SEMMELWEIS EGYETEM

DOKTORI ISKOLA

Ph.D. értekezések

2980.

FARKAS MÁRK KRISTÓF

Krónikus betegségek gyermekkori prevenciója
című program

Programvezető: Dr. Szabó Attila, egyetemi tanár

Konzulens: Dr. Cseh Áron, egyetemi adjunktus

Novel pharmacological treatment options in pediatric epilepsy
Evaluation of efficacy, safety, tolerability and pharmacokinetics of pregabalin, lacosamide and brivaracetam in pediatric epilepsy

PhD thesis

Márk Kristóf Farkas

Károly Rácz Doctoral School of Clinical Medicine

Semmelweis University

Consultant: Áron Cseh, MD, Ph.D

Official reviewers: Balázs Legeza, MD, Ph.D
Gergely Milosevits, MD, Ph.D

Head of the Complex Examination Committee: György Fekete, MD, D.Sc

Members of the Complex Examination Committee:
Ákos Zsembery, MD, Ph.D
János Major MD, Ph.D

Budapest
2024

Table of Contents

List of Abbreviations

AE	adverse event
AED	antiepileptic drug
ANCOVA	analysis of covariance
ASM	antiseizure medication
BID	two times a day
BRV	brivaracetam
C-SSRS	Columbia–Suicide Severity Rating Scale
CBCL	Child Behavior Checklist
CI	confidence interval
ECG	electrocardiogram
FOS	focal onset seizure
IIB	initiating intravenous brivaracetam
ILAE	International League Against Epilepsy
IOB	initiating oral brivaracetam
IV	intravenous
LS	least squares
MedDRA	Medical Dictionary for Regulatory Activities
N/A	not available
OLB	open-label brivaracetam
PK	pharmacokinetics
PK-PPS	pharmacokinetic per-protocol set
RxB	prescribed brivaracetam
SAE	serious adverse event
SD	standrad deviation
SS	Safety Set
TEAE	treatment-emergent adverse event
TID	three times a day
V-EEG	video-electroencephalogram
VNS	vagus nerve stimulation

I. Introduction

Epilepsy is a chronic neurologic disorder characterized by recurrent, unprovoked seizures. More than half of the cases present under the age of 18 years. About 5% of the world's population will have a seizure during the course of their lifetime and of these, 10% to 20% will develop epilepsy (repeated unprovoked seizures). The incidence of epilepsy varies depending on the age. It is estimated that almost 70 million people suffer from epilepsy worldwide (1). In 2013, approximately 4.3 million adults in the United States aged ≥18 years (1.8%) had a diagnosis of epilepsy or seizure disorder and 750,000 children aged ≤17 years (1%) had a diagnosis of epilepsy or seizure disorder (2, 3, 4).

The incidence of epilepsy in children has been reported to range from 41 to 187 new cases per 100 000 children per year (5). In spite of this, few epilepsy medications are approved for treatment of pediatric populations. The widespread prevalence of epilepsy presents a global health burden in need of effective and safe treatments for pediatric patients with epilepsy. Although some forms of epilepsy may respond to surgical treatment and others may not require any treatment at all, most patients with epilepsy require appropriate chronic pharmacological therapy (6). For the different types of epileptic seizures and epilepsy syndromes several treatment options have been introduced, including antiepileptic drugs (AEDs), vagus nerve stimulation (VNS), responsive neurostimulation and ketogenic diet (7).

The terminology of epileptic seizures and classification of epilepsy syndromes are regularly revised by the International League Against Epilepsy (ILAE). The most recent revision was performed in 2017, which updated the previous terminology from 2010 (8, 9). The previously applied "partial onset seizure" has been updated to "focal onset seizures" (FOS). Similarly, simple partial is now labeled as focal aware seizure, complex partial as focal impaired awareness seizure, and partial becoming secondarily generalized corresponds to a focal to bilateral tonic-clonic seizure. Data available prior to the terminology revision will apply the original terminology in this thesis, published data after the revision will use the updated terms (9).

Existing treatment options for seizures in pediatric patients generally follow the treatment options for seizures in adults, with clinical experience suggesting that children achieve similar results to adults with antiseizure medications (ASMs) (10). Whereas seizures can often be effectively managed with AEDs in many pediatric patients, 25%-40% of patients may not be adequately controlled and/or may experience troublesome side effects, despite advances in pharmacologic management reflected in the development of new antiepileptic drugs that have been approved in adults and children in monotherapy or rational polytherapy (11, 12, 13). There remains a need for potent AEDs with a positive benefit-risk profile in this population therefore, a need for novel treatments with improved effectiveness and tolerability to address seizure control is critical for pediatric patients living with these conditions (14).

In addition to oral formulations, intravenous formulations of AEDs are particularly helpful in the clinical practice as short-term replacements when use of oral formulations is not possible or feasible (e.g., pre and postoperative patients, patients with acute gastrointestinal disorders, patients with acute swallowing disorders, patients with acute infectious disease and fever) especially in pediatric age. Such formulations allow patients to be maintained on the same AED on their stable dose when they are unable to take the drug orally. Intravenous formulations may also be helpful in the initiation of treatment in certain situations when the patient is unable to take oral medications or emergency situations.

In the recent years several new AEDs were introduced in the adult population including pregabalin, lacosamide and brivaracetam. However, the approved indication of these novel antiseizure medications differ in the European Union and in the United States. There is limited clinical experience with oral pregabalin and intravenous lacosamide and brivaracetam in pediatric patients (15, 16, 17, 18, 19, 20).

Pregabalin is approved in multiple countries worldwide as an adjunctive therapy for partial onset seizures in adults (17, 18). Pregabalin [CI-1008, (S)-3-(aminomethyl)-5-methylhexanoic acid] binds with high affinity to the $\alpha 2\delta$ site (an auxiliary subunit of voltage-gated calcium channels) in central nervous system tissues (18). In studies of adult subjects with partial onset seizures, pregabalin as adjunctive therapy has been shown to be efficacious and well tolerated (compared with placebo) for reducing seizure frequency

and for achieving 50% responder rates (defined as ≥50% reduction in partial seizure frequency) at doses ranging from 150 to 600 mg/day administered 2 or 3 times daily (17, 18).

The safety, tolerability, and pharmacokinetic of pregabalin evaluated in 65 children (1 month to 16 years of age) with partial onset seizures was reported (21). This phase I trial determined pregabalin doses that might be appropriate for study in subsequent efficacy and safety trials. In this study, pregabalin was well tolerated at doses up to 10 mg/kg/day. Standard pharmacokinetic parameters were derived, with pharmacokinetic evaluations showing increased pregabalin clearance per kilogram of body weight for children weighing <30 kg. As such, a 40% higher dose (on a milligrams-per-kilogram basis) would be required by these subjects to achieve similar pharmacokinetic exposure as children weighing ≥30 kg and adults (21).

The active substance, lacosamide (R-2-acetamido-N-benzyl-3-methoxypropionamide) is a functionalized amino acid.
The precise mechanism by which lacosamide exerts its antiepileptic effect in humans remains to be fully elucidated. *In vitro* electrophysiological studies have shown that lacosamide selectively enhances slow inactivation of voltage-gated sodium channels, resulting in stabilization of hyperexcitable neuronal membranes (16).

Lacosamide has been indicated for the treatment of focal seizures in patients 1 month of age and older in the United States, and in patients 2 years of age and older in the European Union. Lacosamide has also been indicated as adjunctive therapy for primary generalized tonic-clonic seizures in patients 4 years of age and older in the United States and the European Union. The intravenous (IV) formulation of lacosamide may be used when oral administration (tablet or oral solution) is temporarily not feasible. The recommended infusion duration is 30-60 minutes (15, 16). Several trials have investigated the efficacy and safety of oral formulations of lacosamide in pediatric patients. The efficacy and tolerability of adjunctive lacosamide in patients aged 4-17 years with uncontrolled focal seizures was demonstrated in a Phase III double-blind trial (22). Another Phase III double-blind trial evaluated adjunctive lacosamide in patients ≥1 month to <4 years with uncontrolled focal seizures; although the primary efficacy endpoint was not met,

lacosamide was generally well tolerated with an acceptable safety profile (23). Data from an open-label, fixed-titration trial support the safety and tolerability of adjunctive lacosamide in patients aged 6 months to 17 years with focal seizures (24). The safety and tolerability of IV lacosamide has been established in adults with focal seizures (25, 26, 27). IV lacosamide has been assessed in pediatric patients with epilepsy in small retrospective and open-label studies only. In a retrospective study of 47 critically ill children ≤12 years of age with focal or generalized seizures, IV lacosamide was well tolerated with mild and reversible adverse events (28). Among 18 children hospitalized because of increased seizure frequency, 16 had a >50% reduction in seizure frequency for 48 hours after initiation of IV lacosamide and daily oral maintenance lacosamide (28). Other studies in pediatric patients with epilepsy and critically ill children have indicated that IV lacosamide is well tolerated (29, 30). At the time our investigation (EP0060; NCT02710890) was conducted, the IV formulation of lacosamide was indicated in the United States for temporary use in patients aged 17 years and older only.

Brivaracetam (BRV) is a racetam derivative. The precise mechanism by which it exerts its anticonvulsant activity is not known. Brivaracetam displays a high and selective affinity for synaptic vesicle protein 2A (SV2A) in the brain, which may contribute to the anticonvulsant effect (20). Brivaracetam at the time of investigation was indicated for the adjunctive treatment of focal seizures in patients 4 years of age and older in the European Union (19) and as monotherapy and adjunctive treatment in patients 1 month of age and older in the United States (20).

A previous Phase IIa, open-label, single-arm, fixed three-step dose-escalation trial showed that adjunctive oral BRV is well tolerated and effective in patients ≥1 month to <16 years of age (31). Its ongoing Phase III, open-label, multi- center, long-term follow-up trial 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 III open-label, multicenter trial is also evaluating long-term safety and tolerability of oral BRV as adjunctive treatment in pediatric patients with epilepsy. Brivaracetam tablets, oral solution, and IV formulations have been shown to be bioequivalent in adults (32, 33, 34).

No randomized controlled clinical trial have evaluated the efficacy of pregabalin for treatment of focal onset seizures in children. No prospective clinical trial evaluated the

safety and tolerability of IV lacosamide infusions and the pharmacokinetics (PK), safety, and tolerability of BRV injection in pediatric patients with epilepsy (35, 36, 37, 38).

II. Objectives

The aim of our research was to provide novel pharmaceutical treatment options for the treatment of pediatric epilepsy. It was aimed to broaden the indication field for the investigated drug, or apply a new route of administration and pharmaceutical form of antiseizure medication already used in pediatric population. The safety, tolerability, efficacy and pharmacokinetics of pregabalin, lacosamide and brivaracetam was evaluated in pediatric patients diagnosed with epilepsy (35, 36, 37, 38). The evaluated parameters and the patient populations were different among the investigated antiseizure medications and among the conducted clinical trials. Different patient populations were investigated based on age and seizure types at the First Department of Pediatrics, Semmelweis University, Budapest, Hungary as part of multicentric international clinical trials. Pregabalin was investigated as add-on oral treatment having the patients' basic antiepileptic drug treatment unchanged (35, 36). Intravenous lacosamide and brivaracetam was evaluated in patients who were already taking the drug in oral formulation or they would receive their first dose during the trials orally, or they would receive their first dose during the trials intravenously (37, 38). The three different antiseizure medications were investigated in altogether four clinical trials (35, 36, 37, 38).

For pregabalin within the A0081041 trial the objective was to evaluate the efficacy and safety of pregabalin 2.5 or 10 mg/kg/day as adjunctive treatment for pediatric subjects 4 to 16 years of age with focal onset seizures (35).

For pregabalin within the A0081042 trial the objective was to evaluate the efficacy and safety of pregabalin (7 and 14 mg/kg/day) as adjunctive treatment for focal onset seizures for pediatric patients 1 month to <4 years of age (36).

For lacosamide within the EP0060 trial the objective was to evaluate the safety and tolerability of intravenous lacosamide infusions in pediatric patients with epilepsy ≥1 month to <17 years of age (37).

For brivaracetam within the EP0065 trial the objective was to evaluate the pharmacokinetics (PK), safety, and tolerability of brivaracetam injection administered as

a 15-min IV infusion and IV bolus injection (≤2-min infusion) in patients with epilepsy ≥1 month to <16 years of age (38).

The detailed information of the clinical trials are described in Table 1.

Table 1. Detailed information of the clinical trials

Trial	Investigated drug	Clinical trial phase	Trial design	Route of administra-tion	Pharmaceutical form	Age range
A0081041 (ClinicalTrials.gov registration NCT01389596; EudraCT #2010-020852-79)	pregabalin	Phase III	Double-blind Placebo-controlled	oral	capsule and liquid (syrup)	4 to 16 years
A0081042 (ClinicalTrials.gov registration NCT02072824; EudraCT #2013-003420-37)	pregabalin	Phase III	Double-blind Placebo-controlled	oral	liquid (syrup)	1 month to <4 years
EP0060 (ClinicalTrials.gov registration NCT02710890; EudraCT # 2014-003294-42)	lacosamide	Phase II/III	Open-label	intravenous	solution	≥1 month to <17 years
EP0065 (ClinicalTrials.gov registration NCT03405714; EudraCT # 2016-002452-25)	brivaracetam	Phase II	Open-label	intravenous	solution	≥1 month to <16 years

III. Methods

Phase II – Phase III multicenter clinical trials were conducted. The details for each clinical trial follow. It applies for all the included clinical trials that the parents or legal guardians gave written informed consent for the subjects to participate; all subjects assented to join the trials when possible. Parents or legal guardians and subjects (where possible) were required to understand and follow the study procedures. The study protocols and amendments were reviewed and approved by the institutional review boards and independent ethics committees of the investigators' institutions and were in compliance with ethical principles of the Declaration of Helsinki and with all International Conference on Harmonization Good Clinical Practice Guidelines (35, 36, 37, 38).

This dissertation is based on the results of international multicenter prospective biomedical research studies. Our research team at Semmelweis University, Budapest, Hungary, First Department of Pediatrics had an outstanding contribution to the successful completion of these investigations. Our site including the author of this dissertation took part in the conduction and evaluation of these multicenter, international clinical trials in a close cooperation with different Clinical Research Organizations and Sponsors. Through the local conduction of the investigations our team was responsible for identifying potential patients, screen and enroll the patients, evaluate clinical trial results. All trial related procedures, including patient identification, patient visits, consenting, determining eligibility, patient education, on site administration of the investigational medicinal product, evaluating and monitoring patient condition, coordinating blood sampling for safety and PK parameters, collecting and reporting adverse events, reviewing seizure diaries and completing patient database was performed at our facility by the same investigator, the author of this dissertation. The high quality and proper conduction and organization of the investigations at our center was evaluated and confirmed by regular Sponsor audits. Besides the local conduction of the trials, due to the high contribution to the successful completion of these trials the author of this dissertation was invited by the Sponsors of the clinical trials to take part in the international data acquisition, data interpretation, manuscript preparation, revision for intellectual content, and manuscript approval for submission during the publications of trial results in

international scientific journals as first or last author. The brivaracetam trial results were presented by the author on international conferences.

III.1 Evaluation of pregabalin

Two separate clinical trials were conducted to evaluate the efficacy and safety of pregabalin as add-on therapy for partial onset seizures in children. One trial aimed for the patient population between the age of 4-16 years. The other trial evaluated the patient population between 1 month through 4 years of age. The main aims of the trials were similar, however, due to the special investigated age groups the trial design, pharmaceutical form of the drug, dosing schedule and the primary and secondary endpoints were different (35, 36).

III.1.1 Evaluation of pregabalin in pediatric patients older than 4 years

Pregabalin as adjunctive treatment for focal onset seizures in pediatric patients 4-16 years of age was investigated in the A0081041 (ClinicalTrials.gov registration NCT01389596; EudraCT #2010-020852-79) Phase III trial. It was a double-blind, placebo-controlled, randomized, parallel-group trial conducted in multiple centers in 18 countries including Hungary between 27/September/2011 and 10/Aug/2016. The trial was sponsored by Pfizer (35).

