


## RESEARCH ARTICLE

# Pharmacokinetics, safety, and tolerability of intravenous brivaracetam in pediatric patients with epilepsy: An open-label trial

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## Abstract

**Objective:** To evaluate the pharmacokinetics, safety, and tolerability of brivaracetam (BRV) as 15-min intravenous (IV) infusion and bolus ( $\leq 2$ -min injection).

**Methods:** EP0065 (ClinicalTrials.gov: NCT03405714) was a Phase 2, multicenter, open-label trial in patients  $\geq 1$  month to  $< 16$  years of age with epilepsy. Patients received up to 5 mg/kg/day BRV (not exceeding 200 mg/day). Enrollment was sequential by descending age, depending on safety review. Outcomes included BRV plasma concentrations before and after IV administration, treatment-emergent adverse events (TEAEs), and discontinuations due to TEAEs.

**Results:** Fifty patients were enrolled, received BRV, and completed the trial. Twenty-six patients (52.0%) received 15-min infusions and 24 (48.0%) received bolus injections. Most patients (80.0%) received one IV dose. In the 15-min infusion group, geometric mean (GeoMean) BRV concentrations 15 ( $\pm 2$ ) min ( $n = 21$ ) and 3 h ( $\pm 15$  min) ( $n = 21$ ) post dose were 1903.0 ng/mL (geometric coefficient of variation [GeoCV]: 60.7%) and 1130.3 ng/mL (58.8%), respectively. In the bolus group, GeoMean BRV concentrations 15 ( $\pm 2$ ) min ( $n = 19$ ) and 3 h ( $\pm 15$  min) ( $n = 21$ ) post dose were 1704.8 ng/mL (GeoCV: 74.5%) and 1383.9 ng/mL (85.0%), respectively. Overall, 14 patients (28.0%) had TEAEs (15-min infusion: 8 [30.8%]; bolus: 6 [25.0%]), most commonly ( $\geq 5\%$  of patients) somnolence (3 [6.0%]). Ten patients (20.0%) had drug-related TEAEs (15-min infusion: 6 [23.1%]; bolus: 4 [16.7%]). No patients discontinued due to TEAEs, and no deaths occurred. **Significance:** IV BRV (up to 200 mg/day) was well tolerated in patients  $\geq 1$  month to  $< 16$  years of age, regardless of whether BRV was administered as 15-min infusion or bolus. No unexpected safety or pharmacokinetic differences were observed between patients receiving 15-min infusions or bolus, and plasma concentrations were in the expected range. Safety results were consistent with the known safety profile of oral BRV, with no new safety concerns identified.

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## KEYWORDS

antiseizure medication, brivaracetam, epilepsy, focal seizure, pediatric

## 1 | INTRODUCTION

The incidence of epilepsy in children has been reported to range from 41 to 187 new cases per 100 000 children per year.<sup>1</sup> Existing treatment options for focal seizures in pediatric patients generally follow the treatment options for focal seizures in adults, with clinical experience suggesting that children achieve similar results to adults with antiseizure medications (ASMs).<sup>2</sup> However, few ASMs are approved for the treatment of focal (partial-onset) seizures in this vulnerable population. In addition to oral formulations, intravenous (IV) formulations of ASMs are particularly helpful as short-term replacements when the use of oral formulations is not possible or feasible (e.g., preoperative and postoperative patients, patients with acute gastrointestinal disorders, and patients with acute swallowing disorders).

Brivaracetam (BRV) is currently indicated for the adjunctive treatment of focal seizures in patients 4 years of age and older in the European Union<sup>3</sup> and as monotherapy and adjunctive treatment in patients 1 month of age and older in the United States.<sup>4</sup>

A previous Phase 2a, open-label, single-arm, fixed three-step dose-escalation trial (N01263; ClinicalTrials.gov: NCT00422422) showed that adjunctive oral BRV is well tolerated and effective in patients  $\geq 1$  month to  $< 16$  years of age.<sup>5</sup> Its ongoing Phase 3, open-label, multicenter, long-term follow-up trial (N01266; NCT01364597) is assessing the long-term safety, tolerability, and efficacy of oral BRV in pediatric patients receiving at least one ASM other than BRV. Another Phase 3 open-label, multicenter trial (EP0156; NCT04715646) is also evaluating long-term safety and tolerability of oral BRV as adjunctive treatment in pediatric patients with epilepsy.

BRV tablets, oral solution, and IV formulations have been shown to be bioequivalent in adults.<sup>6-8</sup> The objective of the present trial (EP0065; NCT03405714) was to evaluate the pharmacokinetics (PK), safety, and tolerability of BRV injection administered as a 15-min IV infusion and IV bolus injection ( $\leq 2$ -min infusion) in patients with epilepsy  $\geq 1$  month to  $< 16$  years of age.

