

**CLINICAL STUDY REPORT SYNOPSIS: N01263**

<b>Name of company:</b> UCB Pharma SA	<b>Individual study table referring to part of the dossier:</b> Not applicable	<i>(For National Authority Use Only)</i>
<b>Name of finished product:</b> Not applicable	<b>Volume:</b> Not applicable	
<b>Name of active ingredient:</b> Brivaracetam	<b>Page:</b> Not applicable	
<b>Title of study:</b> Open-Label, Single-Arm, Multicenter, Pharmacokinetic, Safety, and Efficacy Study of Adjunctive Administration of Brivaracetam in Subjects from $\geq 1$ Month to $< 16$ Years Old with Epilepsy		
<b>Investigators:</b> This was a multicenter study in which 26 Investigators enrolled subjects.		
<b>Study sites:</b> Twenty-nine sites participated in the study (ie, screened subjects) and were located the US, Mexico, and the EU (Belgium, Czech Republic, Poland, and Spain).		
<b>Publication(s) (reference[s]):</b> None		
<b>Study period:</b> 1 year, 8 months, 11 days  <b>First subject enrolled:</b> 05 Jul 2011 <b>Last subject completed:</b> 15 Mar 2013		<b>Phase of development:</b> Phase 2a
<p><b>Objective(s):</b> The primary objectives were to characterize the steady-state pharmacokinetics (PK) of brivaracetam (BRV) and its metabolites in subjects from <math>\geq 1</math> month to <math>&lt; 16</math> years of age, evaluate their relationship with physiological developmental variables, and develop dosing adaptations.</p> <p>The secondary objectives were as follows: to document the short-term safety and tolerability of BRV; to gain preliminary information on the efficacy of BRV in pediatric subjects with various epileptic syndromes; and to assess compliance to study drug oral solution.</p> <p>An exploratory objective was to explore direct medical resources use and cost parameters.</p>		
<p><b>Methodology:</b> This was a Phase 2a, open-label, single-arm, multicenter, fixed 3-step up-titration study in subjects with epilepsy evaluating the PK, safety, and efficacy of BRV. Subjects were aged between <math>\geq 1</math> month and <math>&lt; 16</math> years with epilepsy. Subject enrollment was stratified by age group (at least 30 infants and toddlers [28 days to 23 months]; at least 30 pediatric subjects [2 to 11 years]; and a maximum of 30 adolescents [12 to <math>&lt; 16</math> years]) to ensure that a substantial number of subjects were included in each category.</p> <p>All subjects completed a 1-week Baseline Period, followed by a 3-week Evaluation Period with weekly fixed 3-step up-titration of the BRV dose. Subjects may have been eligible for conversion to a long-term follow-up study (LTFU) study (N01266) upon completion of at least the lowest dose level (DL) of the Evaluation Period. Subjects not choosing the option to enter N01266 or subjects discontinuing due to not being able to tolerate the lowest BRV dose or due to</p>		

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other reasons entered a Down-Titration Period of up to 2 weeks followed by a 2-week study drug-free Safety Period and a Final Safety Visit.

Brivaracetam oral solution was administered at weekly increasing doses of approximately 0.4mg/kg, 0.8mg/kg, and 1.6mg/kg twice daily (bid) for subjects  $\geq 8$  years of age and 0.5mg/kg, 1.0mg/kg, and 2.0mg/kg bid for subjects  $< 8$  years of age.

Two or 3 blood samples for the PK assessment of BRV and its metabolites were obtained on Day 7 (Visit [V] 3), Day 14 (V4), and Day 21 (V5) (or at the Early Discontinuation Visit [EDV], in case the subject exited the study prematurely) in 1 of the 3 possible defined time brackets. In addition, a PK blood sample should have been taken whenever a subject reported an SAE.

A Data and Safety Monitoring Board (DSMB) was set up for the duration of this study.

**Number of subjects (planned and analyzed):** Approximately 100 pediatric subjects were planned to be enrolled in N01263 at sites in the US, Mexico, and the EU, and the number of subjects with partial-onset seizures (POS) was to be limited to a maximum of 50% of all subjects.

Of the 100 subjects who enrolled and were not screen failures, 99 were included in the Safety Set (SS); 1 subject who did not take any study drug was excluded from the SS. Ninety-six subjects were included in the Pharmacokinetic-Per Protocol Set (PK-PPS); 4 subjects were excluded from the PK-PPS because at least 1 measurable plasma sample (with recorded sampling time) on at least 1 visit with documented drug intake times was not provided. Ninety-seven subjects were included in the Full Analysis Set (FAS); 3 subjects were excluded from the FAS because they did not have a Baseline daily record card (DRC) or electroencephalogram (EEG) and at least 1 completed post-Baseline DRC or EEG.