III.1.1.1 Study design and patient selection

Subjects were 4 to 16 years of age, male and female, with a diagnosis of epilepsy with partial onset seizures (focal onset seizures) classified as simple partial, complex partial, or partial becoming secondarily generalized according to the International League Against Epilepsy (ILAE, 2010) (8, 35).

Patients and/or their legal guardians recorded seizures in the patient daily diary for this study. Epilepsy diagnosis and seizure classification were reviewed by an external expert central reviewer to ensure clarity and consistency of seizure descriptions prior to each subject being randomized. The minimum requirement for seizure occurrence was ≥ 3 focal onset seizures in the 28-day period before screening and a focal onset seizure

frequency of ≥ 6 seizures with no continuous 4-week seizure-free period during the 8-week baseline phase before randomization. Subjects must have been receiving a stable regimen of 1 to 3 antiepileptic drugs within 28 days prior to screening, with no changes in antiepileptic drugs or dose adjustments to existing antiepileptic drugs permitted for the duration of the study (35).

III.1.1.2 Treatments and Study Schedule

Study treatments included pregabalin 2.5 mg/kg/day, pregabalin 10 mg/kg/day, or placebo. Study treatment was administered as either capsules or as liquid oral solution. Because of increased pregabalin clearance per kilogram of body weight in subjects with body weight <30 kg, a daily weight-normalized dose 40% higher was needed to achieve similar exposure to that of adults or pediatric subjects weighing ≥30 kg. Thus, for subjects with body weight of ≥30 kg, the dose was pregabalin 2.5 mg/kg/day or 10 mg/kg/day. For subjects weighing <30 kg, the daily dose was increased by 40% to either 3.5 or 14 mg/kg/day, respectively. Regardless of each subject's weight, the maximum dose for the pregabalin treatment groups was 150 mg/day for pregabalin 2.5 mg/kg/day and 600 mg/day for pregabalin 10 mg/kg/day (35).

Figure 1. summarizes the study design, which consisted of an 8-week screening and baseline phase, 12-week double-blind treatment phase (2-week dose escalation and 10-week fixed dose), and a 1-week taper phase. Subjects self-reported seizures in a daily diary, or parents/ legal guardians of the subjects maintained daily seizure diaries, which were reviewed at each clinic visit. Qualifying subjects were randomized in a 1:1:1 ratio to receive 1 of 2 dose levels of pregabalin or placebo, administered orally twice daily in equally divided doses. Subjects randomized to pregabalin 2.5 mg/kg/day or placebo initiated double-blind study drug on the treatments to which they were randomized (ie, no dose escalation). Subjects randomized to pregabalin 10 mg/kg/day had doses escalated, starting with 2.5 mg/kg/day for week 1; 5 mg/kg/day for week 2; and then 10 mg/kg/day for the remainder of the double-blind treatment. Subject who completed a minimum of 4 weeks of double-blind treatment during study A0081041 were able to be evaluated for entry into a 1-year open-label extension trial (A0081106; ClinicalTrials.gov

registration NCT01463306; EudraCT no. 2010-020852-79) evaluating the long-term safety and efficacy of pregabalin for focal onset seizures (35).

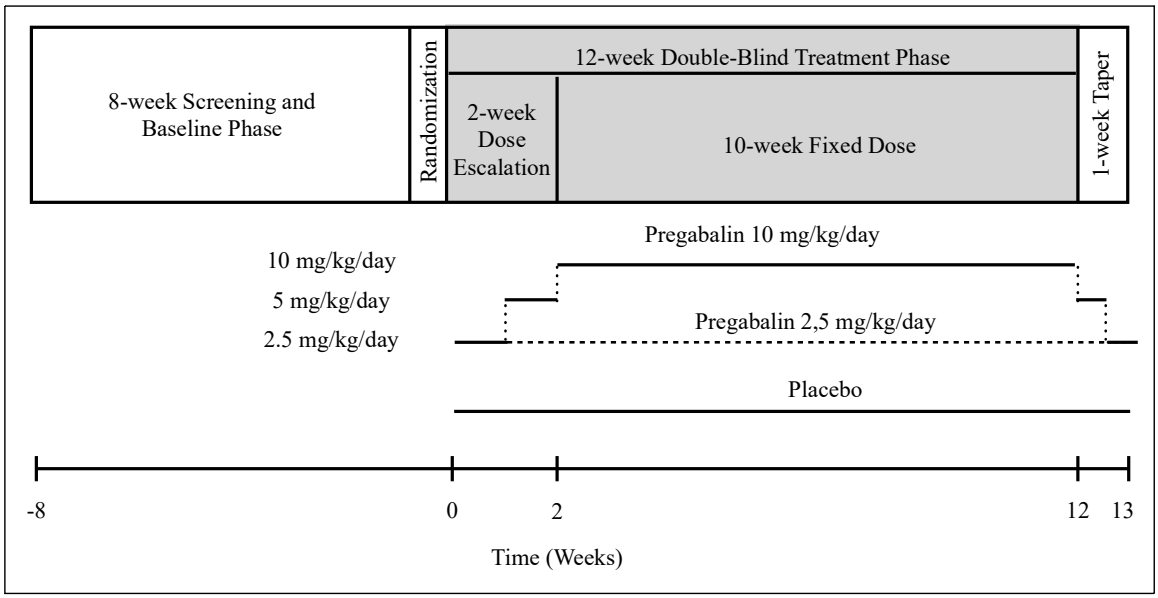


Figure 1. A0081041 clinical trial design (35).

III.1.1.3 Assessments and Study Endpoints

The primary efficacy endpoint was the natural log–transformed 28- day seizure rate of all focal onset seizures during the 12-week double- blind treatment phase and did not include seizure data recorded during the taper phase. The 28-day seizure rate was calculated as

$$\text{28-day seizure rate} = \frac{\text{no. of seizures in a phase}}{[\text{no. of days in phase} - \text{no. of missing diary days in phase}]} \times 28$$

Phase refers to the duration in days during baseline to calculate the baseline seizure rate and the duration in days of double-blind treatment to calculate the double-blind seizure rate (35).

In addition, responder rate, defined as ≥50% reduction in focal onset seizure frequency during double-blind treatment compared with baseline, was assessed. Safety and tolerability of pregabalin was assessed by evaluating reported adverse events, including data on the incidence, nature, severity, potential relationship to study drug, and whether the adverse events qualified as serious adverse events (ie, any adverse event that resulted in new or prolonged hospitalization, caused a congenital anomaly or birth defect, was debilitating, was life-threatening, and/ or resulted in death). The Medical Dictionary for Regulatory Activities (MedDRA, v 19.0) was used for coding of adverse events. In addition, physical and neurologic examinations, laboratory, and ECGs were conducted. Potential suicidal ideation and behavior was monitored using the Columbia–Suicide Severity Rating Scale (C-SSRS) for subjects aged 6 to 16 years, and the Child Behavior Checklist (CBCL) for subjects aged <6 years. The CogState battery test was also performed to assess psychomotor function and attention at randomization and completion of the double-blind treatment phase (35).

III.1.1.4 Statistical Analyses

The primary efficacy analysis was performed on the log- transformed 28-day seizure rate ($\log_e$[28-day seizure rate +1]) using a linear model with ordinary least squares estimation with treatment, weight group, and geographical region as fixed factor effects as well as $\log_e$(baseline seizure rate + 1) as a continuous covariate. SAS® (SAS Institute, NC, USA) software was used. When the log-transformation was used, the quantity 1 was added to the 28-day seizure rate for all subjects, to account for any possible 0 seizure incidence. A sequential stepwise testing procedure was used to control for multiplicity of testing such that the experiment-wise type I error rate would not exceed the 5% level of significance (35).

1, Step 1 tested the null hypothesis of equal treatment group means (μ) of pregabalin 10 mg/kg/day versus placebo at $\alpha = 0.05$ two-sided for the primary endpoint

H_{01}: μPGB 10 μPBO = 0

H_{a1}: μPGB 10 μPBO $\neq$ 0

2, Step 2 was tested only when (H_{01}) was rejected. Step 2 tested the null hypothesis of equal treatment group means (μ) of pregabalin 2.5 mg/kg/day versus placebo at $\alpha = 0.05$ two-sided for the primary endpoint

H_{02}: μPGB 2.5 μPBO = 0

Ha2: μPGB 2.5 μPBO $\neq$ 0

Missing values for seizures were handled by subtracting the number of missing diary days from the denominator of 28-day seizure rate equation (see above). Each dose of pregabalin and placebo was compared in a pairwise manner using a sequential stepwise testing procedure. Two-sided 95% confidence intervals (CIs) of the difference between the least squares means were calculated using the appropriate least squares means and their standard errors. Results were also reported as "percentage reduction in seizures" relative to placebo. Percentage reduction was calculated by back-transformation of seizure log (exponentiation of log seizure rate) by the following equation: 100%*[exp(X) − 1] where x is the log of the seizure. The change from baseline in 28-day seizure rate, with and without natural log- transformation, was analyzed descriptively for each treatment group using tables and plots. A post hoc descriptive statistics analysis was conducted for percentage change from baseline in seizure rate. As a sensitivity analysis of the primary endpoint, multiple imputation methods were used to evaluate the impact of missing data for subjects who discontinued from the study. Subjects who discontinued for insufficient clinical response, adverse events, or death were imputed based on the observed placebo distribution, regardless of randomized treatment assignment. Imputation was based on baseline $\log_e$(28-day seizure rate + 1), geographical region, and weight group. Subjects who discontinued the study for other reasons, or who completed the study but had a missing double-blind seizure rate, were imputed based on observed subjects in the same randomized group. Imputation was based on treatment, baseline $\log_e$(28-days seizure rate + 1), geographical region, and weight group. Responder rate was analyzed using a logistic regression model with fixed covariate terms for treatment group, weight group, and geographical region. Subjects who did not qualify for the definition of 50% responder were classified as nonresponders. Comparisons were performed for each pregabalin dose versus placebo using maximum likelihood tests and 95% CIs. Each dose of pregabalin and placebo was compared using a sequential stepwise

testing procedure. Treatment group comparisons were summarized with odds ratios of achieving responder status. Adverse events are reported using descriptive statistics (e.g. counts and percentages) (35).

III.1.2 Evaluation of pregabalin in pediatric patients younger than 4 years

Pregabalin adjunctive therapy for focal onset seizures in children 1 month to <4 years of age was investigated in the A0081042 (ClinicalTrials.gov registration NCT02072824; EudraCT #2013-003420-37) Phase III trial. It was a double- blind, placebo-controlled, randomized, parallel-group design trial conducted between 16/September/2014 and 13/Aug/2018. Patients were screened in 22 countries including Hungary in altogether 113 centers. The trial was sponsored by Pfizer (36).

III.1.2.1 Study design and patient selection

Patients aged between 1 month and <4 years, of either sex, were screened for inclusion on the basis of a diagnosis of epilepsy with focal onset seizures. The study was conducted utilizing the 2010 ILAE seizure terminology (8), consistent with study protocol, and used the term partial onset seizures (36).

Frequency of FOS was required to be at least three seizures in the month prior to screening as observed by the parents/caregivers, and at least two FOS recorded during the 48- to 72-hour baseline V-EEG monitoring as determined by the investigator. Patients must have been receiving a stable regimen of at least one and up to three AEDs within 7 days prior to screening and with the AEDs and dose remaining stable throughout the study. Benzodiazepines used on a regular basis at a stable dosage and use of a VNS (present and active) were each considered to be one of the concurrent antiepileptic treatments (36).

III.1.2.2 Treatments and study schedule

At the baseline visit, patients meeting other inclusion/exclusion criteria for the study underwent continuous V-EEG monitoring for 48-72 hours. Investigators reviewed baseline V-EEG to determine that patients had at least two FOS to fulfill inclusion criteria for randomization at day 1 (Figure 2.). Patients completing the 48- to 72-hour baseline phase and who met the eligibility criteria were randomized to receive one of three treatments in a 2:1:2 ratio (pregabalin 7 mg/kg/day, pregabalin 14 mg/kg/day, or placebo). Dose reductions were planned for patients of 1-3 months of age to reflect potentially lower pregabalin clearance in these younger patients (6 mg/kg/day and 12 mg/kg/day, respectively), but no patients up to 3 months of age were randomized to treatment (36).

Randomization was stratified by study site and patient age strata as follows: stratum 1, <1 year of age; stratum 2, 1-2 years of age; stratum 3, >2 years of age. There was no prespecified number to be enrolled per strata. Randomized patients underwent 14 days of double-blind treatment (5-day dose escalation, 9-day fixed dose including V-EEG monitoring of 48-72 hours over final 3 days) and a 7-day double-blind taper phase (see Figure 2) (36).

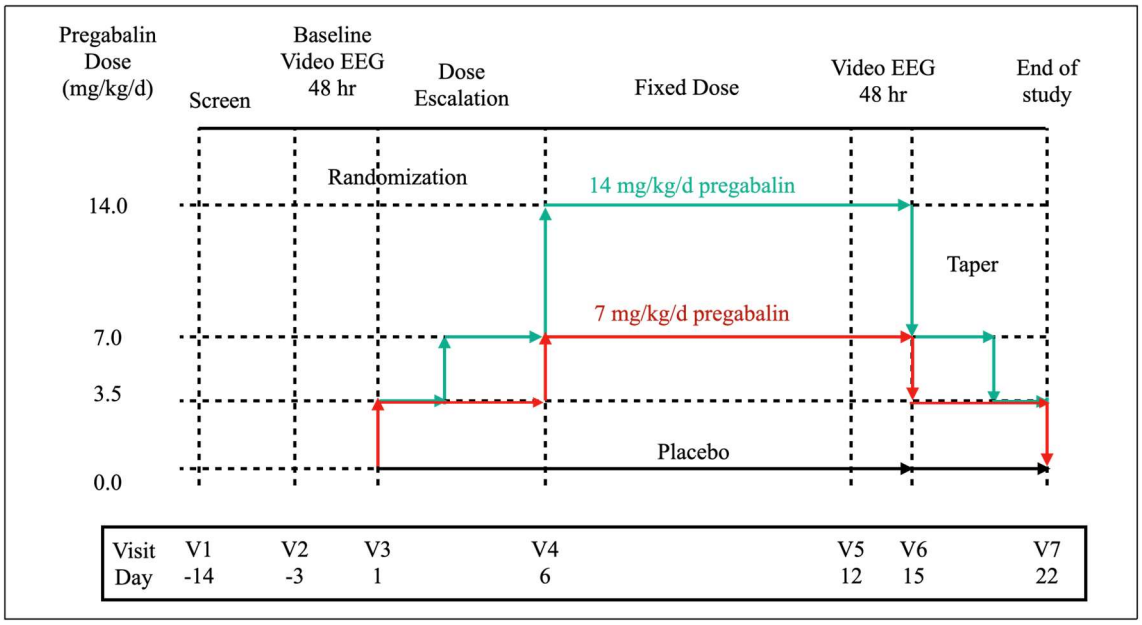


Figure 2. A0081042 trial design (36).

Pregabalin or matching placebo was administered as a 20-mg/mL oral solution in three equally divided doses TID. Doses of study drug and placebo were identical in appearance

to achieve study blinding. Treatment was initially dispensed at randomization, using a telerandomization system according to the agreed randomization code to maintain blinding procedures. The dose was based on the age and weight of the patient. The double-blind fixed-dose treatment was administered by parent(s)/guardian(s)/caregiver(s) according to provided instructions from day 6 to day 15. Treatment compliance was monitored by dosing diaries and the volume of study medication used on return of the study medication bottle. The 48- to 72-hour double-blind V-EEG monitoring took place from day 12 to day 15. The 1-week taper medication was dispensed from day 15 to day 22 (end of fixed-dose phase) or, for those patients who discontinued before completing 2 weeks of treatment, at an unscheduled early termination visit (36).

Full physical and neurological examinations were performed at screening and at the end of study, with height/ length and weight recorded at screening and randomization. Brief physical and neurological examinations documenting significant changes from baseline were performed at randomization. A clinical assessment of vital signs (blood pressure and pulse) was recorded at each visit. Blood and urine samples for hematology, clinical chemistry, and urinalysis were collected during screening and at the beginning and end of the double-blind treatment phase, and blood samples for plasma concentration for pharmacokinetic analysis were collected at the beginning and end of the double-blind treatment phase. A 12-lead ECG was performed at screening and at end of study or early termination (36).