## 2 | METHODS

### 2.1 | Trial design and patients

This Phase 2, multicenter, open-label trial was conducted at 37 sites across seven countries (Czech Republic, Germany,

### Key Points

- Treatment with intravenous brivaracetam (IV BRV) (15-min infusion and bolus) was well tolerated in patients  $\geq 1$  month to  $< 16$  years of age with epilepsy.
- Safety results are consistent with the known safety profile of BRV in adult and pediatric patients  $\geq 4$  years of age receiving oral BRV.
- BRV plasma concentrations rapidly increased during the first 15 min post IV administration, with decreases over the following 3 h.
- No unexpected safety or pharmacokinetic (PK) differences were observed across age cohorts, between the 15-min infusion and bolus groups, or weight groups.
- Results of this trial and adult bioequivalence studies support the use of an IV BRV dose that is a mg-to-mg equivalent of the oral dose.

Hungary, Italy, Mexico, Spain, and the United States). The trial was conducted in accordance with the current version of the applicable regulatory and International Conference on Harmonization Good Clinical Practice requirements, the ethical principles as stated in the Declaration of Helsinki, and the local laws of the countries involved. The trial protocol, amendments, and patient informed consent forms were reviewed and approved by an independent ethics committee or institutional review board. Written informed consent was obtained from patients or their parents/guardians, and assent forms, where required, were signed and dated by minors.

Children  $\geq 1$  month and  $< 16$  years of age with an epilepsy diagnosis and receiving at least one ASM (including BRV) without a change of dose regimen for  $\geq 7$  days before screening were enrolled in this trial. Patients were excluded if they were likely to require a change in concomitant ASMs, dose of concomitant ASMs, or formulation of ASMs during the 7 days before IV BRV treatment or if they were likely to require rescue medication during BRV treatment. Patients were grouped in the following age-based cohorts:  $\geq 1$  month to  $< 2$  years,  $\geq 2$  to  $< 6$  years,  $\geq 6$  to  $< 12$  years, and  $\geq 12$  to  $< 16$  years. Due to the challenges associated with recruiting pediatric patients and the anticipated low number of pediatric patients who would be eligible for this trial, four BRV treatment categories

were included to maximize enrollment. Patients were eligible to be included if they were currently receiving oral BRV in a long-term, open-label trial (open-label BRV [OLB] patients), they were currently receiving prescribed oral BRV from a commercial supply (prescribed BRV [RxB] patients), they would receive their first dose of BRV during the trial orally (initiating oral BRV [IOB] patients), or they would receive their first dose of BRV during the trial intravenously (initiating IV BRV [IIB] patients).

## 2.2 | Treatment schedule

The maximum doses planned to be administered during the trial were 5 mg/kg/day for OLB and RxB patients and 4 mg/kg/day for IOB and IIB patients (to be administered twice daily [bid] in equally divided doses), not exceeding 200 mg/day. The doses of IV BRV used in this trial were chosen based on modeling of PK data from the pediatric trial N01263,<sup>5</sup> as well as a study in healthy adult volunteers (N01256; UCB Pharma, data on file).

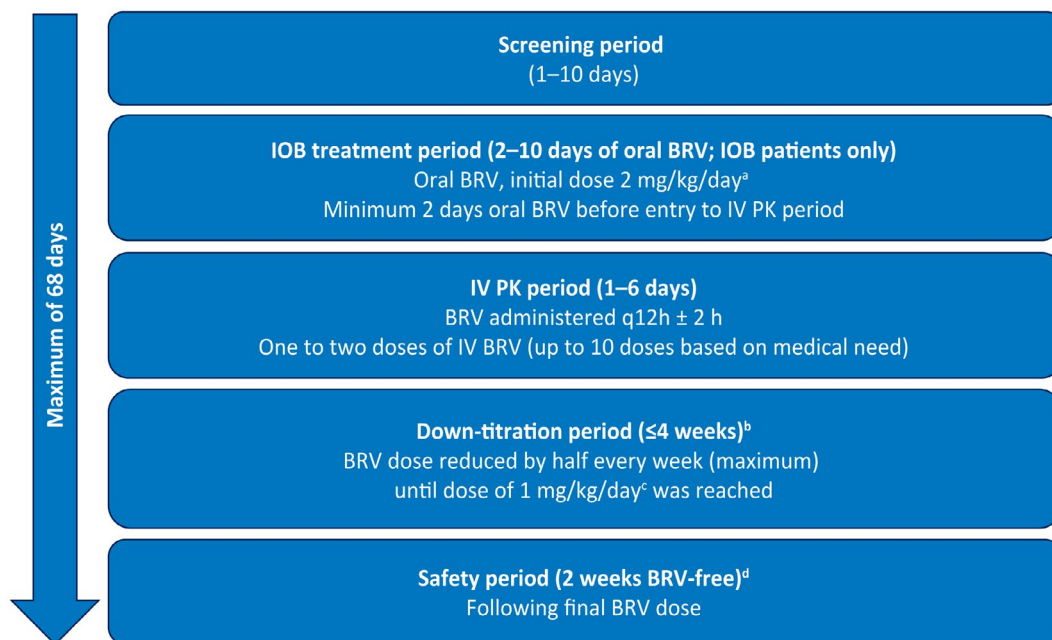
The trial period consisted of a screening period (1–10 days), IOB treatment period (2–10 days of oral BRV; for IOB patients only), IV PK period (1–6 days of IV BRV), down-titration period ( $\geq 4$  weeks), and safety (BRV-free) period (2 weeks) (Figure 1). In the IV PK period, patients may have received up to 10 IV BRV doses. Patients who were not

