epilepsy and 2 subjects (28.6%) with generalized epilepsy. Overall, 13 subjects (50.0%) discontinued from the study. The most common reasons for discontinuation from the study included subject choice (5 subjects [19.2%]) and lack of efficacy (4 subjects [15.4%]).

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

- All subjects in the SS (26 subjects) received at least 1 dose of BRV for a total of 54.1 subject-years of exposure. Most subjects (19 subjects; 73.1%) received a modal dose of ≥200mg/day. No subject received a total daily dose >200mg. Approximately two-thirds of the subjects (18 subjects [69.2%]) had ≥24 months of exposure to BRV.
- A total of 21 subjects reported at least 1 TEAE (80.8%; 282 events) and the most commonly reported TEAEs (by preferred term [PT]) included headache (8 subjects [30.8%]), urinary tract infection, back pain, and convulsion (4 subjects [15.4%] each), nausea, bronchitis, fatigue, upper respiratory tract infection, and dizziness (3 subjects [11.5%] each).
- A total of 9 subjects (34.6%) and 2 subjects (7.7%) reported TEAEs of maximum intensity considered to be moderate or mild, respectively. Severe TEAEs were reported by 10 subjects (38.5%). The only severe TEAEs reported by ≥2 subjects were convulsion and status epilepticus (7.7% each). None of the severe TEAEs were considered related to study drug by the Investigator.
- Drug-related TEAEs were reported for 4 subjects (15.4%) and included lymphopenia,

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neutrophilia, vertigo, vaginal infection, protein urine present, and renal colic (1 subject [3.8%] each).

- A total of 7 subjects (26.9%) reported treatment-emergent SAEs:
  - One subject (Subject [redacted]) died. This subject experienced 2 severe SAEs on Post-Treatment Day 53 of cardio-respiratory arrest and drowning that resulted in a fatal outcome. Both SAEs were considered not related to study drug by the Investigator.
  - A total of 6 subjects reported nonfatal treatment-emergent SAEs; all were considered not related to study drug by the Investigator. The most common treatment-emergent SAEs by PT were convulsion and status epilepticus (2 subjects [7.7%] each).
- No clinically relevant findings were observed for any changes from Baseline in hematology, blood chemistry, urinalysis parameters, vital signs, or ECGs.
- There were no abnormal, clinically significant physical examination, neurological examination, psychiatric, or mental status findings reported during the study.

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

- During the On-Treatment Period, subjects with focal epilepsy and generalized epilepsy reported an overall median POS frequency and number of generalized seizure days, respectively, of 0.4 seizures and 0.4 seizure days per 28-day period. Median POS frequency values and number of generalized seizure days decreased over time (ie, subjects remaining in the study and on BRV treatment reported fewer POS or generalized seizure days over time).
- Overall, during the On-Treatment Period, subjects with focal epilepsy and generalized epilepsy reported a median reduction in POS frequency and generalized seizure days, respectively, from Baseline of 56.3% and 90.9% per 28-day period, respectively. Subjects with focal epilepsy who remained in the study and on BRV treatment reported increasing median percent reductions in POS frequency from Baseline at each efficacy time interval assessed through 30 months (range: 45.6% to 86.0%). The median percent reduction in generalized seizure days from Baseline generally remained constant over time.
- Overall, during the On-Treatment Period, the 50% responder rates for subjects with focal epilepsy and generalized seizures were 54.5% (6 subjects) and 83.3% (5 subjects), respectively. The 50% responder rates for subjects with focal epilepsy and generalized epilepsy were generally consistent across exposure duration cohorts through the 30-Month and 24-Month cohorts, respectively.
- For each exposure duration cohort, continuous seizure freedom for subjects with focal

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epilepsy declined over time and remained stable over time for subjects with generalized epilepsy.

- Each of the overall QOLIE-31-P total and subscale scores showed a mean (SD) increase of ≥10 points on a 100-point scale to the Last Value recorded, with higher scores indicating better function. The largest increase was reported for Medication Effects, where the mean (SD) change from Baseline to the Last Value was 30.7 (31.3). The trend of improvement for QOLIE-31-P distress items was consistent with that of the total and subscale mean scores.

Conclusions: N01372 provided LTFU continuation of treatment for subjects who participated in N01395. The primary objective of N01372 was to evaluate the long-term safety and tolerability of BRV at individualized doses with a maximum dose of 200mg/day as adjunctive treatment in adult subjects with epilepsy.

- Subjects in N01372 received BRV for a total of 54.1 subject-years of exposure. Approximately two-thirds of the subjects (18 subjects [69.2%]) had ≥24 months of exposure to BRV.
- Based on a combination of retrospective and prospective Baseline data, the overall median POS frequency and number of generalized seizure days decreased over time. The QOLIE-31-P total and subscale scores demonstrated a mean increase in quality of life measures for subjects with focal and generalized epilepsy.
- The safety profile of BRV demonstrated in N01372 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 as an adjunctive treatment in adult subjects with epilepsy and no new observations related to safety were made.

Report date: 31 Mar 2017