**Diagnosis and main criteria for inclusion:** This study enrolled male or female pediatric subjects aged between  $\geq 1$  month and  $< 16$  years of age at Visit (V)1 and with epilepsy (ie, localization-related, generalized, or undetermined whether focal or generalized epileptic syndrome, and other symptomatic generalized epilepsies) according to the International League Against Epilepsy (ILAE) classification. Subjects took stable doses of  $\geq 1$  to  $\leq 3$  concomitant antiepileptic drugs (AEDs). All AEDs needed to be at a stable dose for at least 7 days prior to V1 and no additions or deletions of AEDs were permitted. The dose of any concomitant AED had to remain stable from V1 through the collection of the PK samples. Vagal nerve stimulation (VNS) was allowed and counted as a concomitant AED; VNS must have been stable for at least 2 weeks before V1. Benzodiazepine taken more than once a week (for any indication) was considered as a concomitant AED. Concomitant use of levetiracetam at V1 and for at least 4 weeks prior to V1 was prohibited. Subjects with a history or presence of status epilepticus during the last month

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prior to V1 or during Baseline were excluded. Subjects with a lifetime history of suicide attempt (including an active attempt, interrupted attempt, or aborted attempt) or suicidal ideation in the past 6 months were excluded.

**Test product, doses and mode of administration, batch numbers:**

The BRV drug product was supplied for oral use as an immediate release oral solution containing 1mg of BRV per milliliter. Brivaracetam was also supplied for oral use as an immediate release oral solution containing 10mg of BRV per milliliter. The drug product was packaged in 150mL (1mg/mL) and 300mL (10mg/mL) type III amber glass bottles with child-resistant, tamper-evident, polypropylene screw closures. Measuring devices were polypropylene syringes of 1mL, 3mL, and 10mL with an adaptor able to fit the 2 bottle sizes.

Brivaracetam oral solution was administered at weekly increasing doses of approximately 0.4mg/kg, 0.8mg/kg, and 1.6mg/kg bid for subjects  $\geq 8$  years of age and 0.5mg/kg, 1.0mg/kg, and 2.0mg/kg bid for subjects  $< 8$  years of age from Week 1 (V3) to Week 3 (V5).

Batch numbers for BRV drug product include:

- BRV 1mg/mL for oral administration: BX1005712, 100483
- BRV 10mg/mL for oral administration: BX1005713, 200677, 200712, 200734, 200759, 200844, 201331, BX1005715, 200679, 200713, 200737, 200760, 201280, 201332, 200096, 200680, 200714, 200738, 200761, 201281, 201333, 200107, 200681, 200715, 200739, 200762, 201286, 201355, 200108, 200682, 200716, 200735, 200763, 201287, 201364, 200322, 200683, 200717, 200736, 200764, 201290, 200323, 200684, 200718, 200742, 200765, 201291, 200334, 200685, 200719, 200743, 200771, 201301, 200631, 200686, 200720, 200744, 200795, 201302, 200635, 200687, 200721, 200745, 200798, 201305, 200636, 200688, 200722, 200746, 200801, 201306, 200651, 200695, 200725, 200747, 200802, 201308, 200652, 200696, 200726, 200748, 200807, 201309, 200653, 200697, 200727, 200749, 200808, 201310, 200654, 200698, 200728, 200750, 200812, 201311, 200663, 200700, 200729, 200752, 200818, 201314, 200669, 200701, 200730, 200753, 200819, 201315, 200670, 200703, 200731, 200756, 200825, 201316, 200671, 200704, 200732, 200757, 200836, 201317, 200672, 200705, 200733, 200758, 200837, 201318, 201279

All doses were adjusted by body weight, and did not exceed a maximum of 50mg/day, 100mg/day, and 200mg/day.

From Day 21 (V5) onwards, subjects not entering the LTFU study, N01266, were to be down-titrated with weekly decreasing doses of approximately 0.8mg/kg and 0.4mg/kg bid for

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subjects  $\geq 8$  years of age and 1.0mg/kg and 0.5mg/kg bid for subjects  $< 8$  years of age at Week 4 and Week 5 (V6).

Subjects discontinuing early for any reason, and therefore not completing the Evaluation Period, were also to be down-titrated by 1 or 2 weekly decrements of approximately 0.8mg/kg and 0.4mg/kg bid for subjects  $\geq 8$  years of age and 1.0mg/kg and 0.5mg/kg bid for subjects  $< 8$  years of age for the first and second weeks. Subjects who reached the highest DL (DL3: 3.2mg/kg per day for subjects  $\geq 8$  years of age or 4.0mg/kg per day for subject  $< 8$  years of age) were to be down-titrated in 2 weeks, and subjects who reached the intermediate DL (DL2: 1.6mg/kg per day or 2.0mg/kg per day) were to be down-titrated in 1 week.