If patients completed through the end of the taper phase, they were able to be evaluated for entry into a 1-year open-label extension trial (A0081106; ClinicalTrials.gov registration NCT01463306; EudraCT #2011-001412-65) evaluating the long-term safety and efficacy of pregabalin for FOS (36).

III.1.2.3 Sample size assessments and study endpoints

The primary efficacy population consisted of randomized patients who took at least one dose of study drug during the double-blind treatment period, had at least one baseline FOS identified with V-EEG, and had at least 24 hours of evaluable V-EEG monitoring at baseline and at the end of double-blind treatment. Efficacy assessments were based on

change in FOS frequency determined from baseline and double-blind V-EEG monitoring. The central reader reviewed V-EEG recordings to determine FOS counts to enable seizure frequency calculations. The baseline 24-hour V-EEG seizure rate and the double-blind 24-hour seizure rate for all FOS at the end of double-blind treatment (48- to 72-hour V-EEG assessment phase) were calculated as follows:

$$\text{Double-blind 24-hour EEG seizure rate} = \frac{\text{\# of seizures in double-blind 48–72 hours assessment phase}}{\text{\# of hours of V-EEG monitoring}} \times 24.$$

A log-transformation was applied to the 24-hour seizure rate for each patient.
The primary endpoint was $\log_e$(24-hour seizure rate + 1); the quantity 1 was added for any possible zero seizure incidence (36).
The secondary efficacy endpoint was responder rate, defined as patients who had ≥50% reduction from baseline in FOS rate during the double-blind V-EEG assessment (36).

Safety and tolerability of pregabalin were assessed by recording adverse events (AEs; considered treatment-emergent AEs [TEAEs] from the first day of study treatment), including data on the occurrence, nature, intensity, and potential relationship to study drug; assessment of clinical laboratory data; and the results of physical examinations, vital signs, neurological examinations, and ECGs. AEs were also classified by whether they qualified as a serious AE (SAE), defined as AEs that were life-threatening or resulted in death, caused new or prolonged hospitalization, resulted in persistent or significant disability or incapacity, or were associated with a congenital anomaly or birth defect. The Medical Dictionary for Regulatory Activities (MedDRA, v20.1) was used for coding of AEs (36).

III.1.2.4 Statistical analyses

The primary analysis utilized a linear model with baseline $\log_e$(24-hour seizure rate + 1) as a continuous covariate and the following fixed-effect terms: geographic region (i.e. Asia-Pacific, North America + Europe + Middle East, rest of the world), treatment group (pregabalin 7 or 14 mg/kg/day, placebo), and age stratum (<1 year of age; 1-2 years of

age; >2 years of age). A sequential stepwise testing procedure was used to control for multiplicity of testing such that the experimentwise type I error rate did not exceed the 5% level of significance. There were two pairwise comparisons of interest: step 1, pregabalin 14 mg/kg/day versus placebo; and step 2, pregabalin 7 mg/kg/day versus placebo. Step 2 was performed only if statistical significance was observed in step 1. Each step was conducted at the 5% level of significance. The log-transformation ($\log_e$[24-hour seizure rate + 1]) was used as the primary endpoint. Least square means were calculated using the observed marginal distribution. Two-sided 95% confidence intervals of the difference between the least square means were calculated by using the appropriate least square means and their standard errors. A back-transformation was used to calculate percent reduction relative to placebo in seizures as follows: 100%*[exp(X) − 1], where X is the estimate of the difference of the log values between the two comparison groups based on the analysis of covariance (ANCOVA) model. Results were reported as "percent change in seizures" relative to placebo. A sensitivity analysis of the $\log_e$(24-hour seizure rate + 1) was also conducted using a rank ANCOVA with treatment, age strata, geographic region, and ranked log-baseline scores as covariates to estimate and compare median output by treatment group. The key secondary endpoint (responder rate) was analyzed using a logistic regression model with the fixed covariate terms of treatment, age strata, and geographical region. SAS® (SAS Institute, NC, USA) software was used. AEs were reported using descriptive statistics (e.g. counts and percentages) (36).

III.2. Evaluation of lacosamide

The safety and tolerability of intravenous lacosamide in pediatric patients with epilepsy was investigated in the EP0060 (ClinicalTrials.gov registration NCT02710890; EudraCT # 2014-003294-42) Phase II/III, multicenter, open-label trial, including Hungary between 30/May/2017 and 28/Jun/2019. The trial was conducted in 23 centers. The trial was sponsored by UCB Pharma (37).

III.2.1 Study design and patient selection

Patients could be enrolled if they were ≥1 month to <17 years of age, had a diagnosis of epilepsy with focal seizures or primary generalized tonic-clonic seizures, weighed ≥4 kg,

and were considered an acceptable candidate for venipuncture and IV infusion. In addition, eligible patients were (i) receiving oral lacosamide as adjunctive treatment or monotherapy in an open-label long-term trial (SP848 or EP0034); (ii) receiving prescribed oral lacosamide from a commercial supply as adjunctive treatment or monotherapy; or (iii) not receiving lacosamide treatment before enrolment (would receive IV lacosamide as a new adjunctive treatment in EP0060) (37).

For patients who were receiving lacosamide upon enrolment, oral lacosamide must have been administered at a dose of 2-12 mg/kg/day (in patients <50 kg) or 100-600 mg/day (in patients ≥50 kg) for ≥2 weeks before screening. Oral lacosamide dose must have been stable for at least 3 days before the first lacosamide infusion. Patients initiating lacosamide had to be on a stable dosage regimen of at least one ASM, which must have been kept constant for ≥2 weeks before screening, and must not have received lacosamide within the 3 months before screening (37).

III.2.2 Lacosamide dosing

The trial consisted of a screening and/or baseline period of up to 7 days; a treatment period; a final visit (1 day); and a safety follow-up via telephone over a period of 1-3 days. Patients received IV lacosamide based on clinical need or elective administration. Clinical need administration applied to patients who needed to undergo a procedure and were being treated at an epilepsy monitoring unit or healthcare facility or were in other situations where IV administration was clinically appropriate and oral administration was not feasible (e.g. surgery). For these patients, the maximum number of IV lacosamide doses was 10 (administered twice daily with an interval of approximately 12 hours, over a duration of ≤5 days). Elective administration applied to patients who were taking oral lacosamide (or any enteric lacosamide administration e.g. by feeding tube), and elected to receive IV lacosamide at an epilepsy monitoring unit or healthcare facility. For these patients, a maximum of two IV lacosamide doses were permitted (over approximately 24 hours). Patients who only required one IV lacosamide infusion could complete all the trial periods in 1 day, provided there was sufficient time for all examinations and the final visit assessments (37).

Patients receiving lacosamide before this trial received IV lacosamide (as adjunctive treatment or monotherapy) as a replacement for oral lacosamide in a twice-daily regimen at the same stable daily dose they had been receiving before the present trial: 2-12 mg/kg/day or 100-600 mg/day, with a maximum dose of 12 mg/kg/day or 600 mg/day, whichever was lower. Patients initiating lacosamide received IV lacosamide as adjunctive treatment only (initiation of IV lacosamide monotherapy was not permitted) in a twice-daily regimen at a dose of 2 mg/kg/day for patients weighing <50 kg, and 100 mg/day for patients weighing ≥50 kg (the dose was to remain unchanged for the duration of the treatment period) (37).

Patients who entered EP0060 from an open-label, long-term trial (SP848 or EP0034) suspended their participation in that trial temporarily to receive IV lacosamide. Upon completion of the EP0060 trial, eligible patients who had received prescribed lacosamide from commercial supply or who were not receiving lacosamide before enrolment had the option to continue oral lacosamide in another open-label trial (SP848) (37).

III.2.3 Outcomes

The primary outcomes were treatment-emergent adverse events, reported spontaneously by the patient and/or caregiver or observed by the investigator, and discontinuations due to TEAEs. Other safety outcomes included changes in 12-lead ECGs, vital sign measurements (blood pressure and pulse rate), physical examinations, and neurological examinations. The Safety Set (SS) was defined as all patients who received at least one dose of lacosamide (oral and/or IV) in this open-label trial. The SS-IV was defined as all patients in the SS who received at least one dose of IV lacosamide and was the primary analysis set for the safety data (37).

III.3 Evaluation of brivaracetam

The pharmacokinetics, safety and tolerability of intravenous brivaracetam in pediatric patients with epilepsy was investigated in the EP0065 (ClinicalTrials.gov registration NCT03405714; EudraCT # 2016-002452-25) Phase II, multicenter, open-label trial, conducted at 37 sites across seven countries including Hungary between 01/Jun/2018 and 04/Nov/2020. The trial was sponsored by UCB Pharma (38).

III.3.1 Study design and patient selection

Children ≥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 ≥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: ≥1 month to <2 years; ≥2 to <6 years; ≥6 to <12 years; and ≥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) (38).

III.3.2 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 (31), as well as a study in healthy adult volunteers (N01256; UCB Pharma).
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 (≥4 weeks), and safety (BRV-free) period (2 weeks) (Figure 3.) (38).

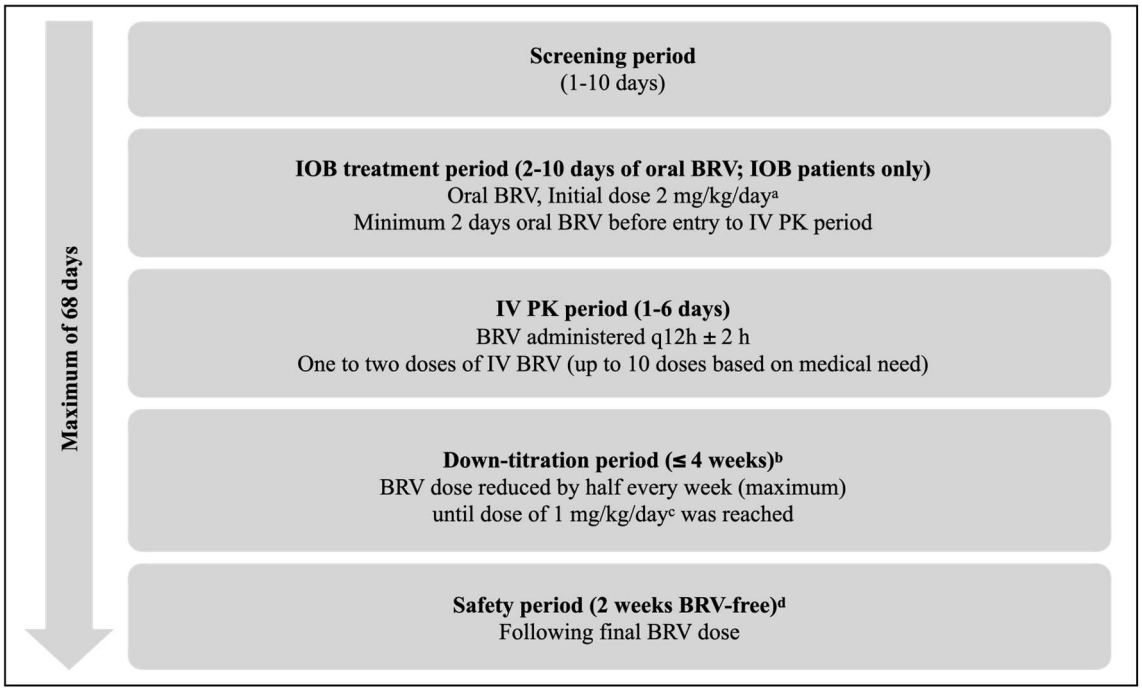


Figure 3. EP0065 trial design and treatment schedule (38).
a, Treatment initiated with oral BRV 2mg/kg/day (not exceeding 100mg/day for body weights ≥50 kg); could have been adjusted to maximum dose of 4 mg/kg/day (not exceeding 200 mg/day for body weights ≥50 kg).
b, Patients who received at least four 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.
c, 50 mg/day if body weight ≥50 kg. d, 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

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: ≥12 to <16 years; ≥6 to <12 years; ≥2 to <6 years; then ≥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 (≤2-min infusion) and the next (younger) cohort began the 15-min infusion (38).

III.3.3 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) (38).

Blood samples for PK analyses were collected for the initial IV BRV administration and one subsequent IV BRV administration only (for patients requiring more than one dose of IV BRV). PK sampling was conducted ≤1 h before 15-min BRV infusion and 15 min and 3 h after infusion, and ≤1 h before bolus injection (≤2-min infusion) and 15 min and 3 h after injection (38).

III.3.4 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. SAS® (SAS Institute, NC, USA) software was used. 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 ≥6 to <16 years of age, and 10 ng/mL in patients ≥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 (38).

IV. Results

IV.1 Pregabalin

IV.1.1 Pregabalin in pediatric patients older than 4 years

IV.1.1.1 Subject Disposition, Baseline Demographics, and Clinical Characteristics

Overall, 372 subjects were screened and 295 were randomized (placebo n = 94; pregabalin 2.5 mg/kg/day n=104; pregabalin 10 mg/kg/day n=97) in the A0081041 trial. Out of the 372 screened patients 29 patients were screened and 26 patients were randomized at our center (35).

The baseline demographics and clinical characteristics were comparable between subjects in each treatment group (Table 2.) (35).

Across all groups, the mean (standard deviation [SD]) age of patients was 10.2 (3.7) years, with 54.9% (n = 162) of subjects being male and the majority being white (69.2%, n = 204) or Asian (28.1%, n = 83). All enrolled subjects had focal onset seizures with subcategorizations including focal aware seizure with a motor component, focal aware seizure without a motor component, focal impaired awareness, or focal to bilateral tonic-clonic seizure. The mean duration since onset of focal onset seizures was ~6 years in all treatment groups, with ~70% of subjects taking 2 to 3 background antiepileptic drugs. At baseline, the 28-day seizure rates were similar across treatment groups (35).

The nontransformed mean + SD 28-day seizure rates were 60.19 + 126.60 (pregabalin 10 mg/kg/day), 53.34 + 73.97 (pregabalin 2.5 mg/kg/day), and 57.87 + 105.64 (placebo). The mean + SD log-transformed 28-day seizure rates were 3.19 + 1.27 (pregabalin 10 mg/kg/day), 3.27 + 1.22 (pregabalin 2.5 mg/kg/day), and 3.18 + 1.30 (placebo) (Table 3.) (35).

Table 2. Baseline Demographics and Clinical Characteristics. Abbreviations: AED, antiepileptic drug; SD, standard deviation (35).

Characteristic	Placebo (n=94)	Pregabalin 2.5 mg/kg/day (n=104)	Pregabalin 10 mg/kg/day (n=97)
Sex, n (%)			
Male	54 (57.4)	52 (50.0)	56 (57.7)
Female	40 (42.6)	52 (50.0)	41 (42.3)
Age, years			
Mean (SD)	10.3 (3.7)	10.2 (3.9)	10.1 (3.5)
Range	4-16	4-16	4-16
Race, n (%)			
White	65 (69.1)	75 (72.1)	64 (66.0)
Black	1 (1.1)	1 (1.0)	2 (2.1)
Asian	28 (29.8)	28 (26.9)	27 (27.8)
Other	0 (0.0)	0 (0.0)	4 (4.1)
Weight, kg, mean (SD)	36.8 (16.8)	36.7 (17.1)	37.2 (18.9)
Ongoing AEDs at screening and randomization, n (%)			
1 AED	26 (27.7)	30 (28.8)	21 (21.6)
2 AEDs	40 (42.6)	39 (37.5)	41 (42.3)
3 AEDs	28 (29.8)	35 (33.7)	35 (36.1)

Table 3. Loge(28-Day Seizure Rates) and Untransformed 28-Day Seizure Rates at Baseline and at the End of the Double-blind Treatment Phase (35).
Abbreviations: CI, confidence interval; LS, least squares; N/A, not available.

[a] One subject in each pregabalin group was not evaluated at the end of the double-blind treatment phase, because they did not return seizure diary data.

