INTERIM CLINICAL STUDY REPORT SYNOPSIS: N01266

Name of company: UCB Pharma SA	**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: Open-Label, Single-Arm, Multicenter, Long-Term Study to Evaluate Safety and Efficacy of Brivaracetam Used as Adjunctive Treatment in Pediatric Subjects with Epilepsy

Investigators: This is an ongoing study; 32 Investigators have enrolled subjects as of the clinical cutoff date of 31 Aug 2016.

Study sites: As of the clinical cutoff date, 32 sites have enrolled subjects in North America, Latin America, Western Europe, and Eastern Europe.

Publications (references): None

Study period: This study is ongoing. Study duration from the first subject enrolled to the clinical cutoff date is approximately 5.2 years. **First subject enrolled:** 05 Jul 2011 **Last subject completed:** This study is ongoing. The clinical cutoff date for this interim report was 31 Aug 2016.	**Phase of development:** Phase 3

Objectives:

The primary objective of N01266 is to document the long-term safety and tolerability of brivaracetam (BRV).

The secondary objective of N01266 is to assess the efficacy of BRV during long-term exposure.

The other objectives of N01266 are:

- To explore direct cost parameters
- To assess the effect of BRV on behavior using the Achenbach Child Behavior Checklist (CBCL) in subjects ≥18 months of age
- To explore the effect of BRV on cognition using the Behavior Rating Inventory of Executive Function®-Preschool Version/Behavior Rating Inventory of Executive Function® (BRIEF-P/BRIEF) in subjects ≥2 years of age
- To assess the effect of BRV on cognition using the Bayley Scales of Infant and Toddler Development®, Third Edition (Bayley-III®) scales in subjects <18 months of age (applicable

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only to long-term follow-up [LTFU] subjects enrolled in English-speaking countries)

- To explore the effect of BRV on health-related quality of life using the Pediatric Quality of Life Inventory™ (PedsQL™) in subjects ≥1 month of age

Full efficacy results, pharmacokinetics (PK), and direct cost parameters are not presented in this interim clinical study report (CSR), but will be fully reported in the final CSR.

Methodology: N01266 is an ongoing Phase 3, open-label, single-arm, multicenter, long-term study to evaluate the safety and efficacy of BRV in up to 600 subjects with epilepsy.

Upon enrollment, eligible LTFU subjects enter the Evaluation Period and continue their BRV treatment in accordance with their individualized dose at the completion of their previous pediatric BRV study. Directly enrolled (DE) subjects are screened and participate in up to 3 weeks of an Up-Titration Period. If a DE subject demonstrates, in the opinion of the Investigator, acceptable tolerability and seizure control on the same daily dose of BRV (no lower than the minimum specified dose) for 7±2 days during the Up-Titration Period, the subject attends the Entry Visit (EV) and enters the Evaluation Period on that dose.

Brivaracetam (tablet and oral solution) is administered twice daily (bid) in 2 equally divided doses. All LTFU subjects must be able to tolerate the minimum BRV dose specified in the previous study to be eligible for entry into the Evaluation Period of N01266. All DE subjects must be able to tolerate at least 1.0mg/kg/day during the Up-Titration Period prior to entering the Evaluation Period of N01266.

For all subjects enrolled in N01266, the maximum BRV dose is 5.0mg/kg/day (2.5mg/kg bid), not to exceed a dose of 200mg/day for subjects with body weight >40kg. Subjects <7 years of age receive oral solution. Subjects ≥7 years of age receive tablets, as appropriate. Dose adjustments of BRV and/or concomitant antiepileptic drugs (AEDs) are allowed at any time based on clinical judgment; however, during the Up-Titration Period, dose adjustments for BRV should be made only as specified by the protocol.

