# CLINICAL STUDY REPORT SYNOPSIS: N01258

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| **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:** A Multicenter, Open-Label, Four-Arm, Randomized Trial Evaluating the Safety and Tolerability of Brivaracetam Intravenous Infusion and Bolus, Administered in bid Regimen as an Adjunctive Antiepileptic Treatment in Subjects from 16 to 70 Years Suffering from Epilepsy

**Investigator(s):** This was a multicenter study in which 17 Investigators enrolled subjects.

**Study site(s):** The study was conducted at 17 sites located in the USA and EU (Poland, Germany, Czech Republic).

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

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| **Study period:** 11 months, 12 days<br><br>**First subject enrolled:** 09 Aug 2011<br>**Last subject completed:** 20 Jul 2012 | **Phase of development:** Phase 3 |

**Objective(s):** The primary objective was to evaluate the safety and tolerability of brivaracetam (BRV) 200mg/day administered intravenously (iv) as an infusion or a bolus, according to an initiation or a conversion scheme, during repeated dosing (100mg/administration twice daily [bid] for 4.5 days) as an adjunctive treatment in adult subjects suffering from localization-related or generalized epilepsy. The maximum allowable daily dose of BRV was increased to 200mg/day from 100mg/day in Protocol Amendment 3.

An exploratory objective in this study was to collect data on healthcare resource utilization.

**Methodology:** This was an open-label, 4-arm, randomized, parallel-group study with a double-blind, placebo (PBO)-controlled Run-In Period, allowing subjects exposure to an initiation scheme (subjects randomized to oral PBO in the Run-In Period and receiving BRV iv afterwards) or to a conversion scheme (subjects randomized to oral BRV in the Run-In Period and receiving BRV iv afterwards). During the 7-day Run-In Period, subjects received tablets of PBO or BRV (200mg/day, 100mg/intake bid), according to randomization. During the Evaluation Period, subjects received BRV iv (200mg/day, 100mg/administration bid) for 4.5 days (9 BRV iv administrations in total) either as a bolus (administered over 2 minutes) or an infusion (administered over 15 minutes). At the end of the Evaluation Period (Visit 7 [V7]), the subject was allowed to enter the long-term follow-up (LTFU) study (N01379) at a dose of BRV 200mg/day (100mg/intake bid) with oral tablets. Subjects enrolled in Germany were not eligible

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to enroll in the LTFU study. Subjects who did not enter N01379 and those who discontinued the study prematurely (before V7) were to down titrate their study drug (using PBO or BRV tablets, depending on the last study drug intake) gradually over a 4-week period. After a 2-week Study Drug-Free Period, the subject completed a final Safety Visit (SV [V8]).

This study enrolled adults (≥16 years to ≤70 years) with localization-related or generalized epilepsy that was not well-controlled with 1 or 2 concomitant antiepileptic drugs (AEDs). Subjects under 18 years of age were included only where legally permitted and ethically accepted.

**Number of subjects (planned and analyzed):** Due to the nature of this study, no formal sample size calculation was performed. One hundred subjects were considered adequate to evaluate the safety and tolerability of BRV in iv administration. Subjects were randomized at V2 before first study drug intake to 4 treatment groups with a ratio 1:1:1:1 (25 subjects/group).

Taking into account a Screening/Baseline failure rate of 20%, 125 subjects were expected to enroll in order to get 100 evaluable subjects.

A total of 105 subjects were analyzed in the Safety Population; 26 subjects each in the PBO/BRV bolus, PBO/BRV infusion, and BRV/BRV infusion groups and 27 subjects in the BRV/BRV bolus group. The Safety iv Population and the Pharmacokinetic Per-Protocol Set (PK-PPS) included all subjects from the Safety Population excluding 1 (Subject [redacted]) from the PBO/BRV bolus group who discontinued the study during the Run-In Period due to an adverse event (AE).

**Diagnosis and main criteria for inclusion:** This study enrolled adults (≥16 years to 70 years) with well-characterized focal or generalized epilepsy or epileptic syndrome according to the International League Against Epilepsy (ILAE) classification that was not well-controlled with 1 or 2 concomitant AEDs. Vagal nerve stimulation (VNS) was allowed and was counted as a concomitant AED. Dosage of permitted concomitant AEDs and VNS (implanted for at least 9 months) must have been stable from at least 1 month (3 months for phenobarbital and primidone) before V1 and expected to be kept stable during the Run-In and Evaluation Periods. Benzodiazepines taken more than once a week (for any indication) were considered as a concomitant AED. Subjects with a history or presence of status epilepticus during 1 year preceding V1 or during Baseline were excluded.

In Germany, subjects <18 years of age were excluded from participation, and in the Czech Republic, subjects either <18 or >65 years of age were excluded from participation, at the request of the Ethics Committees for those countries.