[b] Post hoc descriptive statistics analysis

Characteristic	Placebo (n=93)	Pregabalin 2.5 mg/kg/day (n=104) [a]	Pregabalin 10 mg/kg/day (n=97) [a]
Loge(28-day seizure rate)			
Baseline, mean (95% CI), n	3.18 (2.91, 3.44)	3.27 (3.03, 3.50)	3.19 (2.93, 3.44)
End of double-blind treatment phase, mean (95% CI), n	2.96 (2.82, 3.10)	2.86 (2.72, 2.99)	2.74 (2.60, 2.88)
LS mean difference vs placebo (95% CI)	N/A	-0.10 (-0.29, 0.08)	-0.22 (-0.41, -0.04)
LS mean % difference vs placebo (95% CI)	N/A	-9.93 (-24.87, 7.99)	-19.90 (-33.39, -3.68)
Untransformed 28-day seizure rate [b]			
Overall change in seizure rate, median (range) [b]	-2.25 (-462.1, 207.8)	-3.53 (-173.3, 82.7)	-4.85 (-399.9, 46.0)
Percentage change in seizure rate, median (range) [b]	-16.91 (-100.0, 380.0)	-27.7 (-100.0, 104.7)	-37.12 (-100.0, 225.9)

IV.1.1.2 Efficacy Endpoints

Pregabalin 10 mg/kg/day resulted in a significant improvement of log-transformed 28-day seizure rate relative to placebo (P = .0185) (Figure 4. and Table 3.). In the step-down analysis of the primary efficacy endpoint, although the seizure rate was numerically reduced with pregabalin 2.5 mg/kg/day relative to placebo, the treatment difference did not achieve statistical significance (P = .2577). These least squares mean differences (pregabalin minus placebo) were –0.22 (pregabalin 10 mg/kg/ day) and –0.10 (pregabalin

2.5 mg/kg/day). These differences were associated with a percentage reduction in seizure rate relative to placebo of –19.90% (pregabalin 10 mg/kg/day) and –9.93% (pregabalin 2.5 mg/kg/day) (Figure 4. and Table 3.) (35).

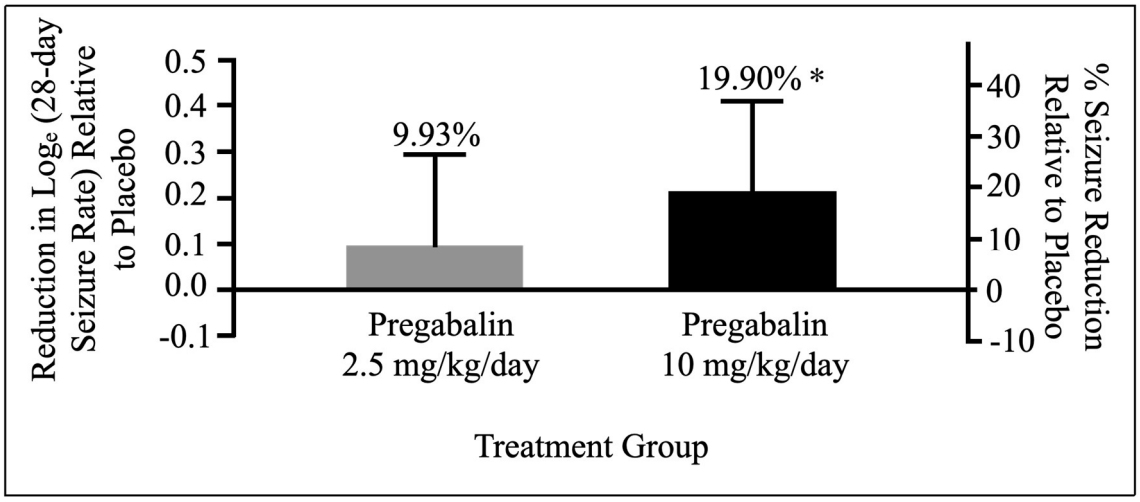


Figure 4. Least squares mean (95% confidence interval) and percentage treatment differences (pregabalin minus placebo) in log- transformed 28-day seizure rate during the double-blind treatment phase (35).
*P = .0185 with pregabalin 10 mg/kg/day; the difference was numeric and not statistically significant with pregabalin 2.5 mg/kg/day

Analysis of responder rates was consistent with the primary efficacy endpoint analysis. The responder rate with pregabalin 10 mg/kg/day was 40.6% and was significantly greater than the responder rate of 22.6% observed with placebo (P = .0068). The responder rate with pregabalin 2.5 mg/kg/day was 29.1% and was numerically greater than with placebo, but the difference was not statistically significant (P = .2600) (Figure 5.) (35).

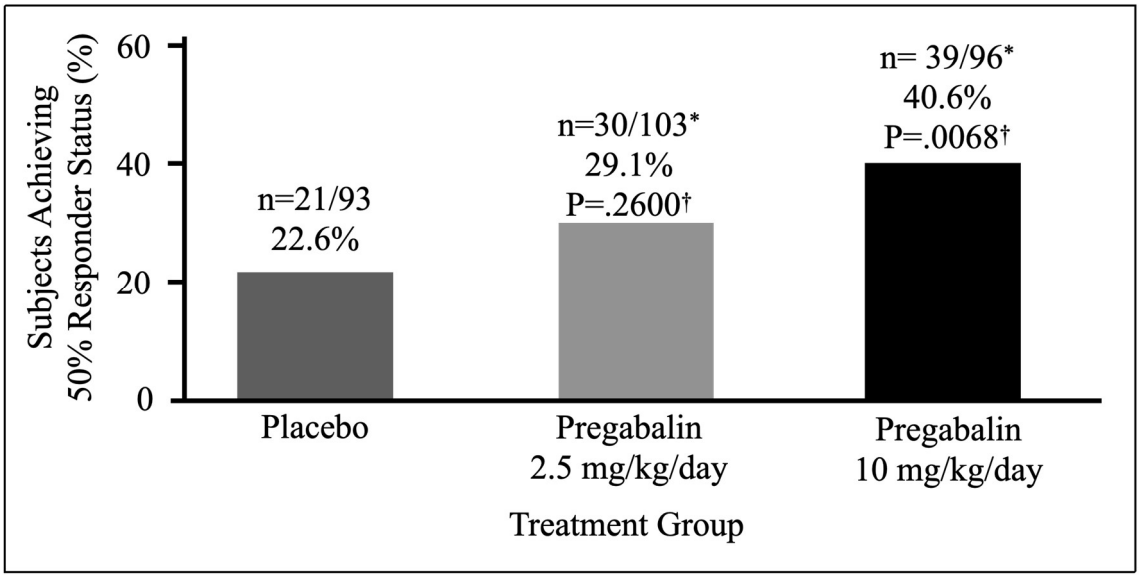


Figure 5. Percentage of subjects achieving 50% responder status (reduction in seizures) during the double-blind treatment phase by treatment group (35).
*One subject in each pregabalin group was not evaluated at the end of the double-blind treatment phase because they did not return seizure diary data.
†P value versus placebo.

In addition, when analyzed by subtype of focal onset seizures (including focal aware seizures with a motor component, focal aware seizures without a motor component, focal impaired awareness seizures, and focal to bilateral tonic-clonic), no subtype appeared less responsive or nonresponsive to pregabalin versus placebo. In a descriptive post hoc analysis, the median and percentage changes from baseline in 28-day seizure rates were numerically larger in both pregabalin dose groups compared with placebo (Table 3.) (35).

IV.1.1.3 Safety and Tolerability

In the placebo, pregabalin 2.5 mg/kg/day, and 10 mg/kg/day groups, respectively, 94, 104, and 97 subjects were evaluable for adverse events (Table 4.) (35).

The most commonly reported treatment-emergent adverse events (all causalities) experienced by ≥10% of subjects in any treatment group were somnolence (placebo, 13 [13.8%]; pregabalin 2.5 mg/kg/day, 18 [17.3%]; pregabalin 10 mg/kg/day, 25 [25.8%]); weight increased (placebo, 4 [4.3%]; pregabalin 2.5 mg/kg/day, 4 [3.8%]; pregabalin 10 mg/kg/day, 13 [13.4%]), and increased appetite (placebo, 4 [4.3%]; pregabalin 2.5 mg/kg/day, 7 [6.7%]; pregabalin 10 mg/kg/day, 10 [10.3%]) (Table 4.) (35).

Table 4. Overview of Adverse Events. Abbreviations: AE, adverse event; SAE, serious adverse event (35).

[a] Medical Dictionary for Regulatory Activities v 19.0 preferred terms.

	Placebo, n (%) (n=94)	Pregabalin 2.5 mg/kg/day, n (%) (n=104)	Pregabalin 10 mg/kg/day, n (%) (n=97)
Subjects with treatment-emergent AEs	56 (59.6)	67 (64.4)	68 (70.1)
Subjects with treatment-related AEs	30 (31.9)	37 (35.6)	46 (47.4)
Subjects with SAEs	7 (7.4)	5 (4.8)	10 (10.3)
Subjects discontinued because of AEs	0	1 (1.0)	4 (4.1)
Most common AEs [a] (≥5% in any treatment group)			
Diarrhea	4 (4.3)	0	5 (5.2)
Vomiting	4 (4.3)	5 (4.8)	5 (5.2)
Fatigue	3 (3.2)	6 (5.8)	4 (4.1)
Pyrexia	7 (7.4)	9 (8.7)	7 (7.2)
Nasopharyngitis	6 (6.4)	9 (8.7)	7 (7.2)
Upper respiratory tract infection	9 (9.6)	10 (9.6)	8 (8.2)
Weight increased	4 (4.3)	4 (3.8)	13 (13.4)
Increased appetite	4 (4.3)	7 (6.7)	4 (4.1)
Headache	6 (6.4)	4 (3.8)	7 (7.2)
Seizure	7 (7.4)	7 (6.7)	4 (4.1)
Somnolence	13 (13.8)	18 (17.3)	25 (25.8)
Cough	3 (3.2)	9 (8.7)	2 (2.1)

Few subjects experienced serious adverse events and of these, 1 subject in each treatment group had a serious adverse event that was classified as treatment-related by the investigator. One treatment-related serious adverse event was increase in seizures

requiring hospitalization (8-year-old Asian girl, placebo group), but did not result in permanent treatment discontinuation. Two other treatment-related serious adverse events led to permanent discontinuation: visual hallucination (8-year-old white girl, pregabalin 2.5 mg/kg/day group; 100 mg/day total dose) and worsening of epilepsy (6-year-old white boy, pregabalin 10 mg/kg/day group; 140 mg/day total dose). Most of the treatment-emergent serious adverse events resolved without sequelae. However, 1 serious adverse event, a thermal burn, required skin transplantation; this serious adverse event was not considered related to study treatment. One death occurred during the study (pregabalin 10 mg/kg/day), which was attributed to pulmonary edema that was considered unrelated to study drug. This subject had a history of seizures attributed to perinatal injury, prematurity, intracerebral hemorrhage, and hydrocephalus, for which a ventriculoperitoneal shunt had been previously inserted. Additional medical history included quadriplegia, cerebral palsy, hypoplasia of the brainstem and cerebellum, microcephaly, and severe intellectual deficiency (35).

No other findings at baseline or post-treatment suggested a clinically significant effect on safety, including laboratory test results, vital signs, ECG parameters, physical examinations, Tanner staging, neurologic examinations, mental health risk assessments, cognitive testing, and assessments of potential suicidality (35).

IV.1.2 Pregabalin in pediatric patients younger than 4 years

IV.1.2.1 Subject Disposition, Baseline Demographics, and Clinical Characteristics

In total 231 were enrolled and 175 patients were randomized to a treatment group: pregabalin 14 mg/kg/day (n = 34), pregabalin 7 mg/kg/day (n = 71), or placebo (n = 70) in the A0081042 trial. Altogether 14 patients were screened at our center and 9 patients were randomized. The baseline demographics were comparable between treatment groups (Table 5.) (36).

Table 5. Baseline demographic and clinical characteristics. Abbreviations: AED, antiepileptic drug; SD, standard deviation (36).

Characteristic	Pregabalin 7 mg/kg/day (n=71)	Pregabalin 14 mg/kg/day (n=34)	Placebo (n=70)
Sex, n (%)			
Male	45 (63)	20 (59)	38 (54)
Female	26 (37)	14 (41)	32 (46)
Age, n (%)			
< 1 year	9 (13)	2 (6)	7 (10)
1-2 years	19 (27)	10 (29)	20 (29)
> 2 years	43 (61)	22 (65)	43 (61)
Race, n (%)			
White	47 (66)	24 (71)	49 (70)
Asian	23 (32)	10 (29)	19 (27)
Other	1 (1)	0 (0.0)	2 (3)
Weight, kg, mean (SD)	11.7 (3.5)	11.4 (3.4)	11.4 (3.1)
Height/length, cm, mean (SD)	86 (12)	84 (10)	86 (11)
Number of AEDs ongoing at randomization, n (%)			

1 AED	22 (31)	11 (32)	25 (36)
2 AEDs	37 (52)	19 (56)	31 (44)
3 AEDs	12 (17)	4 (12)	14 (20)

The mean (SD) age of patients across all groups was 28.2 (12.6) months, with the youngest patient being 3 months of age. There was a total of 18 patients in stratum 1 (<1 year of age), 49 patients in stratum 2 (1-2 years of age), and 108 patients in stratum 3 (>2 years of age). The majority of patients were male (59%); 69% of patients were white, and 30% were Asian. At randomization, the majority (50%) were taking two AEDs other than pregabalin, with the remaining patients taking one other AED (33%) or three other AEDs (17%; Table 5) (36).

At screening, investigators characterized patients' FOS based on medical history. The mean duration since onset of FOS was similar across treatment groups, with an overall mean duration of 1.6 years (range = 0.1 to 3.8 years) (36).

There were differences across treatment groups in baseline seizure frequencies (see Table 6). Overall, baseline median 24-hour seizure frequency was 4.4, and overall baseline mean (SD) 24-hour seizure frequency was 12.2 (29.3) (36).

Table 6. Untransformed 24-hour seizure rate (FOS) during baseline. Abbreviations: FOS, focal onset seizure; SD, standard deviation (36).

	Pregabalin 7 mg/kg/day (n=59)	Pregabalin 14 mg/kg/day (n=28)	Placebo (n=53)
Untransformed 24-hour seizure rate (FOS) during baseline			
Min	0.7	0.3	0.3
Median	4.7	5.4	2.9
Max	254.9	42.7	56.2
Mean (SD)	18.0 (43.2)	8.8 (9.8)	7.4 (10.2)

IV.1.2.2 Primary efficacy endpoint

Randomized patients were included in the primary efficacy endpoint analysis if they took at least one dose of study drug during the double-blind treatment phase, had at least one

FOS identified by V-EEG monitoring at baseline, and had treatment phase V-EEG data (Figure 6). Pregabalin 14 mg/ kg/d resulted in −35% (95% CI = −54% to −6.0%) change relative to placebo in log-transformed FOS frequency, which was statistically significant (*P* = .022; Figure 6). There was a 12% (95% CI = −17 to 52) increase relative to placebo in log-transformed FOS frequency with pregabalin 7 mg/kg/day, which was not statistically significant (*P* = .461; Figure 6.) (36).