For LTFU subjects, the EV is the first study visit. For DE subjects, the EV is the visit at which subjects enter the Evaluation Period and occurs after subjects have completed the Screening Visit (ScrV) and at least 1 Titration Visit (TV). For subjects who continue in the study until it ends, the Evaluation Period will extend from the EV to the Final Visit (FV). For subjects who prematurely discontinue the study, the Evaluation Period will last from the EV until the Early Discontinuation Visit (EDV). Following the EDV, subjects will have their dose of BRV down titrated over a maximum of 4 weeks (Down-Titration Period). After 2 weeks free of study drug (Safety Period), subjects will complete the Safety Visit (SV).

During the Evaluation Period, Minimal Evaluation Visits (MEVs) and Full Evaluation Visits

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(FEVs) are performed alternatively every month during the first 3 months and every 3 months, thereafter, with a Yearly Evaluation Visit (YEV) every 12 months.

Number of subjects (planned and analyzed): Up to 600 subjects are planned to be enrolled at sites in North America, Latin America, Eastern Europe, and Western Europe. As of the clinical cutoff date, 213 subjects had enrolled in the study and 206 subjects had received at least 1 dose of BRV and were included in the Safety Set (SS), including 86 subjects in the LTFU cohort and 120 subjects in the DE cohort. A total of 126 subjects (61.2%) are ongoing; of these, 41 subjects (47.7%) are in the LTFU cohort and 85 subjects (70.8%) are in the DE cohort.

Diagnosis and main criteria for inclusion: Subjects who enroll in N01266 from N01263 or another pediatric BRV study (ie, LTFU subjects) must have been <16 years of age upon entry in their previous study. Eligible subjects who have partial-onset seizures (POS; according to the International League Against Epilepsy classification and substantiated by an electroencephalogram compatible with the clinical diagnosis of POS) and enroll in N01266 without having participated in a previous pediatric BRV study (ie, DE subjects) must be ≥4 years to <17 years of age. In addition, DE subjects must have had at least 1 POS during the 3 weeks before the ScrV and have been on a stable dose of at least 1 AED 7 days before the ScrV. All female subjects with childbearing potential who were sexually active were eligible if they used a medically accepted contraceptive method.

Test product, doses and mode of administration, batch numbers: Batch numbers used in this study as of the clinical cutoff date were:

- BRV 1.0mg/mL oral solution: BX1005746, BX1013116, BX1005725
- BRV 10mg/mL oral solution: BX1005735, BX1005747, BX1007409, BX1007410, BX1009576, BX1009577, BX1011058, BX1011402, BX1011403, BX1011989, BX1013177
- BRV 10mg tablets: BX1005761, BX1007188, BX1009319, BX1010898, BX1011416, BX1013126
- BRV 25mg tablets: BX1005763, BX1006679 , BX1009071, BX1009320, BX1010899, BX1011417, BX1013127
- BRV 50mg tablets: BX1005764, BX1007189, BX1009321, BX1010900, BX1011418

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Duration of treatment: Subjects will continue to receive BRV treatment in this study for approximately 3 years, until approval for BRV has been obtained for pediatric subjects in their age range, or until the investigational product development is stopped by the Sponsor.

Reference therapy, doses and mode of administration, batch numbers: None

Criteria for evaluation:

Efficacy: Efficacy assessments are not included in this interim CSR.

Pharmacokinetics: PK assessments are not included in this interim CSR.

Safety: The safety variables of N01266 are as follows:

- Adverse event (AE) reporting
- Safety laboratory tests (hematology, biochemistry, including hepatic monitoring of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, and gamma-glutamyltransferase, and endocrinology for all subjects, urinalysis for subjects ≥4 years of age, and pregnancy testing for female subjects with Tanner stage >1)
- Electrocardiogram (ECG)
- Physical examination (Tanner scale, if applicable depending on subject's developmental status) and neurological examination
- Psychiatric and mental status
- Vital signs (blood pressure, pulse rate, and body temperature)
- Body weight and height
- Assessment of suicidality

Other variables: The other variables for this interim CSR include the following:

- Change from Baseline in the Achenbach CBCL score: the Achenbach CBCL/1½-5 for children from 1½ to 5 years old at the Baseline assessment and the Achenbach CBCL/6-18 for children 6 years and older at the Baseline assessment
- Change from Baseline in the BRIEF-P/BRIEF score for subjects ≥2 years of age

Statistical methods: N01266 is an ongoing study. The database for this interim CSR is based on a clinical cutoff date of 31 Aug 2016; data reported after this date for the ongoing subjects were not included. Efficacy and PK assessments are not included in this interim CSR, but will be fully

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reported in the final CSR.