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**Test product, dose(s) and mode of administration, batch number(s):** During the Run-In and Down-Titration Periods, BRV was administered orally in a tablet formulation:

- BRV 10mg tablets for oral administration (Batch number: 0000065256)
- BRV 25mg tablets for oral administration (Batch number: BX1004186)
- BRV 50mg tablets for oral administration (Batch number: BX1004759)

During the Evaluation Period, BRV was administered iv as a bolus or an infusion as a 10mg/mL solution (Batch number: BX1005675, BX1005676):

- Bolus: 10mL (=100mg) of BRV/administration injected pure over 2 minutes bid.
- Infusion: 10mL (=100mg) of BRV/administration diluted in 100mL 0.9% isotonic saline sterile solution for iv administration infused over 15 minutes bid.

**Duration of treatment:** Maximum treatment exposure for each subject was planned to be 40 days, and the maximum study duration was planned to be 61 days. The study consisted of the following periods:

- Baseline Period: 1 week starting at Screening (V1).
- Run-In Period: 1 week double-blind, PBO or BRV oral tablet treatment starting at Randomization (V2).
- Evaluation Period: 4.5 days iv treatment, infusion or bolus from V3 to V7.
- Down-Titration Period: (4 weeks) or immediate switch to oral treatment in the LTFU study (N01379); subjects enrolled in Germany were not eligible to enroll in the LTFU study.
- Study Drug-Free Period: (2 weeks) for those subjects who did not enter the LTFU study and for those who discontinued the study prematurely.

**Reference therapy, dose(s) and mode of administration, batch number(s):** During the Run-In and Down-Titration Periods, PBO was administered orally in a tablet formulation:

- PBO matching 10mg tablets for oral administration (Batch number: BX1004772)
- PBO matching 25mg tablets for oral administration (Batch number: BX1004773)
- PBO matching 50mg tablets for oral administration (Batch number: BX1004050)

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**Criteria for evaluation:** As this was an open-label study with the primary objective to evaluate the safety and tolerability of BRV 200mg/day administered iv as an infusion or a bolus, no efficacy variables were assessed.

**Safety:** Safety variables included:

- Adverse events, with special attention to injection related AEs (local site and systemic reactions) and seizure worsening
- Seizure counts
- Laboratory tests (hematology, biochemistry, urinalysis, and BRV and AED plasma concentrations)
- Electrocardiograms (ECGs), including cardiac telemetry
- Vital signs (including orthostatic measurement), body weight, and height
- Physical and neurological examinations
- Psychiatric and mental status

**Exploratory:** Exploratory variables included the following healthcare resource utilization data: concomitant medications, medical procedures, hospital stays, and healthcare provider consultations not foreseen by the protocol.

**Statistical methods:**

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. Denominators for percentages were generally based on the set of subjects with at least 1 assessment at the time point or at least 1 assessment during the time interval being summarized. No statistical hypothesis testing was planned.

Summaries for disposition, protocol deviations, demographics and baseline characteristics, medical history, epilepsy history, AEDs, and non-AEDs, medical resource use, socio-professional data, Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P), Hospital Anxiety and Depression Scale (HADS), and most safety outcomes were presented by individual treatment groups and all treatment groups combined. Summaries of study drug compliance, seizure counts, and AEs were presented by individual treatment groups, all groups combined, initiation/conversion scheme groups, and the pooled bolus and infusion

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groups. Summaries of study drug exposure and BRV plasma levels were presented by individual treatment groups.

All analyses were based on randomized treatment assignment. Treatment groups were presented as follows:

- PBO tablets/BRV bolus
- PBO tablets/BRV infusion
- BRV tablets/BRV bolus
- BRV tablets/BRV infusion

Some summaries were also repeated on the Safety iv Population presented by initiation and conversion scheme groups and pooled iv treatment groups:

- Initiation scheme: PBO/BRV (bolus or infusion excluding Run-In)
- Conversion scheme: BRV/BRV(bolus or infusion excluding Run-In)
- BRV bolus (excluding Run-In)
- BRV infusion (excluding Run-In)

Baseline for seizure frequency was based on the 28-day adjusted seizure frequency calculated from seizure diary days over the Baseline Period. Baseline for QOLIE-31-P scores, HADS scores, and socio-professional data was based on the assessments performed at V2. Baseline for laboratory parameters and body weight was based on the latest scheduled or unscheduled assessment prior to or on the date of V2. Baseline was determined separately for each individual clinical laboratory parameter for hematology, blood chemistry, and urinalysis assessments. For analyses of vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], and pulse rate) and ECG parameters, Baseline was defined as V3 am predose.