able to receive oral BRV for down-titration may have received additional IV BRV doses during the down-titration period at the investigator's discretion. A sequential cohort enrollment design was used, with cohorts enrolled sequentially by descending age:  $\geq 12$  to  $<16$  years,  $\geq 6$  to  $<12$  years,  $\geq 2$  to  $<6$  years, then  $\geq 1$  month to  $<2$  years. For each cohort, the first half received the 15-min infusion, then, after review of safety and (where available) PK data by the data monitoring committee, the remaining half received IV BRV as a bolus ( $\leq 2$ -min infusion) and the next (younger) cohort began the 15-min infusion.

## 2.3 | Trial end points and outcome measures

The PK end point for this trial was the plasma concentrations of BRV before and after IV BRV administration. The primary safety and tolerability end points were treatment-emergent adverse events (TEAEs) occurring throughout the trial and patient withdrawals due to TEAEs. Secondary safety end points were electrocardiography results and vital signs (measured before and after initiation of IV BRV administration) and clinical laboratory and urinalysis parameters (assessed pre- and post-treatment).

Blood samples for PK analyses were collected for the initial IV BRV administration and one subsequent IV BRV



**FIGURE 1** Trial design and treatment schedule. <sup>a</sup>Treatment initiated with oral BRV 2 mg/kg/day (not exceeding 100 mg/day for body weights  $\geq 50$  kg); could have been adjusted to maximum dose of 4 mg/kg/day (not exceeding 200 mg/day for body weights  $\geq 50$  kg). <sup>b</sup>Patients who received at least four BRV doses during IOB or IV PK period who did not plan to continue BRV or discontinued BRV entered this period; those who received less than four BRV doses may have entered this period at the discretion of the investigator. <sup>c</sup>50 mg/day if body weight  $\geq 50$  kg. <sup>d</sup>Only patients who down-titrated had a safety (BRV-free) period. BRV, brivaracetam; h, hour; IOB, initiating oral brivaracetam; IV, intravenous; PK, pharmacokinetic; q12h, every 12 h

administration only (for patients requiring more than one dose of IV BRV). PK sampling was conducted  $\leq 1$  h before 15-min BRV infusion and 15 min and 3 h after infusion, and  $\leq 1$  h before bolus injection ( $\leq 2$ -min infusion) and 15 min and 3 h after injection.

## 2.4 | Statistical methods

The safety set-IV (SS-IV) consisted of all patients who received at least one dose of IV BRV. The PK per-protocol set consisted of all patients in SS-IV with at least one measurable post-dose plasma concentration (with recorded sampling time) during the IV PK period and documented IV BRV infusion time without any important protocol deviations affecting the interpretability of the PK analyses. All summaries are descriptive; no statistical hypothesis testing was planned. Descriptive statistics for PK include the number of observed values, geometric mean, 95% confidence interval (CI) for geometric mean, geometric coefficient of variation, mean, standard deviation (SD), median, minimum value, and maximum value. Values below the limit of quantification were set to the limit of quantification for all calculations. The limit of quantification was 2 ng/mL in patients  $\geq 6$  to  $< 16$  years of age, and 10 ng/mL in patients  $\geq 1$  month to  $< 6$  years of age because blood samples in young children were

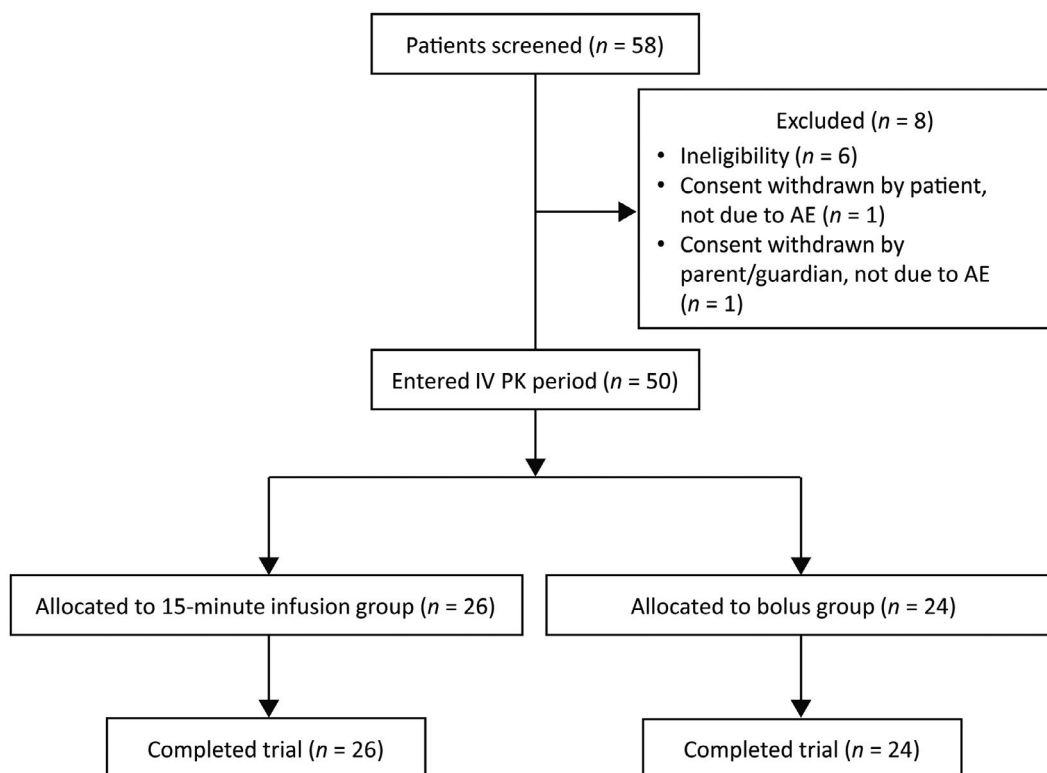
collected in capillaries and had to be diluted 5-fold due to the small volume.