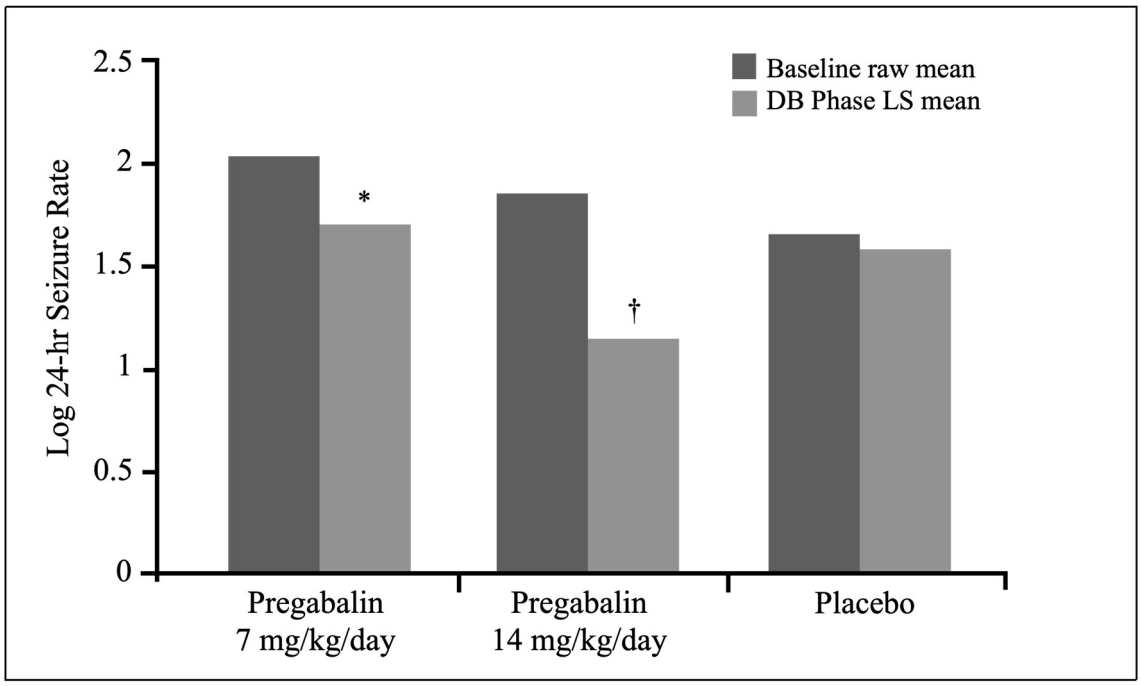


Figure 6. Least squares (LS) mean $\log_e$(24-day seizure rate + 1) for focal onset seizures for each treatment group during double-blind (DB) treatment phase. (36). **P* = .4606 relative to placebo, †*P* = .0223 relative to placebo

IV.1.2.3 Planned sensitivity analysis

Median percent change from baseline in untransformed 24- hour seizure rate was −70%, −17%, and −22% for pregabalin 14 mg/kg/day; pregabalin 7 mg/kg/day; and placebo; respectively (Figure 7.) (36).

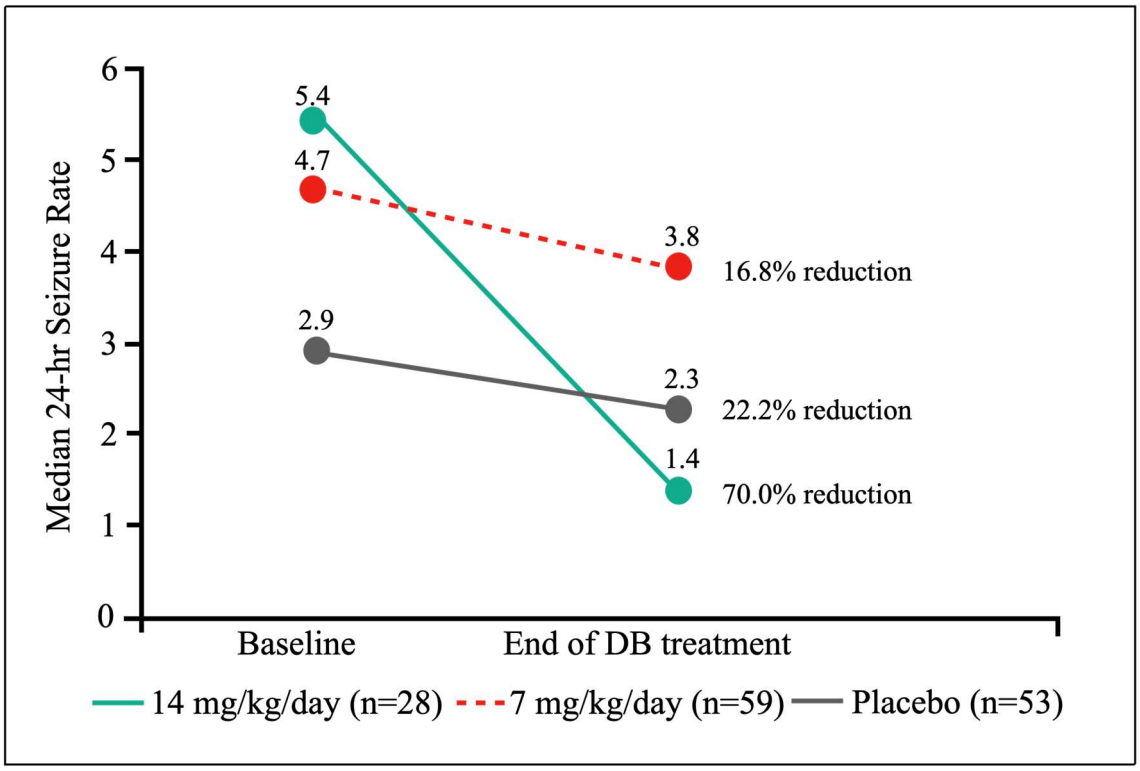


Figure 7. Median change from baseline in untransformed 24-hour seizure rate by treatment. Baseline = video- electroencephalographic (V-EEG) seizure observed up to 72 hours. Double-blind (DB) phase = up to 72-h V-EEG performed at the end of the DB treatment phase (36).

IV.1.2.4 Post hoc sensitivity analysis

Due to the variation in baseline seizure rates among treatment groups, post hoc nonparametric sensitivity analyses were performed using the change from baseline in log 24- hour focal onset seizure rate as the dependent variable. These outcomes supported the results of the primary analysis (pregabalin vs placebo) using ranked ANCOVA (P = .053 for pregabalin 14 mg/kg/day and P = .515 for pregabalin 7 mg/kg/day) and using a Wilcoxon-Mann-Whitney test (P = .026 for pregabalin 14 mg/kg/day and P = .556 for pregabalin 7 mg/kg/day). (36).

IV.1.2.5 Secondary efficacy endpoint

There were no significant differences in 50% responder rate between pregabalin 14 mg/kg/day and placebo (P = .305), or pregabalin 7 mg/kg/day and placebo (P = .242). Responder rates for pregabalin 14 mg/kg/day, pregabalin 7 mg/kg/day, and placebo were 54%, 31%, and 42%, respectively (Table 7.) (36).

Table 7. Statistical summary of logistic regression of responder rate based on 50% reduction in 24-hour focal onset seizure rate during the double-blind treatment phase by treatment group. Abbreviation: CI, confidence interval (36).

	Pregabalin 14 mg/kg/day (n=28)	Pregabalin 7 mg/kg/day (n=59)	Placebo (n=53)
Responder, n (%)	15 (54)	18 (31)	22 (42)
Nonresponder, n (%)	13 (46)	41 (69)	31 (58)
Versus placebo			
Odds ratio	1.6	0.6	
95% CI	0.6-4.1	0.3-1.4	
p value	.305	.242	

IV.1.2.6 Safety and tolerability

A total of 175 patients were included in the safety analysis and 169 (96.6%) patients completed the study. Table 8. shows a summary of TEAEs (36).

Table 8. Summary of treatment-emergent AEs (all causality). Abbreviation: AE, adverse event; SAE, serious adverse event (36).
[a]AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) v20.1 preferred terms.

	Pregabalin 7 mg/kg/day, n=71	Pregabalin 14 mg/kg/day, n=34	Placebo, n=70
Patients with treatment-emergent AEs, n (%)	32 (45.1)	17 (50)	38 (54.3)
Subjects with severe intensity AEs, n (%)	0	0	0
Patients with SAEs, n (%)	0	1 (2.9)	4 (5.7)
Patients discontinued due to AEs, n (%)	0	0	1 (1.4)
Patients with dose reduced or temporary discontinuation due to AEs, n (%)	0	0	2 (2.9)
Most common AEs [a] (all causality; ≥5% in any treatment group), n (%)			
Somnolence	8 (11.3)	6 (17.6)	4 (5.7)
Upper respiratory tract infection	5 (7.0)	4 (11.8)	8 (11.4)
Pneumonia	1 (1.4)	3 (8.8)	0
Nasopharyngitis	1 (1.4)	2 (5.9)	3 (4.3)
Pyrexia	4 (5.6)	2 (5.9)	4 (5.7)
Seizure	1 (1.4)	2 (5.9)	3 (4.3)
Viral infection	2 (2.8)	2 (5.9)	2 (2.9)

Vomiting	1 (1.4)	0	6 (8.6)

The most frequently reported TEAEs in the pregabalin groups were somnolence (11.3% for pregabalin 7 mg/kg/day; 17.6% for pregabalin 14 mg/kg/day; and 5.7% for placebo) and upper respiratory tract infection (7.0% for pregabalin 7 mg/kg/day; 11.8% for pregabalin 14 mg/kg/day; and 11.4% for placebo). The majority of TEAEs were mild in severity (95% of events in the pregabalin 7 mg/kg/day group, 64% in the pregabalin 14 mg/kg/day group, and 78% in the placebo group), with no severe events reported in any group (36).

Treatment-emergent SAEs were reported for five patients, including one treated with pregabalin 14 mg/kg/day (hospitalized with pneumonia) and four treated with placebo (all four were hospitalized; one was due to acute rhinitis, one was due to increasing frequency of seizures, one was due to dehydration, and one was due to choking related to oral secretion) (36).

Six patients (3.4%) discontinued from the study, including two (2.8%) patients in the pregabalin 7 mg/kg/day group, one (2.9%) patient in the pregabalin 14 mg/kg/day group, and three (4.3%) patients in the placebo group. One patient in the placebo group discontinued due to vomiting that was considered of moderate severity. No other discontinuations were due to an AE, and no patients died. Across all treatment groups, no clinically significant findings were identified for other safety assessments including laboratory results, physical and neurological examinations, vital signs, and ECG data (36).

IV.2 Lacosamide

IV.2.1 Patient disposition and baseline characteristics

103 patients were enrolled and completed the EP0060 open-label trial (SS; 77 from Europe, 26 from North America). Out of 103 patients worldwide, including the 77 patients from Europe, our team enrolled 20 patients. Most patients (96 [93.2%]) were

White. Fifty-five patients were ≥8 to <17 years of age (cohort 1) and 48 were ≥1 month to <8 years of age (cohort 2). Patients had a mean age of 8.6 years, and 57 (55.3%) were female (Table 9. and Table 10.). During the 4 weeks before the screening visit, 74 (71.8%) patients had focal seizures, 12 (11.7%) had generalized seizures, and two (1.9%) had unclassified seizures (patients could have had more than one type of seizure, and some

Characteristic	Patients ≥1 month to <8 years of age (N = 48)	Patients ≥8 to <17 years of age (N = 55)	All patients (N = 103)
Age, mean (SD), years	3.84 (2.33)	12.66 (2.41)	8.55 (5.01)
Female, *n* (%)	26 (54.2)	31 (56.4)	57 (55.3)
Patients entering EP0060, n (%)			
From an open-label long-term trial[a]	0	3 (5.5)	3 (2.9)
Receiving prescribed oral lacosamide	6 (12.5)	20 (36.4)	26 (25.2)
Not receiving lacosamide before enrolment	42 (87.5)	32 (58.2)	74 (71.8)
Previous and ongoing medical conditions in ≥10% of all patients, n (%)			
Any previous and ongoing medical conditions	41 (85.4)	42 (76.4)	83 (80.6)
Mental retardation	21 (43.8)	9 (16.4)	30 (29.1)
Cerebral palsy	13 (27.1)	8 (14.5)	21 (20.4)
Hypokinesia	15 (31.3)	1 (1.8)	16 (15.5)
Speech disorder developmental	11 (22.9)	2 (3.6)	13 (12.6)
History of epilepsy			
Time since first epileptic seizure, mean (SD), years	2.52 (2.02)	6.61 (4.64)[b]	4.68 (4.17)[c]
Age at diagnosis, mean (SD), years	1.69 (1.71)	6.29 (4.51)	4.15 (4.17)

were seizure-free during this time period). The most common concomitant ASMs taken during the trial (≥20% of all patients) were levetiracetam (43 [41.7%]) and valproic acid (35 [34.0%]). (37).

Table 9. Baseline demographics, medical conditions, epilepsy characteristics (37)., [a]Trial SP848 or EP0034. [b]*n* = 54. [c]*n* = 102.

Table 10. Baseline epilepsy characteristics, concomitant ASMs, and target infusion duration(SS- IV) (37). Abbreviations: ASM, antiseizure medication; IV, intravenous; SS-IV, intravenous Safety Set.

[a]Patients could have more than one response in a classification level and/or category; seizure types are listed per the International League Against Epilepsy (ILAE) 1981 classification, with the newer terminology provided in parentheses.

[b]Concomitant medications are medications taken on ≥1 day in common with IV lacosamide during the Treatment Period.

[c]Lacosamide was reported as a concomitant ASM in patients who replaced one of their two daily oral doses with IV lacosamide

IV.2.2 Lacosamide exposure

Most patients (74 [71.8%]) initiated lacosamide as adjunctive IV treatment upon enrolment, 26 (25.2%) received IV lacosamide as a replacement for prescribed oral lacosamide from a commercial supply, and three (2.9%) patients received IV lacosamide

Characteristic	Patients ≥1 month to <8 years of age (N = 48)	Patients ≥8 to <17 years of age (N = 55)	All patients (N = 103)
Seizure classification history during 4 weeks before screening[a]*, n (%)*			
Any partial-onset seizures (*focal seizures*)	44 (91.7)	30 (54.5)	74 (71.8)
Simple partial (*focal aware*)	2 (4.2)	6 (10.9)	8 (7.8)
Complex partial (*focal impaired awareness*)	21 (43.8)	18 (32.7)	39 (37.9)
Partial evolving to secondary generalized (*focal to bilateral tonic-clonic*)	26 (54.2)	13 (23.6)	39 (37.9)
Any generalized seizures	1 (2.1)	11 (20.0)	12 (11.7)
Absence	0	1 (1.8)	1 (1.0)
Myoclonic	0	1 (1.8)	1 (1.0)
Clonic	1 (2.1)	0	1 (1.0)
Tonic	1 (2.1)	2 (3.6)	3 (2.9)
Tonic-clonic	0	7 (12.7)	7 (6.8)
Atonic	0	1 (1.8)	1 (1.0)
Unclassified epileptic seizures	2 (4.2)	0	2 (1.9)
Any concomitant ASMs, *n* (%)[b]	48 (100)	54 (98.2)	102 (99.0)
Concomitant ASMs, taken by ≥10% of all patients, n (%)			
Levetiracetam	18 (37.5)	25 (45.5)	43 (41.7)
Valproic acid	24 (50.0)	11 (20.0)	35 (34.0)
Carbamazepine	11 (22.9)	8 (14.5)	19 (18.4)
Oxcarbazepine	4 (8.3)	9 (16.4)	13 (12.6)
Topiramate	5 (10.4)	7 (12.7)	12 (11.7)
Lacosamide[c]	1 (2.1)	10 (18.2)	11 (10.7)
Target infusion duration, n (%)			
15-30 minutes	8 (16.7)	14 (25.5)	22 (21.4)
30-60 minutes	40 (83.3)	41 (74.5)	81 (78.6)

as a replacement for oral lacosamide received in another open-label, long-term trial. The

mean overall duration of exposure to IV lacosamide was 1.18 days (median: 1 day; range: 1-5 days; standard deviation [SD]: 0.71). The mean duration of exposure was 1.10 days (range: 1.0-2.0 days; SD: 0.31) for patients ≥1 month to <8 years of age; and 1.25 days (range: 1.0-5.0 days; SD: 0.93) for patients ≥8 years to <17 years of age. Most (81 [78.6%]) patients had a target IV lacosamide infusion duration of 30-60 minutes rather than 15-30 minutes (22 [21.4%]). Seventy-nine (76.7%) patients had one IV lacosamide infusion, 20 (19.4%) had two infusions, one (1.0%) had three infusions, and three (2.9%) had 10 infusions (Figure 8.). No patients in the ≥1 month to <8 years age cohort received more than two infusions (37).