Descriptive statistics are displayed to provide an overview of the study results. For categorical parameters, the number and percentage of subjects in each category are presented. The denominator for percentages is based on the number of subjects appropriate for the purpose of analysis. For continuous parameters, descriptive statistics include number of subjects (n), mean, standard deviation, median, minimum, and maximum. All summaries are descriptive; no statistical hypothesis testing is planned.

Baseline for laboratory parameters, vital signs (systolic blood pressure, diastolic blood pressure, and pulse rate), body weight, and ECGs are based on the latest nonmissing scheduled or unscheduled assessment prior to or on the date of the first administration of BRV. Baseline is determined separately for each individual clinical laboratory parameter for hematology, biochemistry, endocrinology, and urinalysis.

The SS consists of all enrolled subjects who took at least 1 dose of BRV in this long-term study. The Full Analysis Set (FAS) consists of all subjects in the SS who have a Baseline and at least 1 completed post-Baseline daily record card or EEG. All safety analyses were performed on the SS.

Adverse events are tabulated by Medical Dictionary for Regulatory Affairs system organ class (SOC) and preferred term (PT). In addition, all AE summaries are presented by 3-month time intervals. Select AE summaries are repeated for the subset of subjects in the SS who have a history of POS prior to entry into N01266. The number and percentage of subjects experiencing each event at least once are summarized.

Observed values of hematology, chemistry, endocrinology parameters, vital signs, and ECGs were summarized for each visit and the Last Value. Change from Baseline for hematology, chemistry, and endocrinology parameters, vital signs, and ECGs was summarized for all post-Baseline visits and the Last Value.

The number and percentage of subjects with possibly clinically significant treatment-emergent (PCST) laboratory or vital sign values are summarized at each post-Baseline visit and Last Value. Percentages are relative to the number of subjects with a value at each time point. The number and percentage of subjects with treatment-emergent ECG abnormalities are presented for each post-Baseline visit and Last Value. Physical examination, neurological examination, psychiatric and mental status, VNS status, neuro-imaging procedures, and assessment of suicidality results were summarized in by-subject listings.

Summary and conclusions:

Subject disposition: As of the clinical cutoff date for this interim CSR, 213 subjects had

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enrolled in the study and 206 subjects were included in the SS, including 86 subjects in the LTFU cohort and 120 subjects in the DE cohort. A total of 126 subjects (61.2%) are ongoing; of these, 41 subjects (47.7%) are in the LTFU cohort and 85 subjects (70.8%) are in the DE cohort. Overall, 80 subjects (38.8%) discontinued from the study, including 45 subjects (52.3%) in the LTFU cohort and 35 subjects (29.2%) in the DE cohort. The most common primary reason for discontinuation was lack of efficacy (28 subjects [13.6%]), followed by consent withdrawn and AEs (18 subjects [8.7%] each). The primary reasons for discontinuation were generally similar between the LTFU and DE cohorts with the exception of AEs (15.1% and 4.2%, respectively) and consent withdrawn (14.0% and 5.0%, respectively).

Efficacy results: Efficacy was not evaluated for this interim CSR.

Pharmacokinetics: PK was not evaluated for this interim CSR.

Safety results: Given the study population, the safety findings in N01266 were generally consistent with the known safety profile of BRV. Findings in N01266 were as expected for the pediatric population in a long-term study (eg, high incidence of infections and associated symptoms). No new safety concerns for the pediatric population from 4 to 16 years of age were identified based on the available data as of the clinical cutoff date.