## 3 | RESULTS

### 3.1 | Patients

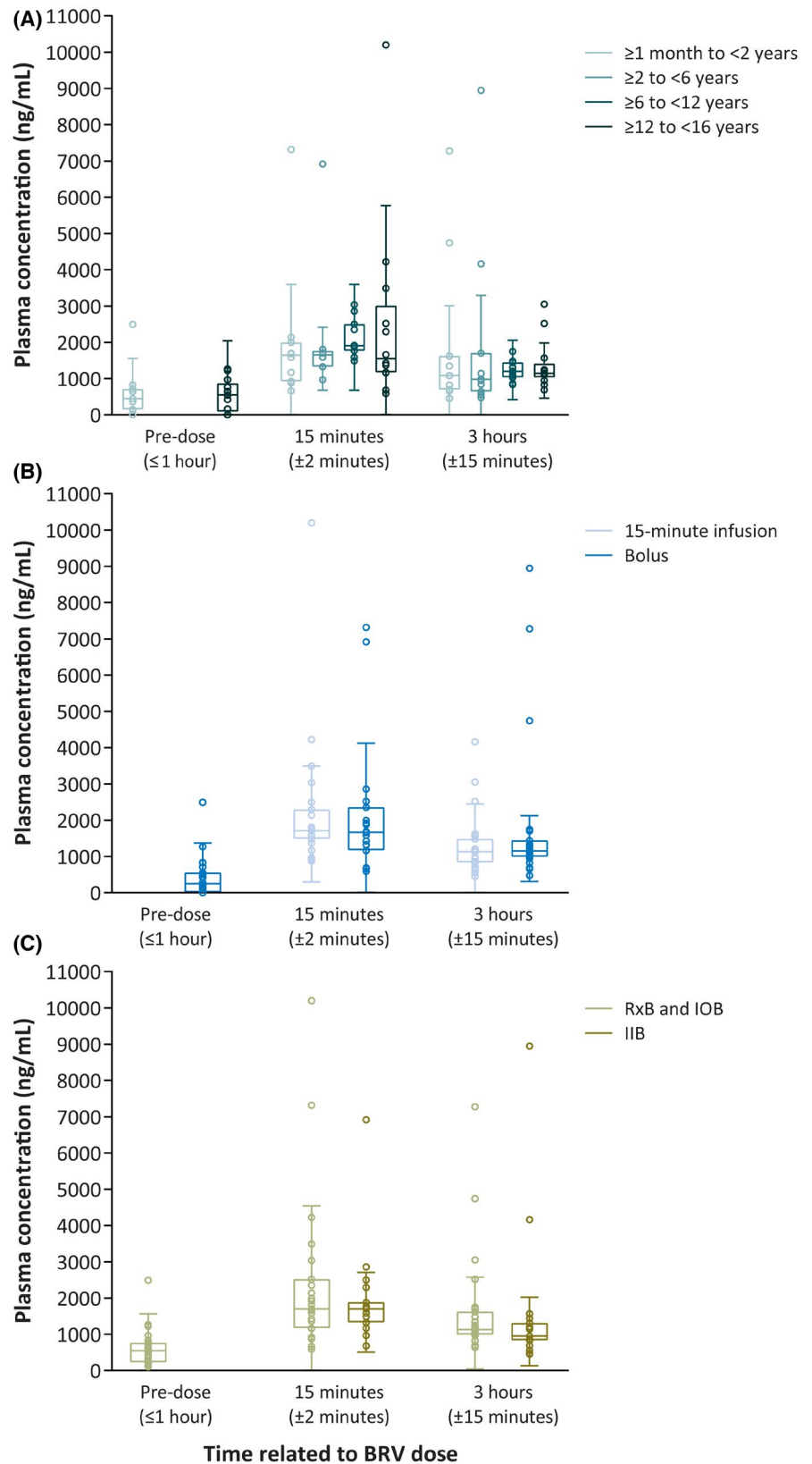
Of 58 screened patients, 50 eligible patients were enrolled in the trial (Figure 2). All 50 patients received IV BRV and were included in the SS-IV. Of these, 22 patients entered and completed the IOB treatment period (IOB patients). All 50 patients (26 patients in the 15-min infusion group and 24 in the bolus group) entered and completed the IV PK period and the follow-up period. There were no discontinuations due to a TEAE or for any other reasons. No patients required down-titration; therefore, none entered the safety period.