**Duration of treatment:** The overall study duration per subject was up to 8 weeks, and the maximum BRV exposure per subject was 5 weeks.

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

**Criteria for evaluation:**

**Pharmacokinetics:** The primary variables were the plasma concentrations of BRV and its metabolites ucb 42145 (acid), ucb 100406-1 (hydroxy), and ucb 107092-1 (hydroxyacid), and plasma concentrations of concomitant AEDs.

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

- Adverse events (AEs)
- Safety laboratory tests (hematology, biochemistry including hepatic monitoring of alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], total bilirubin, and gamma-glutamyltransferase [GGT], endocrinology, and urinalysis for subjects  $\geq 4$  years of age)
- Electrocardiograms (ECGs)
- Vital signs (blood pressure, pulse rate, and body temperature)
- Physical (including Tanner scale) and neurological examination
- Psychiatric and mental status
- Body weight and height
- Achenbach Child Behavior Checklist (CBCL) at Baseline for pediatric subjects 18 months and older (CBCL/1½-5 and CBCL/6-18) for assessing behavior

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- Bayley-III scales at Baseline for pediatric subjects <18 months of age (applicable only to subjects enrolled in English speaking countries)

**Efficacy:** The efficacy variables in this study were the following:

- For subjects <2 years of age: shift from Baseline to the end of the Evaluation Period for seizure freedom based on the 24-hour EEG
- For all subjects: responder rate based on 50% reduction from Baseline to the end of the Evaluation Period for the number of seizure days standardized to a 28-day duration based on the DRC data

Exploratory efficacy variables were the following:

- Exploratory efficacy variable for seizure data collected on 1 hour EEG (for subjects with absence seizures at Baseline)
  - Shift from Baseline to the end of the Evaluation Period for seizure freedom for absence seizures based on the 1-hour EEG
- Exploratory efficacy variables for seizure data collected on DRC (for all subjects)
  - Number of seizure days over the Evaluation Period standardized to a 28-day duration
  - Absolute and percentage reduction from Baseline to the end of the Evaluation Period in the number of seizure days standardized to a 28-day duration
  - Categorized percentage reduction from Baseline to the end of the Evaluation Period for the number of seizure days standardized to a 28-day duration (<-25%, -25% to <25%, 25% to <50%, 50% to <75%, 75% to <100%, and 100%)
  - Seizure freedom rate over the Evaluation Period
  - Proportion of seizure-free days over the Evaluation Period

Other exploratory efficacy variable for nonseizure data in this study was the following:

- Direct cost parameters: concomitant medications, medical procedures, healthcare provider consultations not foreseen by the protocol, and hospital stays during the Evaluation Period

**Statistical methods:**  
Descriptive statistics, such as the mean, standard deviation (SD), median, 25<sup>th</sup> percentile, 75<sup>th</sup> percentile, minimum value, and maximum value for quantitative variables, and counts and

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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.

Summaries of disposition, demographics and baseline characteristics were presented by age group, seizure category, and overall. Summaries of protocol deviations, medical history, concomitant diseases and conditions, epilepsy history (including AED and non-AED use), treatment compliance, safety outcomes, and most efficacy outcomes (including direct cost parameters) were presented by age group and overall. Plasma concentrations of BRV, BRV metabolites, and concomitant AEDs were presented by age group. Some AE summaries were also presented by seizure category or DL.

Efficacy parameters related to seizures were summarized overall descriptively, by seizure categories (POS and primary generalized seizures [PGS]), and by seizure types and syndromes (occurring in at least 3 subjects). Seizure freedom based on 24-hour EEG data was summarized for subjects  $\geq 1$  month to  $< 2$  years of age, and seizure freedom based on 1-hour EEG, responder rate based on DRC, and seizure data based on DRC were summarized for all subjects. The number of seizure days was standardized to a 28-day duration.

For the primary PK analysis, descriptive statistics, including geometric mean and coefficient of variation (CV), for dose-normalized BRV plasma concentrations and its metabolites ucb 42145 (acid), ucb 100406-1 (hydroxy), and ucb 107092-1 (hydroxyacid) were computed.

The following study periods were defined:

- Baseline: On or after the date of V1 and prior to the date of first dose of study drug (note: data collected at V2 prior to the first dose of study drug were used as baseline values)
- Evaluation : On or after the date of first dose of study drug, and prior to or on the date of V5/EDV
- Down-Titration: After the date of V5/EDV and prior to or on the date of V7 for subjects who entered the Down-Titration Period
- Post-Treatment: After the date of V7 for subjects who entered the Down-Titration Period; after the date of V5/EDV for subjects who did not enter the Down-Titration Period

The Post-Baseline Period was defined as the combined Evaluation, Down-Titration, and Post-Treatment Periods.