Three analysis sets were utilized to evaluate the data. The Safety Population consisted of all subjects who took at least 1 dose of study drug. The Safety iv Population consisted of all subjects who received at least 1 iv dose of BRV. The PK-PPS consisted of all subjects having provided at least 1 measurable plasma sample (with recorded sampling time) on at least 1 visit with documented drug intake times.

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**Summary and conclusions:**

**Subject disposition:** A total of 114 subjects were screened and 105 subjects were randomized to 4 different treatment groups: PBO/BRV bolus, n=26; PBO/BRV infusion, n=26; BRV/BRV bolus, n=27; BRV/BRV infusion, n=26.

A total of 103 randomized subjects completed the entire study (Run-In and Evaluation Periods) and 2 subjects discontinued early. Of the 2 subjects who discontinued early, 1 subject in the PBO/BRV bolus group (Subject [redacted]) discontinued during the Run-In Period (ie, while on PBO treatment) due to an AE of rash and 1 subject in the PBO/BRV infusion group (Subject [redacted]) discontinued during the Evaluation Period (ie, while on BRV infusion treatment) due to an AE of anxiety.

Of the 103 subjects who completed the Evaluation Period, 14 subjects entered the Down-Titration Period and continued to the Post-Treatment Period (PBO/BRV bolus, n=2; PBO/BRV infusion, n=5; BRV/BRV bolus, n=3; BRV/BRV infusion, n=4). Of note, 7 of these 14 subjects were from Germany and were not eligible (per the Central Ethics Committee in Germany) to enroll in the LTFU study. All remaining subjects planned to enter the LTFU study (N01379).

**Pharmacokinetics/pharmacodynamics results:**

- At the start of the Evaluation Period, 15min postdose of the first iv BRV administration, those subjects who received BRV during the Run-In Period (in the BRV/BRV bolus and infusion groups) had 83% to 88% higher plasma concentrations of BRV compared with those subjects who received PBO during the Run-In Period at 15min postdose of the first iv BRV administration. This difference was consistent with the expected accumulation factor at steady-state.
- At the end of the Evaluation Period, postdose BRV plasma concentrations were similar across the treatment groups regardless of whether subjects received a bolus or infusion of BRV.

**Safety results:**

Treatment-emergent AEs (TEAEs) for all subjects and by treatment group

- Overall, 76.2% of subjects reported a TEAE, and this incidence was similar across treatment groups (ranging from 73.1% to 77.8%). The most common TEAEs overall were somnolence (29.5% of all subjects) and dizziness (14.3% of all subjects), and the incidences of these TEAEs were similar across treatment groups. The majority of subjects (67.6%) reported a TEAE during the Evaluation Period (ie, during iv BRV treatment), and the most common

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TEAEs during this period were somnolence (21.9%) and dizziness (7.6%).

- One subject (in the BRV/BRV bolus treatment group) reported severe TEAEs (vertigo and nausea). All other TEAEs were mild or moderate in intensity.
- Overall, 63.8% of subjects reported a drug-related TEAE, and the incidence was similar across treatment groups (ranging from 57.7% to 69.2%). The most common drug-related TEAEs overall were somnolence (28.6% of all subjects) and dizziness (12.4% of all subjects), and the incidences of these TEAEs were similar across treatment groups.
- The overall incidence of injection-related TEAEs was low (10.5%). Across all treatment groups, infusion site pain (3.8%), injection site erythema (1.9%), injection site extravasation (1.9%), and injection site pain (1.9%) were the most common injection-related TEAEs.
- Discontinuations due to TEAEs were infrequent (1.9% of subjects overall) and were reported by 1 subject (3.8%) each in the PBO/BRV bolus and PBO/BRV infusion treatment groups.
- There were no treatment-emergent SAEs or deaths reported in this study.
- No TEAEs of special interest (ie, convulsion) were identified by medical review.
- No pregnancies were reported during the study.

<u>Treatment-emergent AEs by scheme and infusion group</u>

- The incidence of TEAEs during the Evaluation Period was similar with regard to an initiation (subjects who had received PBO during the Run-In Period followed by iv BRV during the Evaluation Period) or a conversion scheme (subjects who had received oral BRV during the Run-In Period followed by iv BRV during the Evaluation Period); 70.6% of subjects in the initiation group compared with 66.0% of subjects in the conversion group reported a TEAE. The incidence of somnolence was similar between the initiation and conversion groups (21.6% and 22.6%, respectively). The incidence of dizziness was higher in the initiation group compared with the conversion group (11.8% and 3.8%, respectively). The overall incidence and type of drug-related TEAEs was similar with regards to an initiation or a conversion scheme of treatment. The incidence of injection-related TEAEs was similar with regards to an initiation or a conversion scheme of treatment (7.8% vs 13.2%).
- The incidence of TEAEs during the Evaluation Period was similar with regard to iv BRV administered as a bolus or infusion; 71.2% of subjects in the BRV bolus group compared with 65.4% of the subjects in the BRV infusion group reported a TEAE. The incidences of the most common TEAEs, somnolence and dizziness, were similar between the bolus and infusion treatment groups over the entire study period (somnolence: 19.2% in the bolus group

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and 25.0% in the infusion group; dizziness: 9.6% in the bolus group and 5.8% in the infusion group). The overall incidence and type of drug-related TEAEs was similar whether iv BRV was administered as a bolus or infusion. The incidence of injection-related TEAEs was similar whether iv BRV was administered as a bolus or infusion (9.6% vs 11.5%).