The mean ages were 8.3 years for patients  $\geq 2$  years of age ( $n = 37$ ) and 11.4 months for patients  $< 2$  years of age ( $n = 13$ ) (Table S1). Approximately half (52.0%) of the patients were male, and most were White (94.0%). Of the 50 patients, 43 weighed  $< 50$  kg and 7 weighed  $\geq 50$  kg. There were no unexpected differences across age cohorts or between the 15-min infusion and bolus groups with respect to demographic characteristics. The proportion of patients in each BRV treatment category were 0% for OLB,



**FIGURE 2** Patient flow diagram. AE, adverse event; IV, intravenous; PK, pharmacokinetic

**FIGURE 3** BRV plasma concentrations at Visit 3 by (A) age cohort, (B) administration, and (C) patient group (IV PK period) (PK-PPS). Values below the limit of quantification were replaced by the value of the limit of quantification in all calculations. Data are only displayed if at least two-thirds of the concentrations were quantified at the respective timepoint. Boxplot whiskers extend out to  $Q3+1.5*IQR$  and  $Q1-1.5*IQR$ . BRV, brivaracetam; IIB, initiating intravenous brivaracetam; IOB, initiating oral brivaracetam; IQR, interquartile range; IV, intravenous; PK, pharmacokinetic; PK-PPS, pharmacokinetic per-protocol set; Q1, 25th percentile; Q3, 75th percentile; RxB, prescribed brivaracetam



16.0% for RxB (8 patients), 44.0% for IOB (22 patients), and 40.0% for IIB (20 patients; BRV-naive before first IV dose). The mean (SD) duration of epilepsy differed by age cohort: 8.2 (8.1) months in the youngest age cohort ( $\geq 1$  month to  $< 2$  years), 34.6 (17.8) months in the  $\geq 2$  to

$< 6$  years cohort, 6.0 (2.4) years in the  $\geq 6$  to  $< 12$  years cohort, and 7.9 (4.5) years in the  $\geq 12$  to  $< 16$  years cohort.

Most patients (49 [98.0%]) reported taking at least one ASM (before their first dose of IV BRV and concomitantly). No differences were observed across age cohorts

or between the 15-min infusion and bolus groups for proportions of patients taking prior and concomitant ASMs (Table S1).

### 3.2 | PK outcomes

PK outcomes were consistent with the expected results and expected ranges for this population (Figure 3; Table S2). No unexpected differences were observed across age cohorts or between the 15-min infusion and bolus groups. BRV plasma concentrations broadly followed a pattern of rapid increases during the first 15 min after IV administration, with a gradual decrease until 3 h post dose. This pattern was not observed in four patients, who had higher BRV concentrations at 3 h post dose compared with their 15-min post-dose time point; one of these four patients had a plasma concentration that was greatest at the pre-dose time point and lowest at the 15-min post-dose time point. There were no unexpected differences observed for plasma concentrations between weight groups (<50 kg and  $\geq$ 50 kg). Within the  $\geq$ 1 month to <2 years and the  $\geq$ 12 to <16 years age cohorts, there was a large variation (geometric coefficient of variation [%]) in pre-dose plasma concentrations (Table S2). Similar 15-min and 3-h post-dose plasma concentrations were observed in the RxB and IOB (non-naive) patients compared with the IIB (BRV-naive before first IV dose) patients (Figure 3; Table S2).

### 3.3 | Safety outcomes

#### 3.3.1 | Exposure to BRV

The overall mean (SD) exposure to BRV (oral and IV) during the trial was 4.0 (3.2) days (range = 1–13 days). There was no difference in mean (SD) BRV exposure between the 15-min infusion and bolus groups: 3.9 (3.1) days vs 4.1 (3.5) days, respectively. Mean (SD) BRV exposure was 4.9 (4.1) days in the youngest cohort ( $\geq$ 1 month to <2 years), 2.9 (2.6) days in the  $\geq$ 2 to <6 years cohort, 3.7 (2.9) days in the  $\geq$ 6 to <12 years cohort, and 4.4 (3.2) days in the  $\geq$ 12 to <16 years cohort.