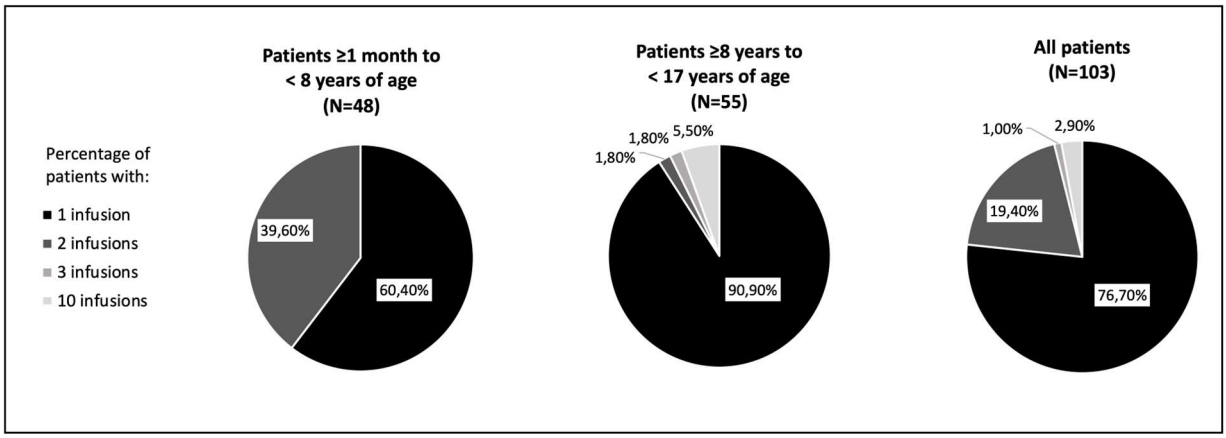


Figure 8. Number of infusions by cohort and overall (SS-IV) (37). Abbreviation SS-IV, intravenous Safety Set

IV.2.3 Safety and tolerability of IV lacosamide

A total of seven TEAEs were reported in five (4.9%) patients following treatment with IV lacosamide (Table 11.). No serious TEAEs, severe TEAEs, or discontinuation due to TEAEs were reported. No TEAEs were considered drug-related by the investigator, and no deaths were reported during the trial (37).

Table 11. Treatment-emergent adverse events (SS-IV). Abbreviations: IV, intravenous; SS-IV, intravenous Safety Set; TEAE, treatment-emergent adverse event (37).
[a] Medical Dictionary for Regulatory Activities Version 16.1 Preferred Term.

	Patients ≥1 month to <8 years of age (N = 48)	Patients ≥8 to <17 years of age (N = 55)	All patients (N = 103)
Any TEAEs, *n* (%)	3 (6.3)	2 (3.6)	5 (4.9)
TEAEs reported during the Post-IV Treatment Period[a], n (%)			
Blood triglycerides increased	0	2 (3.6)	2 (1.9)
Blood cholesterol increased	0	1 (1.8)	1 (1.0)
Functional gastrointestinal disorder	1 (2.1)	0	1 (1.0)
Pyrexia	1 (2.1)	0	1 (1.0)
Respiratory tract infection	1 (2.1)	0	1 (1.0)
Respiratory tract infection viral	1 (2.1)	0	1 (1.0)

The only TEAEs reported in two or more patients were increased blood triglycerides. One event occurred in a 10-year-old male who had a blood triglyceride level of 1.72 mmol/L at screening and 2.52 mmol/L at the final visit (normal range: 0.27-1.55 mmol/L). This TEAE was considered moderate in severity. The patient was taking oral lacosamide and levetiracetam at baseline and had discontinued oxcarbazepine 8 days previously. The other event occurred in a 12-year-old female who had a blood triglyceride level of 1.45 mmol/L at screening, 0.90 mmol/L at baseline, and 1.71 mmol/L at the final visit (normal range: 0.42-1.47 mmol/L). This TEAE was considered mild in severity. The patient was taking oral lacosamide and levetiracetam at baseline. Of note, triglyceride levels rise after eating. Patients were not required to fast prior to assessment of lipid panel (37).

Mean values for the majority of haematology and clinical chemistry parameters remained within the normal ranges for the duration of the trial. No consistent or clinically relevant changes from baseline were observed in vital sign parameters. There were no treatment-emergent clinically significant ECG findings, and no ECG-related TEAEs were reported. None of the relatively small changes from baseline in 12-lead ECG parameters (heart rate, QT interval, QT interval corrected for heart rate [QTcB and QTcF]) appeared to be clinically relevant. Mean changes from baseline to visit 2 and the final visit were small

and similar between cohorts for PR interval, QRS duration, and QTcB and QTcF. At all post-baseline time points, there was no evidence of QT, QTcB, or QTcF prolongation following treatment with lacosamide (37).

IV.3 Brivaracetam

IV.3.1 Patient disposition and baseline characteristics

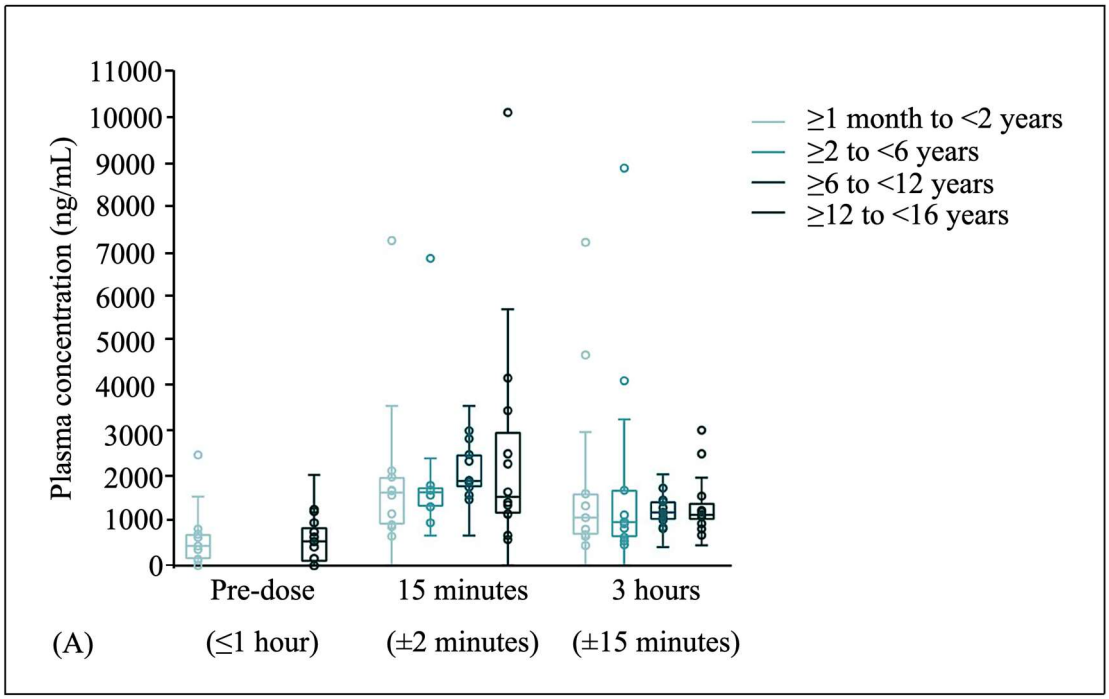
Of 58 screened patients, 50 eligible patients were enrolled in the EP0065 trial. Out of the 50 eligible patients 13 were screened and enrolled at our center. All 50 patients received IV BRV and were included in the SS-IV. Of these, 22 patients entered and completed the IOB treatment period (IOB patients). 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 (38).

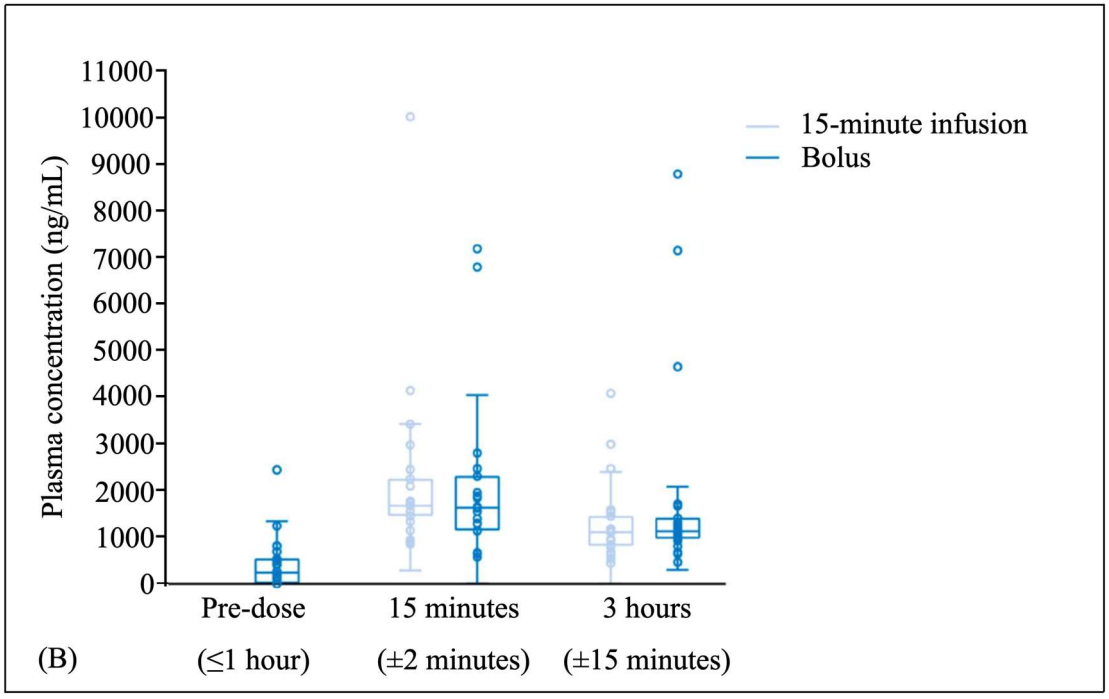
The mean ages were 8.3 years for patients ≥2 years of age (n = 37) and 11.4 months for patients <2 years of age (n = 13). Approximately half (52.0%) of the patients were male, and most were White (94.0%). Of the 50 patients, 43 weighed <50 kg and 7 weighed ≥50 kg. There were no unexpected differences 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, 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 (≥1 month to <2 years); 34.6 (17.8) months in the ≥2 to <6 years cohort; 6.0 (2.4) years in the ≥6 to <12 years cohort; and 7.9 (4.5) years in the ≥12 to <16 years cohort (38).

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 (38).

IV.3.2 Pharmacokinetic outcomes

PK outcomes were consistent with the expected results and expected ranges for this population (Figure 9.) (38).





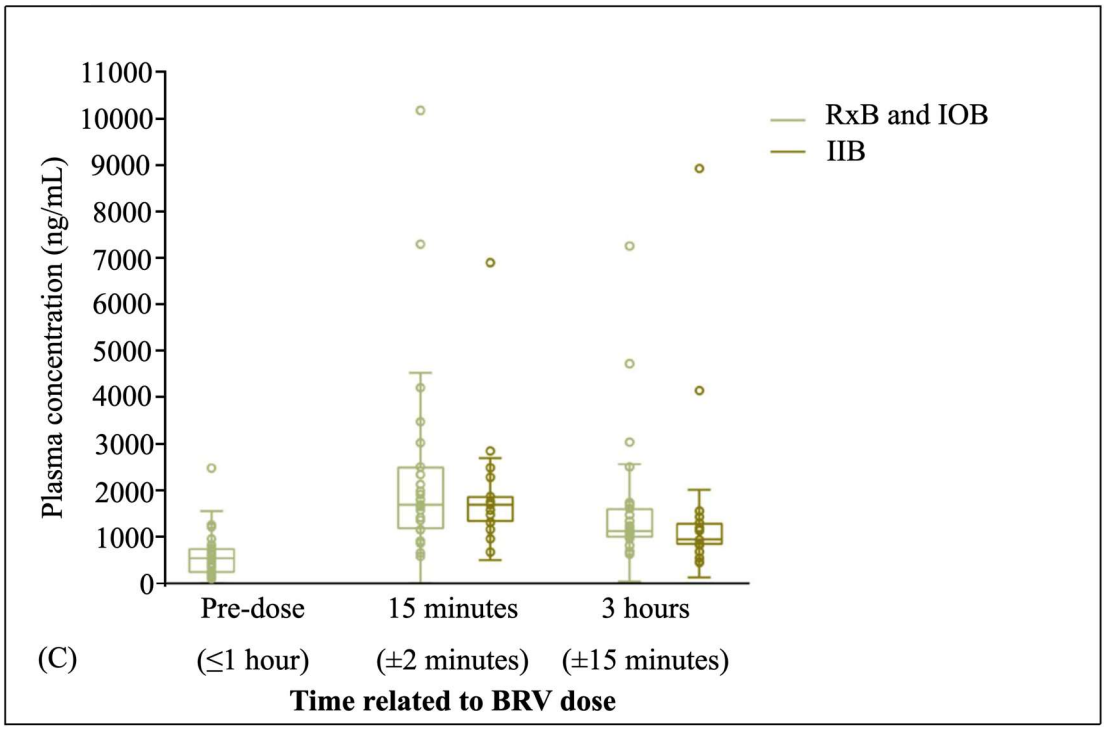


Figure 9. Brivaracetam plasma concentrations at Visit 3 by
(A) age cohort,
(B) administration, and
(C) patient group (IV PK period) (PK-PPS) (38).
Values below the limit of quantification were replaced by the value of the limit of quantification in all calculations. Data are only displayed if at least 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

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 ≥50 kg). Within the ≥1 month to <2 years and the ≥12 to <16 years age cohorts, there was a large variation (geometric coefficient of variation [%]) in pre-dose plasma concentrations. 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 9) (38).

IV.3.3 Safety outcomes

IV.3.3.1 Exposure to brivaracetam

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 (≥1 month to <2 years), 2.9 (2.6) days in the ≥2 to <6 years cohort, 3.7 (2.9) days in the ≥6 to <12 years cohort, and 4.4 (3.2) days in the ≥12 to <16 years cohort (38).

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. 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 ≥50 kg (38).

IV.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 12.). 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 (38).

TEAEs were numerically highest in the ≥2 to <6 years age cohort (*n* = 6; 46.2%) compared with the ≥1 month to <2 years (*n* = 2; 15.4%), the ≥6 to <12 years (*n* = 3; 25.0%), and the ≥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 ≥2 to <6 years cohort. There was no obvious difference in the incidences of TEAEs between the 15-min infusion and bolus groups (38).

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 12.) (38).

Somnolence was experienced in the two youngest age cohorts only; dizziness was experienced only in the oldest age cohort of ≥12 to <16 years; pyrexia was experienced only in the ≥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 ≤15 min, >15 to ≤60 min, >60 min to ≤12 h, >12 h). In the bolus group, one patient experienced pruritus >5 to ≤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 ≤15 min (somnolence and rash), >15 to ≤60 min (somnolence), >60 min to ≤12 h (fatigue, pyrexia, and insomnia), and >12 h (somnolence) after infusion start (38).

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%) (38).

Table 12. Treatment-emergent adverse events reported during the trial (SS-IV) (38).
[a]Medical Dictionary for Regulatory Activities (Version 18.1) Preferred Terms.
Note: TEAEs were defined as those events which 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 IV BRV; IOB, initiating oral BRV; RxB, Prescribed BRV; SS-IV, Safety Set intravenous; TEAE, treatment-emergent adverse event.

	Age cohort				Infusion group		Treatment category		
Patients, n (%)	≥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-minute 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[a] 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)

A total of seven patients (14.0%) had eight TEAEs during the IV PK period (Table 13.) (38).

Table 13. Treatment-emergent adverse events reported during the IV PK period (SS-IV) (38).
[a]Medical Dictionary for Regulatory Activities (Version 18.1) Preferred Terms.
Note: TEAEs were defined as those events which 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 IV BRV; IOB, initiating oral BRV; IV, intravenous; PK, pharmacokinetic; RxB, Prescribed BRV; SS-IV, Safety Set intravenous; TEAE, treatment-emergent adverse event.

	Age cohort				Infusion group		Treatment category		
Patients, n (%)	≥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-minute 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[a] 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)

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 (38).

There were no clinically significant changes observed in vital signs or electrocardiogram parameters. No deaths occurred in the trial (38).

V. Discussion

The optimal goal of epilepsy treatment is cessation of seizures or at a minimum significantly reducing seizure frequency, effectively managing seizure rate reduces the associated risks of epilepsy, including medical incidents, injury (39), and sudden unexpected death (40).

Even with new pharmacologic therapeutic options becoming available for the treatment of childhood epilepsy, treatment options for children suffering from difficult-to-treat epilepsies remain a serious challenge for pediatric neurologists.

Only a few prospective studies have focused exclusively on the clinical outcomes of pharmacotherapies in pediatric populations, in whom the forms and course of epilepsy can be quite diverse (41, 42, 43, 44).