Baseline for seizure days was based on the 28-day adjusted seizure days calculated from seizure diary days over the Baseline Period. Baseline for laboratory parameters, vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], and pulse rate), body weight, and ECGs

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were based on the latest nonmissing scheduled or unscheduled assessment prior to or on the date of V2. Baseline was determined separately for each individual clinical laboratory parameter for hematology, biochemistry, endocrinology, and urinalysis assessments.

Three analysis sets were utilized to evaluate the data. The PK-PPS consisted of all subjects who had at least 1 measurable plasma sample (with recorded sampling time) on at least 1 visit with documented drug intake times. The SS consisted of all subjects who received at least 1 dose of study drug. The FAS included all subjects from the SS with a Baseline DRC or EEG and at least 1 completed post-Baseline DRC or EEG.

**Summary and conclusions:**

**Subject disposition:**

A total of 110 subjects were screened, 10 of whom were screen failures for reasons including AEs (1 subject [0.9% of all subjects]), ineligibility (5 subjects [4.5% of all subjects]), lost to follow up (1 subject [0.9% of all subjects]), and withdrawal by subject (3 subjects [2.7% of all subjects]). A total of 100 subjects were enrolled in the study in the following age groups: 30 subjects in the  $\geq 1$  month to  $< 2$  years group, 52 subjects in the  $\geq 2$  to  $< 12$  years group, and 18 subjects in the  $\geq 12$  to  $< 16$  years group.

Of the 100 enrolled subjects, 90 subjects (90.0% of all subjects) completed the study: 27 subjects (90.0%) in the  $\geq 1$  month to  $< 2$  years group; 47 subjects (90.4%) in the  $\geq 2$  to  $< 12$  years group; and 16 subjects (88.9%) in the  $\geq 12$  to  $< 16$  years group. Ten subjects (10.0% of all subjects) discontinued the study prematurely, and the percentage of subjects who discontinued the study prematurely was similar across age groups. Overall, the most common reasons for discontinuing the study prematurely was an AE (6 subjects [6.0% of all subjects]), followed by withdrawal of subject consent (2 subjects [2.0% of all subjects]), lack of efficacy (1 subject [1.0% of all subjects]), and protocol violation (1 subject [1.0% of all subjects]). Among subjects who discontinued the study due to an AE, 1 subject (3.3%) was in the  $\geq 1$  month to  $< 2$  years group, 3 subjects (5.8%) were in the  $\geq 2$  to  $< 12$  years group, and 2 subjects (11.1%) were in the  $\geq 12$  to  $< 16$  years group.

Of those 90 subjects who completed, 8 subjects entered the Down-Titration Period.

**Pharmacokinetics results:**

- The presence of detectable BRV and BRV metabolites in the plasma indicated that all subjects in the PK-PPS were exposed to BRV.
- Trough BRV plasma concentration increased proportionally to the dose, as indicated by the approximate doubling of trough BRV plasma concentration with every doubling of the BRV

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<p>dose. Despite the already implemented dose adjustment in the subjects &lt;8 years of age, trough concentration in the <math>\geq 1</math> month to &lt;2 years group was approximately 30% to 45% lower than in adolescents, suggesting that further dose adjustments may be required.</p> <ul style="list-style-type: none"> <li>Trough BRV plasma concentration increased with increasing age (at DL3: 0.596, 0.827, and 1.065 <math>\mu\text{g/mL}</math> in <math>\geq 1</math> month to &lt;2 years, <math>\geq 2</math> to &lt;12 years and <math>\geq 12</math> to &lt;16 years groups, respectively).</li> <li>In general, the trough geometric mean BRV metabolite plasma trough concentrations were similar across age groups at each visit. For all age groups, the postdose BRV metabolite plasma concentrations appeared to increase dose proportionally.</li> <li>In general, the geometric mean plasma concentrations of the most commonly used (ie, used by <math>\geq 10\%</math> of all subjects) concomitant AEDs were similar between V1 (Screening) and V5 for all age groups, as expected for subjects on stable doses of concomitant AEDs.</li> <li>Intersubject variability was high for all summary statistics of BRV, BRV metabolite, and concomitant AED plasma concentrations.</li> </ul>		
<p><b>Safety results:</b></p> <p>Meaningful comparisons across age groups should be interpreted with caution and considered as preliminary due to the limited sample size, particularly in the <math>\geq 12</math> to &lt;16 years group, and the open-label design of the study.</p> <p><u>Treatment-emergent AEs for all subjects and by age group</u></p> <ul style="list-style-type: none"> <li>Overall, 66 subjects (66.7% of all subjects) had TEAEs during the Post-Baseline Period. The most common TEAEs (by PT) overall were convulsion (10 subjects [10.1% of all subjects]) and somnolence, irritability, and pyrexia (8 subjects [8.1% of all subjects] each). The majority of subjects had <math>\geq 1</math> TEAE during the Evaluation Period (63 subjects [63.6% of all subjects]). The most common TEAEs overall during the Evaluation Period were convulsion, somnolence, and irritability (8 subjects [8.1% of all subjects] each).</li> <li>Eight subjects entered the Down-Titration Period, and 15 subjects entered the Post-Treatment Period. Approximately half of the subjects had TEAEs (4 subjects [50% of all subjects] and 7 subjects [46.7% of all subjects], respectively) during each period. The TEAEs of convulsion were reported during the Post-Treatment Period but not during the Down-Titration Period and were considered potentially related to withdrawal or rebound phenomena; no other TEAEs during either period were considered potentially related to these</li> </ul>		