Most patients (40 [80.0%]) received one BRV administration during the IV PK period. Of the patients who received more than one administration, one (2.0%) received 2 administrations, eight (16.0%) received 3, and one (2.0%) received 10 administrations (Table S3). The mean (SD) exposure to BRV during the IV PK period was 1.3 (0.7) days (range = 1–5.4 days). The mean (SD) IV BRV dose was 1.1 (0.3) mg/kg (range = 0.8–2.3 mg/kg). There were no obvious differences across age cohorts in the mean IV dose; however, only patients in the three youngest age cohorts

received more than one BRV administration. In addition, there were no obvious differences in mean IV dose between patients receiving 15-min infusions or bolus injections (1.1 [SD = 0.24; range = 0.8–2.0] mg/kg in the 15-min infusion group and 1.1 [SD = 0.4; range = 0.9–2.3] mg/kg in the bolus group); however, more patients received more than one BRV administration in the 15-min infusion group compared with the bolus group. Likewise, the mean IV dose was similar between weight groups: 1.1 mg/kg in both patients who weighed <50 kg and  $\geq$ 50 kg.

#### 3.3.2 | Safety

Overall, 14 patients (28.0%) experienced 18 TEAEs during the trial, including one patient (2.0%) with a severe TEAE (somnolence) (Table 1). One patient (2.0%) had a serious TEAE (cough), which occurred during the IOB period (i.e., before the patient received IV BRV) and was not considered drug related. There were no discontinuations due to TEAEs.

TEAEs were numerically highest in the  $\geq$ 2 to <6 years age cohort ( $n = 6$ ; 46.2%) compared with the  $\geq$ 1 month to <2 years ( $n = 2$ ; 15.4%), the  $\geq$ 6 to <12 years ( $n = 3$ ; 25.0%), and the  $\geq$ 12 to <16 years ( $n = 3$ ; 25.0%) age cohorts. The incidence of TEAEs considered related to the trial drug was also numerically highest in the  $\geq$ 2 to <6 years cohort. There was no obvious difference in the incidences of TEAEs between the 15-min infusion and bolus groups.

The most common TEAE was somnolence (three patients [6.0%]), followed by dizziness, fatigue, pyrexia, and rash (two patients [4.0%] each). Incidences of individual TEAEs were generally similar across age groups (Table 1). Somnolence was experienced in the two youngest age cohorts only; dizziness was experienced only in the oldest age cohort of  $\geq$ 12 to <16 years; pyrexia was experienced only in the  $\geq$ 2 to <6 years age cohort. There was no obvious difference in individual TEAEs between the 15-min infusion and bolus groups except for somnolence, which was experienced by three patients on 15-min infusion vs none in the bolus group. No TEAEs occurred within the first 5 min after BRV administration in either the 15-min infusion or bolus group, and no TEAE was experienced by more than one patient within any given time window (>5 to  $\leq$ 15 min, >15 to  $\leq$ 60 min, >60 min to  $\leq$ 12 h, >12 h). In the bolus group, one patient experienced pruritus >5 to  $\leq$ 15 min after the start of BRV administration, and one patient experienced rash >12 h after the start of BRV administration. Within the 15-min infusion group, TEAEs were experienced >5 to  $\leq$ 15 min (somnolence and rash), >15 to  $\leq$ 60 min (somnolence), >60 min to  $\leq$ 12 h (fatigue, pyrexia, and insomnia), and >12 h (somnolence) after infusion start.

**TABLE 1** TEAEs reported during the trial (SS-IV)

Patients, n (%)	Age cohort				Administration			Patient group		
	≥1 month to <2 years (N = 13)	≥2 to <6 years (N = 13)	≥6 to <12 years (N = 12)	≥12 to <16 years (N = 12)	15-min infusion (N = 26)	Bolus (N = 24)	RxB and IOB (N = 30)	IIB (N = 20)	All patients (N = 50)	
Any TEAE	2 (15.4)	6 (46.2)	3 (25.0)	3 (25.0)	8 (30.8)	6 (25.0)	7 (23.3)	7 (35.0)	14 (28.0)	
Serious TEAE	1 (7.7)	0	0	0	1 (3.8)	0	1 (3.3)	0	1 (2.0)	
Severe TEAEs	1 (7.7)	0	0	0	1 (3.8)	0	0	1 (5.0)	1 (2.0)	
Drug-related TEAEs	1 (7.7)	5 (38.5)	2 (16.7)	2 (16.7)	6 (23.1)	4 (16.7)	4 (13.3)	6 (30.0)	10 (20.0)	
Individual TEAEs <sup>a</sup> reported during the trial										
Somnolence	1 (7.7)	2 (15.4)	0	0	3 (11.5)	0	0	3 (15.0)	3 (6.0)	
Dizziness	0	0	0	2 (16.7)	0	2 (8.3)	2 (6.7)	0	2 (4.0)	
Fatigue	0	1 (7.7)	1 (8.3)	0	2 (7.7)	0	1 (3.3)	1 (5.0)	2 (4.0)	
Pyrexia	0	2 (15.4)	0	0	1 (3.8)	1 (4.2)	1 (3.3)	1 (5.0)	2 (4.0)	
Rash	0	1 (7.7)	1 (8.3)	0	1 (3.8)	1 (4.2)	0	2 (10.0)	2 (4.0)	
Aggression	0	1 (7.7)	0	0	0	1 (4.2)	1 (3.3)	0	1 (2.0)	
Cough	1 (7.7)	0	0	0	1 (3.8)	0	1 (3.3)	0	1 (2.0)	
Ear infection	0	1 (7.7)	0	0	0	1 (4.2)	1 (3.3)	0	1 (2.0)	
Insomnia	0	0	1 (8.3)	0	1 (3.8)	0	0	1 (5.0)	1 (2.0)	
Pharyngitis	0	0	0	1 (8.3)	0	1 (4.2)	1 (3.3)	0	1 (2.0)	
Pruritus	0	0	1 (8.3)	0	0	1 (4.2)	0	1 (5.0)	1 (2.0)	
Upper respiratory tract infection	1 (7.7)	0	0	0	1 (3.8)	0	1 (3.3)	0	1 (2.0)	