In a prospective longitudinal study of 118 pediatric subjects, 23% met the criteria for pharmacoresistance (failure of 2 adequately used drugs) (42). Two-thirds of these subjects were not seizure free after initiation of medication (45). Therefore, there is a clinical need for new effective pharmacotherapy options, and new form of administration of the already available effective treatments.

V.1 Pregabalin

The A0081041 and A0081042 trials focused on patients with focal onset seizures. The main difference between the two trials were the target age group of pediatric patients with

epilepsy with focal onset seizures. The A0081041 trial investigated children and adolescents aged 4-16 years and that A0081042 trial investigated patients 1 month to <4 years of age. The difference in the patient population required different trial designs and efficacy endpoints (35, 36).

Based on the results of the A0081041 trial, the focal onset seizure frequency was significantly reduced in children aged 4-16 years treated with pregabalin 10 mg/kg/day. The 2.5 mg/kg/day pregabalin dose resulted in a numerical lowering of the seizure rate that was not statistically significant. Both doses were well tolerated with the most common treatment-emergent adverse events of somnolence, weight increase, and increased appetite being consistent with previous studies of pregabalin in adults (46, 47, 48).

Dizziness - one of the most common adverse events in adult studies of pregabalin for partial onset seizures (focal onset seizures) (46, 47, 48) was reported infrequently in this pediatric population (placebo, 1 [1.1%]; pregabalin 2.5 mg/kg/day, 4 [3.8%]; pregabalin 10 mg/kg/day, 3 [3.1%]). No other clinically significant impacts were found on other physical, neurologic, cognitive, or psychological safety evaluations (35).

The A0081042 trial demonstrated the efficacy of pregabalin in reducing the frequency of FOS in children < 4 years of age. This analysis showed a statistically significant reduction in $\log_e$(24-hour seizure rate + 1) with pregabalin 14 mg/kg/day compared with placebo using V-EEG monitoring to record seizures over 48-72 hours at baseline compared with the last 3 days of double-blind treatment. Sensitivity analysis supported the primary efficacy findings. The significant reduction in seizure rate from baseline with pregabalin 14 mg/kg/day versus placebo in this study is consistent with the primary efficacy outcome in older children with FOS (35, 36).

The safety and tolerability assessment indicated that pregabalin administered at both 7 mg/kg/day and 14 mg/kg/day was well tolerated within this pediatric population. Consistent with the clinical trial of children aged 4 to 16 years (35, 36), the most common TEAE in both pregabalin groups in this trial was somnolence. However, in contrast to older children (35), weight gain and increased appetite were not commonly reported in

children under 4 years. Only one discontinuation in the A0081042 study's placebo group was due to an AE, and no AE-associated discontinuations occurred in either pregabalin group (36). The data in the A0081042 trial were also consistent with the pharmacokinetic profile of pregabalin evaluated in 65 children (1 month to 16 years of age) with FOS (49).

Pregabalin 7 mg/kg/day did not show improvement in V-EEG $\log_e$(24-hour seizure rate + 1) from baseline to end of study in comparison with placebo (P = .461; Figure 6). The lack of efficacy seen at the lower dose of pregabalin in these children, aged 1 month to <4 years, is similar to the observation seen in older children (4-16 years) (35). Although the reduction in seizure frequency with lower doses in both studies was not significant, the impact of the relatively high placebo effect in the studies may confound evaluation of the lower doses of pregabalin studied (35, 36).

In children aged 1 month to <4 years the 50% responder rate was numerically greater for pregabalin 14 mg/kg/day relative to placebo, but the effect was not statistically significant. In children aged 4-16 years, 50% responder rate significantly favored the higher dose of pregabalin (10 mg/kg/day), although not the lower dose (2.5 mg/kg/day). However, there was a nonsignificant trend in 50% responder rate in favor of 14 mg/kg/day versus placebo (54% vs 42%), a difference of 12% in children 1 month to <4 years of age. The lack of statistical significance may perhaps have been due to the smaller sample sizes and the magnitude of the placebo response as noted above (36).

There were baseline differences among treatment groups in the trials that should also be noted. For example, there were group differences in baseline seizure frequency. The primary and secondary data, and the sensitivity analysis of primary endpoint, were all adjusted for known factors such as baseline seizure rate, age strata, and geographical region. However, other factors that are associated with refractory seizures in children such as seizure etiology and neurodevelopmental deficits (50) may also have differed between groups at baseline. Examination of other known factors in our dataset (e.g. subpopulations analyses including sex, race, number of AEDs, other neurodevelopmental abnormality, duration of epilepsy by treatment, etc.) can be considered to further explore their impact in the dataset of the two studies (35, 36).

The present studies had some limitations. In children 4 to 16 years of age for example, although serious adverse events (e.g. worsening of epilepsy, visual hallucinations) were rare and not dose dependent, other treatment-emergent adverse events (e.g. weight gain, increased appetite, somnolence) were more common. To evaluate potential long-term outcomes of these adverse events, follow-up studies would be required in pediatric populations. Finally, although the A0081041 trial enrolled subjects from 4 to 16 years of age, it was not designed to evaluate differences in efficacy and safety between children of different developmental stages (e.g. ages, function statuses) (35). Moreover, since seizures are not a regular phenomenon and the very nature of seizures is paroxysmal and erratic, the 48- to 72-hour duration of V-EEG monitoring in the A0081042 trial may have limited the comparison between the treatment groups. However, because of the very young age of these children, it would have been difficult to monitor V-EEG for a longer period due to potential skin/ scalp impact or a patient's nonacceptance of electrode placement. Moreover, the inclusion of a placebo control for longer periods of treatment would likely be unacceptable to all concerned. In addition, although participants with a history of myoclonic seizures were excluded, the principle investigators could diagnose myoclonic seizures as part of their patient care, and myoclonic seizures were reported for one patient in the 14 mg/kg/day group in the A0081042 trial. Subanalyses of ILAE seizure subtype and other potential subcategorizations (e.g., genetic classifications, age strata) would not have been possible in this study due to the lack of statistical power if the low patient number was further divided into subgroups. Evaluation of AEDs in this pediatric population, particularly those younger than 2 years, is uncommon, so the 9-day fixed-dose period (based on treatment in adult populations) may not be adequate time to observe effects of treatment in this age group (36).

These 2 study reports represent the first reports of the efficacy of pregabalin in pediatric populations to be published in a peer- reviewed journals. Clinicians treating children with epilepsy face challenges when choosing pharmacotherapy. Compared with adults, children may have differences in pharmacokinetic and pharmacodynamic profiles (51). The results of these studies support the appropriateness of the weight-based dose adjustment in pediatric patients (35, 36).

The US Food and Drug Administration and European Medicines Agency have endorsed the extrapolation of data supporting efficacy of AEDs for FOS in adults to pediatric patients 4 years of age and older (52, 53). Such an extrapolation at least partially reflects the challenges, costs, and resources required to conduct pediatric epilepsy studies; considerations of exposure of pediatric epilepsy patients to placebo; and higher than anticipated responses to placebo (52, 53). Because of this, efficacy studies in pediatric populations of 4 years of age and older with FOS would not be strictly required in the future and clinical trials like A0081041 trial, will likely evolve reflecting alternate approaches to development of future antiepileptic drugs. Discussions are ongoing among the academic community, pharmaceutical industry sponsors of epilepsy studies, and regulatory agencies on the topic of extending extrapolation of adult epilepsy data to children younger than 4 years (35, 36).

The efficacy and safety findings from the A0081042 clinical trial therefore provide evidence of an alternative option in the treatment of pediatric patients with FOS. Data from our investigation could be considered in meta-analyses of completed trials for support of an extrapolation recommendation in children <4 years of age (36).

V.2 Lacosamide

The EP0060 open-label, multicenter trial is the largest prospective investigation of the safety and tolerability of IV lacosamide in pediatric patients with epilepsy. Patients had focal seizures or primary generalized tonic-clonic seizures. IV lacosamide (2-12 mg/kg/day or 100-600 mg/day) was generally well tolerated in patients ≥1 month to <17 years of age, and no new safety concerns were identified. Nearly 72% of patients had not received lacosamide treatment in the 3 months preceding the trial, and most of the remaining patients were receiving oral lacosamide from a commercial supply. There was a mean overall exposure of IV lacosamide of 1.18 days, and most patients received one dose as a 30- to 60-minute infusion (37). Bioequivalence of IV and oral lacosamide has been established in adults (54). In oral and IV lacosamide pediatric pharmacokinetic modelling, simulations of IV lacosamide infused over 15-30 minutes resulted in similar exposure to oral administration (55).

Using weight-based dosing adaptations, it was predicted that the lacosamide concentration at steady state in children would be similar to that in adults for both oral and IV lacosamide. Based on PK modelling, the use of IV lacosamide was expected to be safe in pediatric patients down to 4 years of age (55). Therefore, enrolment of patients aged ≥4 to <17 years in two age-based cohorts was initially planned, with initiation of the younger cohort subject to an Independent Data Monitoring Committee review. During the course of the trial, new safety information for lacosamide in patients aged ≥1 month to 4 years was published (28, 30). As no specific risks were identified for this age group, the minimum age limit for the trial was lowered to ≥1 month (37).

As has been previously observed in studies of IV lacosamide in pediatric patients with epilepsy and in critically ill children, TEAEs were reported in few patients (15, 28, 56). The observed safety profile is consistent with the known safety profile of IV lacosamide in adults (25, 26, 27) and of oral lacosamide in pediatric patients (22, 23, 24). No severe or serious TEAEs or discontinuation due to TEAEs were reported, and no TEAEs were considered related to lacosamide by the investigators. Two patients had TEAEs of increased blood triglycerides. Given the short duration of the trial, assessment of the lipid panel in a non-fasting state, concomitant treatment with other ASMs, and elevated baseline triglycerides in one of the two patients, these changes in lipid levels are likely not related to treatment with IV lacosamide and are not clinically significant. Further, a post hoc analysis of serological data from a randomized monotherapy trial showed no change from baseline in serum lipid levels following 12 months of oral lacosamide therapy (57). ECG outcomes showed no clinically relevant changes (37). This is consistent with observations from a retrospective trial of critically ill children with focal or generalized seizures treated with IV lacosamide, in which no cardiac events were noted in 37 children who had continuous ECG monitoring before, during, and after infusion (28).

The design of this trial was intended to maximize the available pool of patients by allowing for entry of individuals who were receiving oral lacosamide as adjunctive treatment or monotherapy (in an open-label long-term trial or by prescription), in addition to those who initiated IV lacosamide as adjunctive treatment following enrolment. Patients with ongoing oral lacosamide treatment were on a stable dose (37).

This trial was limited by its open-label, uncontrolled design with no comparator or placebo group. The patient population was mostly White; the results may not be generalizable across racial groups. However, no relevant differences in the pharmacokinetics of lacosamide have been observed between healthy Asian, Black, and Caucasian individuals (15). Given the study design, some drug-related TEAEs may not have been detected. The study did not explore prolonged periods of infusion with IV lacosamide; longer-term administration of IV treatment may be required for critically ill children or those who cannot tolerate oral medications for several days or longer (37).

V.3 Brivaracetam

The EP0065 was a multicenter, open-label trial in patients ≥1 month to <16 years of age with epilepsy, to evaluate the pharmacokinetics, safety, and tolerability of brivaracetam as 15-min intravenous (IV) infusion and bolus (≤2-min injection) (38).

Treatment with IV BRV was well tolerated in pediatric patients 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 ≥4 years of age receiving oral therapy. In pooled Phase II and Phase III placebo-controlled adult trials, acceptable safety and tolerability profiles were demonstrated with adjunctive BRV treatment: the most frequently reported TEAEs with BRV (≥5.0% of patients) vs. placebo were somnolence, headache, dizziness, and fatigue (58). 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 ≥4 to <16 years of age, with the most common drug-related TEAE being somnolence (59). No new safety concerns for BRV in the pediatric population were identified in the present trial (38).

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 (38).

There were no unexpected PK differences observed across age cohorts, 15-min infusion and bolus groups, or weight groups (<50 kg vs ≥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 IIa, open-label, multicenter trial (N01263) in patients ≥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 hours post dose. Of note, this pattern was not observed in four patients, who had higher BRV concentrations at 3 hours 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-individual variability. Although a previously performed population PK analysis comparing Caucasian and non-Caucasian patients showed no significant pharmacokinetic differences (20, 60), most patients enrolled in this trial were White, which may limit generalizability of these results to other racial groups (38).

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. Based on PK modeling results, a 15-min IV infusion or a bolus injection (≤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 ≥50 kg) in patients ≥1 month to ≤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 (38).

Studies in adult patients have previously demonstrated bioequivalence between BRV tablets, oral solution, and IV formulations (32, 34). The results of the present trial in patients ≥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 (38).

VI. Conclusions

The results of our research confirmed the efficacy of pregabalin as add-on treatment for focal onset seizures in children and adolescent patients. The safety and tolerability profile of pregabalin in the investigated age groups was acceptable. No new safety concerns were identified in pediatric patients compared to adult data. Pregabalin 10 mg/kg/day as an adjunctive therapy demonstrated efficacy compared with placebo for the treatment of focal onset seizures for pediatric subjects aged 4 – 16 years. Pregabalin 2.5 mg/kg/day showed a nonsignificant trend for reducing seizure frequency in this age group. Both doses of pregabalin were generally safe and well tolerated (35).
Pregabalin 14 mg/kg/day TID resulted in a statistically significant reduction in focal onset seizure frequency compared with placebo in pediatric patients 1 month to <4 years of age, when assessed using V-EEG. Pregabalin 7 mg/kg/day TID did not show improvements in seizure reduction relative to placebo in this patient population. Both pregabalin 7 and 14 mg/kg/day were generally safe and well tolerated (36).

The investigation for the use of intravenous lacosamide in pediatric patients with epilepsy as a 15-30 minutes or 30- to 60- minute infusion did not identify any new safety concerns compared to the oral use in pediatric and intravenous use of lacosamide in adult patients. IV lacosamide had an acceptable tolerability profile in pediatric patients ≥1 month to <17 years of age with epilepsy and focal seizures or primary generalized tonic-clonic seizures (37).

The intravenous use of brivaracetam as bolus injection or 15- minute infusion was well tolerated by pediatric patients regardless to whether they have received oral brivaracetam treatment prior to the intravenous administration. The safety and tolerability findings of IV brivaracetam were generally consistent with the known safety profile of BRV, with no new safety concerns identified for the pediatric population from ≥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 (38).

VII. Summary

A few epilepsy medications are approved for treatment of pediatric populations. The widespread prevalence of epilepsy presents a global health burden in need of effective and safe treatments for pediatric patients with epilepsy (5).

No randomized controlled clinical trials have evaluated the efficacy of pregabalin for treatment of focal onset seizures in children. No prospective clinical trial evaluated the safety and tolerability of IV lacosamide infusions and the pharmacokinetics, safety, and tolerability of iv brivaracetam injection in pediatric patients with epilepsy.

The aim of our research as Phase II-III clinical trials were to provide novel pharmaceutical treatment options for the treatment of pediatric epilepsy. The safety, tolerability, efficacy and pharmacokinetics of pregabalin, lacosamide and brivaracetam was evaluated in pediatric patients diagnosed with epilepsy (35, 36, 37, 38).

Pregabalin 10 mg/kg/day as an adjunctive therapy demonstrated efficacy compared with placebo for the treatment of focal onset seizures for pediatric subjects aged 4 - 16 years and was generally safe and well tolerated (35).

Pregabalin 14 mg/kg/day three times a day resulted in a statistically significant reduction in focal onset seizure frequency compared with placebo in pediatric patients 1 month to <4 years of age, when assessed using V-EEG and was generally safe and well tolerated (36).

IV lacosamide had an acceptable tolerability profile in pediatric patients ≥1 month to <17 years of age with epilepsy and focal seizures or primary generalized tonic-clonic seizures (37).

The safety and tolerability findings of IV brivaracetam were generally consistent with the known safety profile of brivaracetam, with no new safety concerns identified for the pediatric population from ≥1 month to <16 years of age. Plasma concentrations were in

the expected range, and no unexpected pharmacokinetic differences were observed between patients receiving 15-min infusions or bolus injections. The results support the use of an IV brivaracetam dose that is a mg-to-mg equivalent of the oral dose (38).