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<p>phenomena. No apparent differences among these subjects were observed regarding seizure frequency and the type or severity of seizures experienced during the Down-Titration or Post-Treatment Periods. These results should be interpreted with caution given the limited number of subjects who entered the Down-Titration and Post-Treatment Periods.</p> <ul style="list-style-type: none"><li>• Two subjects in the <math>\geq 1</math> month to <math>&lt; 2</math> years group had severe TEAEs of convulsion (1 TEAE per subject; 2.0% of all subjects), and 1 subject in the <math>\geq 1</math> month to <math>&lt; 2</math> years group had a severe TEAE of laryngitis (1.0% of all subjects). These TEAEs were considered to be not related to study drug by the Investigator. Overall, TEAEs that were mild or moderate in intensity were reported for most subjects (43 subjects [43.4% of all subjects] and 20 subjects [20.2% of all subjects], respectively).</li><li>• Overall, drug-related TEAEs were reported for 32 subjects (32.3% of all subjects). The most common drug-related TEAEs overall were somnolence (7 subjects [7.1% of all subjects]) and decreased appetite (6 subjects [6.1% of all subjects]).</li><li>• The overall incidence of discontinuations due to TEAEs was low (6.1% of all subjects). The only TEAE leading to permanent study drug discontinuation reported for more than 1 subject was aggression (2 subjects [2.0% of all subjects]), which was reported for 1 subject each in the <math>\geq 2</math> to <math>&lt; 12</math> years (2.0%) and <math>\geq 12</math> to <math>&lt; 16</math> years (5.6%) groups.</li><li>• Overall, 12 treatment-emergent SAEs were reported for 8 subjects (8.1% of all subjects). The most common treatment-emergent SAE was convulsion, which was reported for 4 subjects (4.0% of all subjects; 1 event each). The majority of SAEs were mild or moderate in intensity (11 of 12 SAEs; 91.7%), considered to be not related to study drug by the Investigator (11 of 12 SAEs; 91.7%), were resolved by the end of the study (11 of 12 SAEs; 91.7%), and did not require a change in study drug intake (9 of 12 SAEs; 75.0%). A drug-related treatment-emergent SAE of convulsion was reported for 1 subject in the <math>\geq 12</math> to <math>&lt; 16</math> years group and resulted in premature discontinuation of the subject from the study. No deaths were reported.</li><li>• No TEAEs in the Blood and lymphatic system disorders SOC, including vascular hemorrhagic disorders, were reported.</li><li>• Overall, TEAEs in the Nervous system disorders SOC were reported for 24 subjects (24.2% of all subjects); the incidences of these TEAEs ranged from 22.2% to 26.7% across age groups. The most commonly reported Nervous system disorder TEAEs overall were convulsion (10 subjects [10.1% of all subjects]) and somnolence (8 subjects [8.1% of all subjects]). Nervous system disorder TEAEs that were mild or moderate in intensity were</li></ul>		