Note: TEAEs were defined as those events that started on or after the first BRV medication taken during trial EP0065. In patients who started the trial on BRV treatment (RxB patients), they were assumed to have taken BRV treatment on the first day of screening.

Abbreviations: BRV, brivaracetam; IIB, initiating intravenous brivaracetam; IOB, initiating oral brivaracetam; RxB, prescribed brivaracetam; SS-IV, safety set-intravenous; TEAE, treatment-emergent adverse event.

<sup>a</sup>Medical Dictionary for Regulatory Activities (Version 18.1) Preferred Terms.

Ten patients (20.0%) experienced TEAEs considered drug related by the investigator; the incidence was similar between patients receiving 15-min infusions or bolus injections, occurring in six patients from the 15-min infusion group and four from the bolus group. Drug-related TEAEs occurred in one RxB patient (12.5%), three IOB patients (13.6%), and six IIB patients (30.0%). The most common drug-related TEAE was somnolence ( $n = 3$ ; 6.0%).

A total of seven patients (14.0%) had eight TEAEs during the IV PK period (Table 2). Somnolence was reported by two patients; all other TEAEs were reported by only one patient. With the exception of one TEAE of insomnia, all TEAEs during the IV PK period were considered drug related. TEAEs during the IV PK period occurred in six patients in the IIB treatment category (BRV-naive before first IV dose) and only one patient in the RxB and IOB (non-naive) treatment category.

There were no clinically significant changes observed in vital signs or electrocardiogram parameters. No deaths occurred in the trial.

## 4 | DISCUSSION

Treatment with IV BRV was well tolerated in pediatric patients  $\geq 1$  month to  $< 16$  years of age with epilepsy when given as a 15-min infusion or bolus injection, regardless of whether patients were BRV treatment-naive or non-naive before the first IV dose. The safety results demonstrated TEAEs during the IV PK period (i.e., somnolence, fatigue, pyrexia, and rash) that are consistent with the safety profile of BRV in adults and pediatric patients  $\geq 4$  years of age receiving oral therapy. In pooled Phase 2 and Phase 3 placebo-controlled adult trials, acceptable safety and tolerability profiles were demonstrated with adjunctive BRV treatment: the most frequently reported TEAEs with BRV ( $\geq 5.0\%$  of patients) vs placebo were somnolence, headache, dizziness, and fatigue.<sup>9</sup> An interim analysis of long-term pooled data from two open-label, single-arm, multicenter pediatric trials (N01263 and N01266) showed that adjunctive oral BRV was generally well tolerated in children with focal seizures  $\geq 4$  to  $< 16$  years of age, with the most common drug-related TEAE being somnolence.<sup>10</sup> No new safety concerns for BRV in the pediatric population were identified in the present trial.

Differences in exposure durations between age groups can be explained by the fact that some patients initiated BRV orally before receiving IV BRV, whereas other patients received IV BRV directly. Most patients only had one IV BRV administration.

There were no unexpected PK differences observed across age cohorts, 15-min infusion and bolus groups, or weight groups ( $< 50$  kg vs  $\geq 50$  kg) in this trial. PK data

were consistent with the expected results and were within the expected ranges for this population. Comparative data from the Phase 2a, open-label, multicenter trial (N01263) in patients  $\geq 1$  month to  $< 16$  years of age receiving increasing doses of BRV oral solution showed that trough BRV plasma concentrations increased with increasing dose and with increasing age; the geometric mean trough BRV metabolite plasma concentrations were similar across age groups at each visit. The BRV plasma concentrations in the present trial increased rapidly during the first 15 min after IV administration, with a gradual decrease until 3 h post dose. Of note, this pattern was not observed in four patients, who had higher BRV concentrations at 3 h post dose than 15 min post dose. The most likely explanation for this would be that samples were switched, but there was no evidence for this, so it remains speculative. No unexpected differences were observed across age cohorts or between 15-min infusion and bolus groups; however, comparison of PK data across age groups is limited due to the small number of patients and high inter-patient variability. Although a previously performed population PK analysis comparing Caucasian and non-Caucasian patients showed no significant pharmacokinetic differences,<sup>4,11</sup> most patients enrolled in this trial were White, which may limit generalizability of these results to other racial groups.