VIII. References

1. Ngugi AK, Kariuki SM, Bottomley C, Kleinschmidt I, Sander JW, Newton CR. Incidence of epilepsy: A systematic review and meta-analysis. Neurology. 2011; 77: 1005–12
2. US Census Bureau, Population Division [database online]. Annual estimates of the resident population by sex, age, race, and Hispanic origin for the United States, States, and Counties: April 1, 2010 to July 1, 2013. Release Date: June 2014. Accessed February 2, 2015.
3. Kobau R, Luo Y, Zack M, Helmers S, Thurman D. Epilepsy in adults and access to care — United States, 2010. MMWR Morb Mortal Wkly Rep. 2012;61:909-913.
4. Russ SA, Larson K, Halfon N. A national profile of childhood epilepsy and seizure disorder. Pediatrics. 2012;129:256–64.
5. Camfield P, Camfield C. Incidence, prevalence and aetiology of seizures and epilepsy in children. Epileptic Disord. 2015;17:117–23
6. Perucca E. Established antiepileptic drugs. Baillieres Clin Neurol. 1996;5:693-722
7. Morrell MJ. Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. Neurology. 2011;77:1295-1304.
8. Berg AT, Berkovic SF, Brodie MJ, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005–2009. Epilepsia. 2010;51:676–85.
9. Fisher R, Shafer P, D'Souza C.2017 revised classification of seizures. Available at: https://www.epilepsy.com/article/2016/12/2017-revised-classification-seizures. Accessed August 2, 2018.

10. Pellock JM, Arzimanoglou A, D'Cruz O, Holmes GL, Nordli D, Shinnar S, et al. Extrapolating evidence of antiepileptic drug efficacy in adults to children ≥2 years of age with focal seizures: the case for disease similarity. Epilepsia. 2017;58:1686–96
11. Camfield PR, Camfield CS, Gordon K, Dooley JM. If a first antiepileptic drug fails to control a child's epilepsy, what are the chances of success with the next drug? J Pediatr. 1997;131:821–4.
12. Pellock JM, Appleton R. Use of new antiepileptic drugs in the treatment of childhood epilepsy. Epilepsia. 1999;40(Suppl 6):s29– 38; discussion S73–4.
13. Beghi E, Giussani G, Sander JW. The natural history and prognosis of epilepsy. Epileptic Disord. 2015;17:243-53.
14. Shorvon SD. Drug treatment of epilepsy in the century of the ILAE: the second 50 years, 1959-2009. Epilepsia. 2009;50(Suppl 3):93-130.
15. UCB Pharma. Vimpat® (lacosamide tablets, injection, oral solution) [US Prescribing Information]. Smyrna, GA: UCB, Inc. Available at: https://www.ucb.com/_up/ucb_com_products/documents/Vimpat_Labeling_Oct_2021.pdf. Accessed November 3, 2021.
16. UCB Pharma. Vimpat® (lacosamide) EMA Summary of Product Characteristics. Braine-l'Alleud, Belgium: UCB Pharma SA. Available at: https://www.ema.europa.eu/en/documents/product-information/vimpat-epar-product-information_en.pdf. Accessed March 30, 2022.
17. Lyrica (pregabalin) [US prescribing information]. Updated December 2016. http://labeling.pfizer.com/ShowLabeling.aspx? id1⁄4561. Accessed March 5, 2018.
18. European Medicines Agency. Lyrica (pregabalin) summary of product characteristics http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000546/WC500046602.pdf. Updated January 15, 2018. Accessed March 5, 2018.
19. UCB Pharma S.A. Briviact® (brivaracetam) summary of product characteristics. European Medicines Agency, 2020. Available at:

https://www.ema.europa.eu/en/documents/product-information/ briviact-epar-product-information_en.pdf Accessed September 16, 2021

20. Briviact® (brivaracetam) prescribing information. UCB, Inc., 2021. Available at: https://www.briviact.com/briviact-PI.pdf Accessed September 16, 2021
21. Mann D, Liu J, Chew ML, et al. Safety, tolerability, and pharmacokinetics of pregabalin in children with refractory partial seizures: a phase 1, randomized controlled study. Epilepsia. 2014;55:1934-1943.
22. Farkas V, Steinborn B, Flamini JR, Zhang Y, Yuen N, Borghs S, et al. Efficacy and tolerability of adjunctive lacosamide in pediatric patients with focal seizures. Neurology. 2019;93:e1212-e1226.
23. Makedonska I, Ng YT, Beller C, Bozorg A, Chu KME, Csikos J, McClung M, Moeltgen H, Farkas MK. Efficacy and tolerability of adjunctive lacosamide in patients aged <4 years with focal seizures: double-blind, randomized controlled trial Neurology (submitted). 2022
24. Ferreira JA, Le Pichon JB, Abdelmoity AT, Dilley D, Dedeken P, Daniels T, et al. Safety and tolerability of adjunctive lacosamide in a pediatric population with focal seizures – an open- label trial Seizure. 2019;71:166–173.
25. Fountain NB, Krauss G, Isojarvi J, Dilley D, Doty P, Rudd GD. Safety and tolerability of adjunctive lacosamide intravenous loading dose in lacosamide-naive patients with partial-onset seizures Epilepsia. 2013;54:58–65.
26. Krauss G, Ben-Menachem E, Mameniskiene R, Vaiciene-Magistris N, Brock M, Whitesides JG, et al. Intravenous lacosamide as short-term replacement for oral lacosamide in partial-onset seizures Epilepsia. 2010;51:951–957.
27. Biton V, Rosenfeld WE, Whitesides J, Fountain NB, Vaiciene N, Rudd GD. Intravenous lacosamide as replacement for oral lacosamide in patients with partial-onset seizures Epilepsia. 2008;49:418–424.
28. Arkilo D, Gustafson M, Ritter FJ. Clinical experience of intravenous lacosamide in infants and young children Eur J Paediatr Neurol. 2016;20:212–217.
29. Ngampoopun M, Suwanpakdee P, Jaisupa N, Nabangchang C. Effectiveness and adverse effect of intravenous lacosamide in nonconvulsive status epilepticus and acute repetitive seizures in children Neurol Res Int. 2018;2018:8432859.

30. Welsh SS, Lin N, Topjian AA, Abend NS. Safety of intravenous lacosamide in critically ill children Seizure. 2017;52:76–80.
31. Liu E, Dilley D, McDonough B, Stockis A, Daniels T. Safety and tolerability of adjunctive brivaracetam in pediatric patients <16 years with epilepsy: an open-label trial. Paediatr Drugs. 2019;21:291–301.
32. Hulhoven R, Scheen A, Watanabe S, Valgaeren A, Troenaru M, Otoul C, et al. Bioavailability and safety of the intravenous administration of brivaracetam. Epilepsia. 2008;49:438.
33. Stockis A, Hartstra J, Mollet M, Hadi S. Bioavailability and bioequivalence comparison of brivaracetam 10, 50, 75, and 100 mg tablets and 100 mg intravenous bolus. Epilepsia. 2016;57:1288–93.
34. Otoul C, Watanabe S, McCabe S, Stockis A. Relative bioavailability and bioequivalence of brivaracetam 10 mg/ml oral solution and 50-mg film-coated tablet. Clin Pharmacol Drug Dev. 2017;6:313–7.
35. Antinew J, Pitrosky B, Knapp L, Almas M, Pitman V, Liu J, Craiu D, Modequillo M , Nordli D, Farkas V, Farkas MK. Pregabalin as Adjunctive Treatment for Focal Onset Seizures in Pediatric Patients: A Randomized Controlled Trial. J Child Neurol 2019;34:248-255.
36. Mann D, Antinew J, Knapp L, Almas M, Liu J, Scavone J, Yang R, Modequillo M, Makedonska I, Ortiz M, Kyrychenko A, Nordli D, Farkas V, Farkas MK. Pregabalin adjunctive therapy for focal onset seizures in children 1 month to <4 years of age: A double-blind, placebo-controlled, video-electroencephalographic trial. Epilepsia 2020;61:617-626.
37. Farkas MK, Beller C, Bozorg A, McClung C, Roebling R, Yates T, Yuen N, Makedonska I.
Safety and tolerability of short-term infusions of intravenous lacosamide in pediatric patients with epilepsy: An open-label, Phase 2/3 trial. Epilepsia Open. 2023 Mar;8(1):146-153.
38. Farkas MK, Kang H, Fogarasi A, Bozorg A, James GD, Krauwinkel W, Morita D, Will E, Elshoff JP. Pharmacokinetics, safety, and tolerability of intravenous brivaracetam in pediatric patients with epilepsy: An open-label trial. Epilepsia 2022;63:855-864

39. Zuberi SM, Symonds JD. Update on diagnosis and management of childhood epilepsies. J Pediatr (Rio J). 2015;91:S67–77.
40. Donner EJ, Camfield P, Brooks L, et al. Understanding death in children with epilepsy. Pediatr Neurol. 2017;70:7–15.
41. Berg AT, Levy SR, Testa FM, D'Souza R. Remission of epilepsy after two drug failures in children: a prospective study. Ann Neurol. 2009;65:510-519.
42. Berg AT,Rychlik K. The course of childhood-onset epilepsy over the first two decades: a prospective, longitudinal study. Epilepsia. 2015;56:40-48.
43. Sillanpaa M, Schmidt D. Early seizure frequency and aetiology predict long-term medical outcome in childhood-onset epilepsy. Brain. 2009;132:989-998.
44. Wirrell EC, Grossardt BR, So EL, Nickels KC. A population-based study of long-term outcomes of cryptogenic focal epilepsy in childhood: cryptogenic epilepsy is probably not symptomatic epilepsy. Epilepsia. 2011;52:738-745.
45. Camfield P, Camfield C. Epileptic syndromes in childhood: clinical features, outcomes, and treatment. Epilepsia. 2002;43(suppl 3):27-32.
46. French JA, Kugler AR, Robbins JL, Knapp LE, Garofalo EA. Dose-response trial of pregabalin adjunctive therapy in patients with partial seizures. Neurology. 2003;60:1631-1637
47. Arroyo S, Anhut H, Kugler AR, et al. Pregabalin add-on treatment: a randomized, double-blind, placebo-controlled, dose-response study in adults with partial seizures. Epilepsia. 2004; 45:20-27.
48. Beydoun A, Uthman BM, Kugler AR, Greiner MJ, Knapp LE, Garofalo EA. Safety and efficacy of two pregabalin regimens for add-on treatment of partial epilepsy. Neurology. 2005;64: 475-480.
49. Mann D, Liu J, Chew ML, et al. Safety, tolerability, and pharmacokinetics of pregabalin in children with refractory partial seizures: a phase 1, randomized controlled study. Epilepsia. 2014;55:1934–43.
50. Seker Yilmaz B, Okuyaz C, Komur M. Predictors of intractable childhood epilepsy. Pediatr Neurol. 2013;48:52–5.
51. Verrotti A, Piccorossi A, Lasorella S, Tambucci R. Pharmacotherapy in pediatric epilepsy: rational drug and dose selection. Expert Opin Drug Metab Toxicol. 2016;12:1393-1396.

52. European Medicines Agency. Guideline on clinical investigation of medicinal products in the treatment of epileptic disorders. 2010. Available at: http://www.ema.europa.eu/docs/en_GB/docum ent_library/Scientific_guideline/2010/01/WC500070043.pdf. Accessed May 30, 2019.
53. Pediatric news. J Pediatr Pharmacol Ther. 2016;21:98.
54. Cawello W, Bonn R, Boekens H. Bioequivalence of intravenous and oral formulations of the antiepileptic drug lacosamide. Pharmacology. 2012;90:40-6
55. Winkler J, Schoemaker R, Stockis A. Modeling and simulation for the evaluation of dose adaptation rules of intravenous lacosamide in children Epilepsy Res. 2019;149:13–16.
56. Ortiz de la Rosa JS, Ladino LD, Rodríguez PJ, Rueda MC, Polanía JP, Castañeda AC. Efficacy of lacosamide in children and adolescents with drug-resistant epilepsy and refractory status epilepticus: a systematic review Seizure. 2018;56:34–40.
57. Mintzer S, Dimova S, Zhang Y, Steiniger-Brach B, De Backer M, Chellun D, et al. Effects of lacosamide and carbamazepine on lipids in a randomized trial Epilepsia. 2020;61:2696–2704.
58. Brandt C, Klein P, Badalamenti V, Gasalla T, Whitesides J. Safety and tolerability of adjunctive brivaracetam in epilepsy: in-depth pooled analysis. Epilepsy Behav. 2020;103:106864.
59. Patel AD, Badalamenti V, Gasalla T, Elmoufti S, Elshoff JP. Safety and tolerability of adjunctive brivaracetam in children with focal seizures: interim analysis of pooled data from two open-label trials. Eur J Paediatr Neurol. 2020;25:68–76.
60. Schoemaker R, Wade JR, Stockis A. Brivaracetam population pharmacokinetics and exposure-response modeling in adult subjects with partial-onset seizures. J Clin Pharmacol. 2016;56:1591–602.

IX. Bibliography of the candidate's publications

IX.1. Publications related to the dissertation

1. Antinew J, Pitrosky B, Knapp L, Almas M, Pitman V, Liu J, Craiu D, Modequillo M, Nordli D, Farkas V, **Farkas MK**. Pregabalin as Adjunctive Treatment for Focal Onset Seizures in Pediatric Patients: A Randomized Controlled Trial. J Child Neurol 2019;34:248-255.
   IF: 1.71

2. Mann D, Antinew J, Knapp L, Almas M, Liu J, Scavone J, Yang R, Modequillo M, Makedonska I, Ortiz M, Kyrychenko A, Nordli D, Farkas V, **Farkas MK**. Pregabalin adjunctive therapy for focal onset seizures in children 1 month to <4 years of age: A double-blind, placebo-controlled, video-electroencephalographic trial. Epilepsia 2020;61:617-626.
   IF: 5.86

3. **Farkas MK**, Kang H, Fogarasi A, Bozorg A, James GD, Krauwinkel W, Morita D, Will E, Elshoff JP. Pharmacokinetics, safety, and tolerability of intravenous brivaracetam in pediatric patients with epilepsy: An open-label trial. Epilepsia 2022;63:855-864
   IF: 5.6

4. **Farkas MK**, Beller C, Bozorg A, McClung C, Roebling R, Yates T, Yuen N, Makedonska I.
   Safety and tolerability of short-term infusions of intravenous lacosamide in pediatric patients with epilepsy: An open-label, Phase 2/3 trial. Epilepsia Open. 2023 Mar;8(1):146-153.
   IF: 3.0

IX.2. Publications not related to the dissertation

1. Cseh A, **Farkas MK**, Derzbach L, Muller K, Vasarhelyi B, Szalay B, Treszl A, Farkas V. Lymphocyte subsets in pediatric migraine. Neurol Sci. 2013;34:1151-5
   IF: 1.49

2. Farooq O, Faden HS, Cohen ME, Ramanathan M, Barrett H, **Farkas MK**, Langan TJ, Yeh EA. Neurologic complications of 2009 influenza-a H1N1 infection in children. J Child Neurol. 2012;27:431-8.
   IF: 1.38

3. **Farkas MK**, Szeifert L, Markia B, Csüllög Zs, Farkas V. Neuronalis ceroid lipofuscinosis 2-es típusában (CLN2) enzimpótló kezeléssel szerzett klinikai tapasztalataink. Clinical experience with enzyme replacement therapy in neuronal ceroid lipofuscinosis type 2 (CLN2). Gyermekgyógyászat 2020, 71. évfolyam 6: 375-380

X. Acknowledgments

I would like to thank Prof. Dr. Attila Szabó for providing the research environment and facilitated the completion of this work. I would like to express my gratitude towards the whole research team at the Neurology Unit, Semmelweis University First Department of Pediatrics and especially my father Dr. Viktor Farkas, who has been an outstanding role model and mentor for me. Without them this work could not have been possible.

I would like to thank the patients and caregivers and the other investigators and their teams who contributed to the successful completion of these trials. I would like to acknowledge my co-authors and UCB Pharma and Pfizer for funding the research.

I am thankful for my consultant Dr. Áron Cseh for his irreplaceable advice.

Last but not least, I am grateful to my family and friends, who supported me all over this work.