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<p>reported for most subjects (11 subjects [11.1% of all subjects] each); with the exception of 6 TEAEs, all of these TEAEs resolved by the end of the study. Two subjects (2.0% of all subjects) had 2 severe TEAEs. Eleven subjects (11.1% of all subjects) had 14 Nervous system disorder TEAEs that were considered to be drug-related by the Investigator. Four subjects (4.0% of all subjects) had 4 Nervous system disorder SAEs (1 each). Two subjects (2.0% of all subjects) had Nervous system disorder TEAEs that resulted in premature discontinuation of the subjects from the study, including 1 SAE of convulsion and 1 TEAE of psychomotor hyperactivity.</p> <ul style="list-style-type: none"><li>• Overall, TEAEs in the Psychiatric disorders SOC were reported for 15 subjects (15.2% of all subjects). The most commonly reported Psychiatric disorder TEAEs were aggression (4 subjects [4.0% of all subjects]), insomnia (2 subjects [2.0% of all subjects]), and sleep disorder (2 subjects [2.0% of all subjects]). All Psychiatric disorder TEAEs were mild or moderate in intensity, and the majority of these TEAEs were resolved by the end of the study (12 of 15 TEAEs; 80.0%). Eleven subjects (11.1% of all subjects) had 11 Psychiatric disorder TEAEs that were considered to be drug-related by the Investigator. No subjects had Psychiatric disorder SAEs. Four subjects (4.0% of all subjects) had Psychiatric disorder TEAEs that resulted in premature discontinuation from the study; these TEAEs included TEAEs of abnormal behavior, aggression, and sleep disorder.</li><li>• Four TEAEs related to skin or other allergic reactions were reported during this study, including roseola, dermatitis diaper, dry skin, and macule; each TEAE was reported for no more than 1 subject each. All skin or other potential allergic reaction-related TEAEs were mild or moderate in intensity, and all of these TEAEs were resolved by the end of the study, with the exception of dry skin. A TEAE of dry skin that was considered to drug-related by the Investigator was reported for 1 subject (1.0% of all subjects). None were SAEs and none resulted in premature discontinuation of the subjects from the study.</li><li>• Two TEAEs related to hepatobiliary disorders were reported for 2 subjects: GGT increased and hypoalbuminemia (1 subject [1.0% of all subjects] for each). The TEAE of hypoalbuminemia was moderate in intensity and had resolved by the end of the study. The TEAE of GGT increased was mild in intensity and did not resolve by the end of the study. Neither of these TEAEs was considered to be drug-related by the Investigator, was an SAE, nor resulted in premature discontinuation of the subjects from the study.</li><li>• Two TEAEs of metabolic acidosis was reported for 2 subjects (2.0% of all subjects) in the <math>\geq 1</math> month to &lt;2 years group (6.7%). One TEAE was mild in intensity and did not resolve by the end of the study, and 1 TEAE was moderate in intensity and was resolving by the end of</li></ul>		

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the study. Both TEAEs were considered to be not related to study drug by the Investigator. Neither event of metabolic acidosis was an SAE nor resulted in premature discontinuation of the subjects from the study.

- No pregnancies were reported during the study.

#### Treatment-emergent AEs by seizure category and DL at onset

- Overall, 38 subjects (76.0% of all subjects) with POS and 28 subjects (57.1% of all subjects) with PGS had TEAEs. Among subjects with POS, the most common TEAEs (by PT) overall were convulsion (6 subjects [12.0% of all subjects]), as well as irritability and pyrexia (5 subjects [10.0% of all subjects] each). Among subjects with PGS, the most common TEAEs (by PT) overall were convulsion and somnolence (4 subjects [8.2% of all subjects] each), as well as fatigue, irritability, pyrexia, and decreased appetite (3 subjects [6.1% of all subjects] each). Due to the limited number of subjects in each age group, meaningful comparisons across age groups were difficult to make.
- Overall, at least 1 TEAE at DL1, DL2, and DL3 was reported for 38 subjects (39.6% of all subjects), 37 subjects (39.8% of all subjects), and 26 subjects (26.8% of all subjects), respectively; the overall incidence of TEAEs did not increase from the lowest dose to the highest dose. The most common TEAE (by PT) overall for DL1 was irritability (7 subjects [7.3% of all subjects]), for DL2 was convulsion (4 subjects [4.3% of all subjects]), and for DL3 was somnolence (5 subjects [5.2% of all subjects]).

#### Clinical laboratory evaluations, vital signs, neurological examination findings, and other observations related to safety

- There were no clinically meaningful differences in baseline hematology and blood chemistry parameters or in the mean changes from Baseline to the Last Value during the Evaluation Period for all age groups. In general, the incidence of PCST hematology values during the Post-Baseline Period was low ( $\leq 6.3\%$  of all subjects for any parameter). The most commonly observed PCST hematology values were high and low leukocyte values (2 subjects [2.1% of all subjects] and 4 subjects [4.2% of all subjects], respectively). In general, the overall incidence of PCST blood chemistry values during the Post-Baseline Period was low ( $\leq 5.4\%$  of all subjects for any parameter), with the exception of the PCST low creatine clearance estimate value (33.0% of all subjects).
- There were no clinically meaningful differences in baseline vital sign parameters or in the mean changes from Baseline to the Last Value in the Post-Baseline Period for all age groups.