- The incidence of TEAEs in the Cardiac disorders SOC was higher in subjects who received iv BRV as a bolus compared with an infusion (9.6% vs 3.8%). All events were mild, most were transient, and none required a change in study drug. Four of 7 subjects had events that were considered to be related to study drug: postural orthostatic tachycardia syndrome (2 subjects), tachycardia (1 subject), and ventricular extrasystoles (1 subject). The ECG abnormalities that were observed post-Baseline were transient, and none were considered to be clinically significant.
- The incidence of Nervous system disorder TEAEs overall and by preferred term (PT) was similar regardless of whether iv BRV was administered as a bolus or infusion. All Nervous system disorder TEAEs were mild or moderate in intensity, and nearly all events were considered to be study drug related.
- The incidence of Psychiatric disorder TEAEs during the Evaluation Period was lower with iv BRV bolus compared with infusion (1.9% vs 7.7%). All Psychiatric disorder TEAEs were mild or moderate in intensity. All events but 1 were considered to be study drug related. Most events were transient and did not require a change in study medication.
- Five subjects reported TEAEs in the Skin and subcutaneous tissue disorders SOC during the Evaluation Period. The incidence of skin reactions was higher in subjects who received iv BRV as a bolus compared with an infusion during the Evaluation Period (7.7% vs 1.9%). All events were mild, were resolved or resolving, and none required a change in study drug. All events but 1 were considered to be not related to study drug.

<u>Laboratory measurements, vital signs, and other assessments related to safety</u>

- The incidence of possibly clinically significant treatment emergent (PCST) hematology values during the Treatment Period was low for subjects overall (<3% for any parameter) and similar across treatment groups, with the exception of PCST low hematocrit in 16 subjects (15.2%) overall. The incidence of PCST low hematocrit values was similar across treatment groups. The incidence of PCST blood chemistry values during the Treatment Period was low for subjects overall (≤1% for any parameter) and similar across treatment groups. The only blood chemistry parameters with values that met PCST criteria were high creatinine and low glucose, which occurred in 1 subject each.

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- Mean changes in vital signs were generally similar between groups and were not clinically meaningful. The incidence of PCST vital sign values was low (<5%) and similar between the treatment groups. Overall, few subjects (<10%) experienced orthostatic hypotension (decrease in SBP ≥20mmHg, decrease in DBP of ≥10mmHg, or both). The most frequent occurrence of orthostatic hypotension was a decrease in DBP of ≥10mmHg that occurred at 3 minutes after standing: 10 (9.5%) subjects overall. There was no consistent trend across treatment groups with regards to the incidence of orthostatic hypertension.
- The percentage of subjects who had a shift from normal to abnormal ECG findings post-Baseline was generally low (<5%) at each time point at V3 am (following first iv BRV dosing) and V7 am (following last iv BRV dosing) and was less than the number of subjects who shifted from abnormal at Baseline to normal post-Baseline at each respective time point. These changes were generally transient, and there was no apparent trend over the 12h time period following iv BRV dosing. No subject had a clinically significant ECG finding at any time point.
- No subject reported suicidal ideation or a suicide attempt during the study.

**Exploratory results:** Few subjects required additional healthcare provider visits, emergency room visits, or hospital stays. Approximately one-quarter of subjects had a concurrent medical procedure. The majority of concurrent medical procedures were related to an AE, most often for iv replacement or relocation.

**Conclusions:**

- Treatment with iv BRV (both bolus and infusion) was [redacted] and well tolerated, regardless of an initiation or a conversion scheme of treatment, as few subjects discontinued due to an AE or had a severe AE, and no treatment-emergent SAEs or deaths were reported.
- The TEAE profile was similar with regards to an initiation or a conversion scheme of treatment and whether iv BRV was administered as a bolus or infusion. There were no clinically meaningful or unexpected changes in laboratory parameters, vital signs, or ECGs.
- Few subjects required additional healthcare provider visits, emergency room visits, or hospital stays. Approximately one-quarter of subjects had a concurrent medical procedure. The majority of concurrent medical procedures were related to an AE, most often for iv replacement or relocation.

**Report date:** 21 Mar 2013