As previously mentioned, PK data from trial N01263 as well as an adult study (N01256) were used to predict the IV dose for patients initiating BRV in the current trial (UCB Pharma, data on file). Based on PK modeling results, a 15-min IV infusion or a bolus injection ( $\leq 2$ -min infusion) of 4 mg/kg/day (2 mg/kg bid; maximum of 200 mg/day [100 mg bid] for patients with body weights  $\geq 50$  kg) in patients  $\geq 1$  month to  $\leq 16$  years of age were expected to result in plasma concentrations in the same range as seen in adults receiving 200 mg/day (100 mg bid), the maximum recommended dose in adults with focal seizures (UCB Pharma, data on file).

Studies in adult patients have previously demonstrated bioequivalence between BRV tablets, oral solution, and IV formulations.<sup>6-8</sup> The results of the present trial in patients  $\geq 1$  month to  $< 16$  years of age, along with data from these adult bioequivalence studies, indicate that no dose adjustment is required when switching from oral to IV administration and support the use of an IV BRV dose that is a mg-to-mg equivalent of the oral dose.

## 5 | CONCLUSIONS

The safety and tolerability findings of trial EP0065 were generally consistent with the known safety profile of BRV, with no new safety concerns identified for the pediatric



**TABLE 2** TEAEs reported during the IV PK period (SS-IV)

Patients, n (%)	Age cohort				Administration			Patient group		
	≥1 month to <2 years (N = 13)	≥2 to <6 years (N = 13)	≥6 to <12 years (N = 12)	≥12 to <16 years (N = 12)	15-min infusion (N = 26)	Bolus (N = 24)	RxB and IOB (N = 30)	IIB (N = 20)	All patients (N = 50)	
Any TEAE	1 (7.7)	3 (23.1)	3 (25.0)	0	5 (19.2)	2 (8.3)	1 (3.3)	6 (30.0)	7 (14.0)	
Serious TEAE	0	0	0	0	0	0	0	0	0	
Severe TEAEs	1 (7.7)	0	0	0	1 (3.8)	0	0	1 (5.0)	1 (2.0)	
Drug-related TEAEs	1 (7.7)	3 (23.1)	2 (16.7)	0	4 (15.4)	2 (8.3)	1 (3.3)	5 (25.0)	6 (12.0)	
Individual TEAEs <sup>a</sup> reported during the IV PK period										
Somnolence	1 (7.7)	1 (7.7)	0	0	2 (7.7)	0	0	2 (10.0)	2 (4.0)	
Fatigue	0	0	1 (8.3)	0	1 (3.8)	0	0	1 (5.0)	1 (2.0)	
Pyrexia	0	1 (7.7)	0	0	1 (3.8)	0	0	1 (5.0)	1 (2.0)	
Rash	0	1 (7.7)	0	0	1 (3.8)	0	0	1 (5.0)	1 (2.0)	
Aggression	0	1 (7.7)	0	0	0	1 (4.2)	1 (3.3)	0	1 (2.0)	
Insomnia	0	0	1 (8.3)	0	1 (3.8)	0	0	1 (5.0)	1 (2.0)	
Pruritus	0	0	1 (8.3)	0	0	1 (4.2)	0	1 (5.0)	1 (2.0)	

*Note:* TEAEs were defined as those events that started on or after the first BRV medication taken during trial EP0065. In patients who started the trial on BRV treatment (RxB patients), they were assumed to have taken BRV treatment on the first day of screening.

Abbreviations: BRV, brivaracetam; IIB, initiating intravenous brivaracetam; IOB, initiating oral brivaracetam; IV, intravenous; PK, pharmacokinetic; RxB, prescribed brivaracetam; SS-IV, safety set-intravenous; TEAE, treatment-emergent adverse event.

<sup>a</sup>Medical Dictionary for Regulatory Activities (Version 18.1) Preferred Terms.

population from  $\geq 1$  month to  $< 16$  years of age. Plasma concentrations were in the expected range, and no unexpected PK differences were observed between patients receiving 15-min infusions or bolus injections. The results of this trial and data from adult bioequivalence studies support the use of an IV BRV dose that is a mg-to-mg equivalent of the oral dose.

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### CONFLICTS OF INTEREST

M.K.F., H.K., and A.F. report no conflicts of interest. A.B., W.K., D.M., E.W., and J.-P.E. are employees of UCB Pharma. A.B., D.M., and J.-P.E. also receive UCB Pharma stocks. G.D.J. is contracted by UCB Pharma for statistical services.

### RESEARCH DATA FOR THIS ARTICLE

Underlying data from this manuscript may be requested by qualified researchers 6 months after product approval in the United States and/or Europe or global development is discontinued and 18 months after trial completion. Investigators may request access to anonymized individual patient-level data and redacted trial documents, which may include: analysis-ready data sets, study protocol, annotated case report form, statistical analysis plan, data set specifications, and clinical study report. Prior to use of the data, proposals need to be approved by an independent review panel at [www.Vivli.org](http://www.Vivli.org) and a signed data sharing agreement will need to be executed. All documents are available in English only, for a pre-specified time, typically 12 months, on a password-protected portal.

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### SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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