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In general, the incidence of PCST vital sign values during the Post-Baseline Period was low ( $\leq 8.5\%$  of all subjects) for PCST SBP, DBP, and pulse rate values and moderate ( $\leq 21.9\%$  of all subjects) for PCST weight values. Across age groups, the incidences of PCST SBP, DBP, and weight values were highest in the  $\geq 1$  month to  $< 2$  years group compared with the older age groups at V3, V4, and V5. Height was only collected at Baseline; it will be measured and analyzed in N01266.

- Overall, the majority of subjects had normal ECG findings at Baseline (83 subjects [84.7% of all subjects]). During the Post-Baseline Period, similar incidences of subjects overall had shifts from normal to abnormal findings at V3 (4.2% of all subjects), V4 (3.2% of all subjects), V5/EDV (3.1% of all subjects), and Last Value (4.2% of all subjects). No clinically meaningful differences in ECG findings across age groups were observed. No subjects had shifts to abnormal that were clinically significant at any time point, with the exception of 2 subjects. For these subjects, none of the abnormal clinically significant ECG findings were associated with TEAEs. One additional subject had 2 mild TEAEs of ventricular extrasystoles, which were not associated with abnormal clinically significant ECG findings.
- Most subjects had no change in neurological examination findings from Baseline to End of Treatment. None of the neurological examination findings were clinically relevant, as no AEs or SAEs that were related to neurological examination findings were reported.
- No suicidal ideation or actual suicide attempts were reported for subjects during the study, and no TEAEs related to suicidal ideation or behavior were reported.

**Efficacy results:**

Efficacy data were analyzed by age group and by seizure category. There were too few subjects in seizure categories to make comparisons across age groups. These results are to be interpreted with caution due to the short duration of exposure, the small number of subjects who were in the different age groups and seizure categories, and the exploratory nature of the efficacy results.

Seizure data were also summarized by seizure types and syndromes occurring in at least 3 subjects. Due to the short duration of treatment in this study, further analysis will be conducted for seizure types and syndromes using long-term data from the N01266 study.

- Seizure status (seizure free/not seizure free) for subjects  $\geq 1$  month to  $< 2$  years of age, based on 24-hour EEG data, did not change from Baseline to V5/EDV for most subjects overall or by seizure category (POS and PGS). A total of 5 subjects (19.2%) who were not seizure free at Baseline were seizure free based on a 24-hour EEG at V5/EDV, and 2 subjects (7.7%) who

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were seizure free at Baseline were not seizure free at V5/EDV.

- Overall, 17 subjects (21.3% of all subjects) were responders during the Evaluation Period. This included 11 subjects (31.4% of all subjects) with POS and 6 subjects (13.3% of all subjects) with PGS. There appeared to be an apparent difference suggesting an increased percentage of responders in older subjects.
- Seizure freedom based on 1-hour EEG data was difficult to interpret, as the number of subjects  $\geq 2$  years of age with typical absence seizures (Type IIA1; n=5) at Baseline and with 1-hour EEG data available at both Baseline and the applicable visit was limited (n=5). Overall, the seizure free/not seizure free status worsened for 1 subject (20.0% of subjects), improved for 1 subject (20.0% of subjects), and did not change for 3 subjects (60.0% of subjects) at V5/EDV.
- The overall mean ( $\pm$ SD) number of seizure days (standardized to a 28-day duration) was 14.4 days ( $\pm$ 11.2 days) during the Evaluation Period. The overall mean number of seizure days was higher in subjects with PGS during the Evaluation Period compared with subjects with POS. The overall mean number of seizure days was highest in the  $\geq 1$  month to  $<2$  years group during the Evaluation Period followed by the  $\geq 2$  to  $<12$  years group and was lowest in the  $\geq 12$  to  $<16$  years group. These observations were consistent with the mean values during the Baseline Period.
- The overall mean ( $\pm$ SD) reduction in the number of seizures days (standardized to a 28-day duration) from the Baseline Period to the Evaluation Period was 1.6 days ( $\pm$ 6.5 days). The median reduction in the number of seizure days from the Baseline Period to the Evaluation Period was 0.0 days. The overall mean reduction was similar in subjects with PGS and subjects with POS (1.7 and 1.5 days, respectively); both groups had a median reduction of 0.0 days. The overall mean and median reduction in the number of seizures days (standardized to a 28-day duration) from the Baseline Period to the Evaluation Period was highest in  $\geq 1$  month to  $<2$  years group compared with the older age groups.
- The overall median percent reduction in the number of seizures days was 4.8%; this was due solely to the reduction observed in subjects with POS (13.6%), as no median percent reduction was observed in subjects with PGS (0.0%). Similar to absolute reductions, the greatest median percent reduction in the number of seizure days was observed in the  $\geq 1$  month to  $<2$  years group compared with older age groups.
- Overall, 47 subjects (58.8% of all subjects) had a  $-25\%$  to  $<25\%$  reduction in the number of seizure days from Baseline to the end of the Evaluation Period and 26 subjects (32.5% of all