- A total of 191 subjects (92.7%) experienced treatment-emergent adverse events (TEAEs), most frequently in the SOC of Infections and infestations (150 subjects [72.8%]) followed by Nervous system disorders (99 subjects [48.1%]), and Gastrointestinal disorders (90 subjects [43.7%]). Overall, the most frequently experienced TEAEs (by PT) were nasopharyngitis (58 subjects [28.2%]), pyrexia (47 subjects [22.8%]), and vomiting (43 subjects [20.9%]).
  - A higher proportion of subjects experiencing TEAEs was observed during the first 3 months of treatment compared with the subsequent time intervals, with an overall trend of decreasing TEAEs over time. For each time interval, the number of TEAEs (by PT) observed was low. The most consistently reported PTs across time intervals were pyrexia and nasopharyngitis.
  - Across total duration of exposure cohorts, the most frequent TEAEs experienced were consistently nasopharyngitis, pyrexia, vomiting, pharyngitis, convulsion, and diarrhea. For subjects who received BRV for longer than 18 months, the additional TEAE of headache was consistently reported. Subjects who remained on BRV for periods longer than 30 months, experienced increased incidence of PTs in the SOC of Infections and infestations (eg, upper respiratory tract infection, gastroenteritis, cough, and rhinitis).
  - During the Up-Titration Period, a total of 22 DE subjects (18.3%) experienced TEAEs,

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most frequently in the SOC of Psychiatric disorders (10 subjects [8.3%]). Overall, the incidence of TEAEs (by PT) was low (<4%) with decreased appetite (4 subjects [3.3%]) and irritability (3 subjects [2.5%]) being most frequently reported.

- Overall, a majority of subjects experienced TEAEs with a maximum intensity of mild (67 subjects [32.5%]) or moderate (97 subjects [47.1%]). A total of 27 subjects (13.1%) experienced severe TEAEs. The most frequently reported severe TEAEs were convulsion (6 subjects [2.9%]), pneumonia (4 subjects [2.9%], and status epilepticus (3 subjects [1.5%]); no other severe TEAEs were experienced more than 1 subject.
- Overall, a total of 63 subjects (30.6%) experienced TEAEs considered by the Investigator to be related to BRV, most frequently in the SOCs of Psychiatric disorders (25 subjects [12.1%]) and Nervous system disorders (23 subjects [11.2%]). By PT, the most frequently experienced drug-related TEAEs were somnolence and decreased appetite (each 8 subjects [3.9%] overall).
- Four subjects have died as of the clinical cutoff date: a [redacted]-month old due to pneumonia, a [redacted]-year-old due to pneumonia and septic shock, a [redacted]-year-old due to acute respiratory failure, aspiration, and circulatory collapse, and a [redacted]-year-old due to circulatory collapse. None of the events which led to the subjects' deaths were considered related to study drug by the Investigator.
- Overall, a total of 54 subjects (26.2%) experienced serious TEAEs, most frequently in the SOC of Nervous system disorders (24 subjects [11.7%]). Convulsion was the most frequent SAE by PT overall (12 subjects [5.8%]).
- A total of 19 subjects (9.2%) discontinued due to TEAEs: 4 subjects (16.0%) in the 1 month to <2 years age group; 8 subjects (6.1%) in the 2 to <12 years age group, and 7 subjects (14.0%) in the 12 to <17 years age group.
- One pregnancy was reported as of the clinical cutoff date, which resulted in a normal, healthy baby.
- No consistent or clinically relevant mean or median changes from Baseline after BRV treatment were observed for hematology, clinical chemistry, or endocrinology parameters.
- No clinically relevant changes from Baseline were observed for vital signs or 12-lead ECGs.
- Fourteen subjects reported a positive response for suicidal ideation and 8 subjects reported a positive response for suicidal behavior. Two post-treatment suicide attempts for 1 subject were reported during the study.

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Conclusions: The interim results from this ongoing long-term study in pediatric subjects are consistent with the known safety profile of BRV in adults; no new safety concerns in the pediatric population have been identified. These results support the continued study of BRV in pediatric subjects.		
Report date: 28 Mar 2017		