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<p>subjects) had <math>\geq 25\%</math> reduction. Similar observations were made overall across age groups and by seizure category. Six subjects (7.5% of all subjects) experienced a 100% reduction in the number of seizure days from Baseline to the end of the Evaluation Period (5 subjects [6.3% of all subjects] with POS and 1 subject [1.3% of all subjects] with PGS). Seven subjects (8.8% of all subjects) experienced <math>&lt; 25\%</math> reduction (ie, an increase in the number of seizure days of <math>&gt; 25\%</math>) in the number of seizure days from Baseline to the end of the Evaluation Period; 3 subjects (3.8% of all subjects) had POS and 4 subjects (5.0% of all subjects) had PGS. None of these subjects had a seizure-related TEAE.</p> <ul style="list-style-type: none"> <li>Overall, 14 subjects (14.4% of all subjects) experienced seizure freedom over the Evaluation Period, based on the DRC data, with the majority of these subjects having POS (POS: 12 subjects [12.4% of all subjects]; PGS: 2 subjects [2.1% of all subjects]). The number of subjects with seizure freedom was highest in the <math>\geq 2</math> to <math>&lt; 12</math> years group (9 subjects [18.0%]), with a similar number of subjects in the <math>\geq 1</math> month to <math>&lt; 2</math> years and <math>\geq 12</math> to <math>&lt; 16</math> years groups (3 subjects [10.0%] and 2 subjects [11.8%], respectively).</li> <li>The overall mean proportion of seizure-free days was 0.5 days (<math>\pm 0.4</math> days) and was similar regardless of age group or seizure type (range: 0.3 to 0.7 days).</li> <li>During the Evaluation Period, most subjects did not have a concurrent medical procedure, additional healthcare provider visits, ER visits, or hospital stays. Younger subjects appeared to utilize healthcare resources more frequently than older subjects.</li> <li>In general, smaller margins of improvements were observed for subjects with PGS-related seizure types and syndromes compared with subjects with POS-related seizure types and syndromes. For PGS-related seizure types, it is more difficult to assess a broad efficacy result considering that the response to treatment varies greatly for absence, myoclonic, and generalized tonic-clonic seizures.</li> <li>In a post hoc analysis, the results for the percentage of responders (standardized to a 7-day duration), as well as overall median percent reduction and the categorized percent reduction in the number of seizure days suggested that there was an increase in the number of responders with increasing dose.</li> </ul>		

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**Conclusions:**

- Trough BRV plasma concentration increased proportionally to the dose, as indicated by the approximate doubling of trough BRV plasma concentration with every doubling of the BRV dose. Despite the already implemented dose adjustment in the subjects  $\leq 8$  years of age, trough concentration in the  $\geq 1$  month to  $< 2$  years group was approximately 30% to 45% lower than in adolescents, suggesting that further dose adjustments may be required.
- Trough BRV plasma concentration increased with increasing age (at DL3: 0.596, 0.827, and 1.065  $\mu\text{g/mL}$  in  $\geq 1$  month to  $< 2$  years,  $\geq 2$  to  $< 12$  years and  $\geq 12$  to  $< 16$  years groups, respectively).
- In general, the trough geometric mean BRV metabolite plasma trough concentrations were similar across age groups at each visit. For all age groups, the postdose BRV metabolite plasma concentrations appeared to increase dose proportionally.
- Treatment with BRV was generally well tolerated. Six subjects discontinued the study due to TEAEs, including 1 SAE that was moderate in intensity. All severe TEAEs and most SAEs were considered to be not related to study drug by the Investigator. No deaths were reported.
- The TEAE profile in pediatric subjects in this study was consistent with the known BRV safety profile in adults with a low incidence of dizziness as the main difference. From the lowest dose to the highest dose, the overall incidence of TEAEs did not increase. In general, there were no clinically meaningful changes in laboratory parameters, vital signs, or ECGs.
- This study provided preliminary evidence of efficacy for short-term BRV treatment in pediatric subjects with various epileptic syndromes, as determined by a reduction in the number of seizure days and seizure freedom based on EEG and DRC data.
- Post hoc analyses for DRC seizure variables showed an efficacy signal with increasing dose in select variables.

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