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

PhD thesis

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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.

The incidence of epilepsy in children has been reported to range from 41 to 187 new cases per 100 000 children per year. 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. 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.

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). 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. 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.

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.

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 (1, 2, 3, 4). 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 (1, 2). 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 (3, 4). The three different antiseizure medications were investigated in altogether four clinical trials (1, 2, 3, 4).

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 (1).

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 (2).

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 (3).

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 (4).

III. Methods

Phase II – Phase III multicenter clinical trials were conducted. 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 (1, 2, 3, 4).

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 (1, 2).

III.1.1 Pregabalin in pediatric patients older than 4 years

Efficacy and safety of pregabalin as adjunctive treatment for children aged 4-16 years with partial-onset seizures were 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 (1).

III.1.2 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 (2).

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 (3).

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 (4).

IV. Results

IV.1.1 Pregabalin in pediatric patients older than 4 years of age

In the trial focusing on pediatric patients older than 4 years 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). Out of the 372 screened patients 29 patients were screened and 26 patients were randomized at our center (1).

Pregabalin 10 mg/kg/day resulted in a significant improvement of log-transformed 28-day seizure rate relative to placebo (P = .0185) (Figure 1). 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 1) (1).

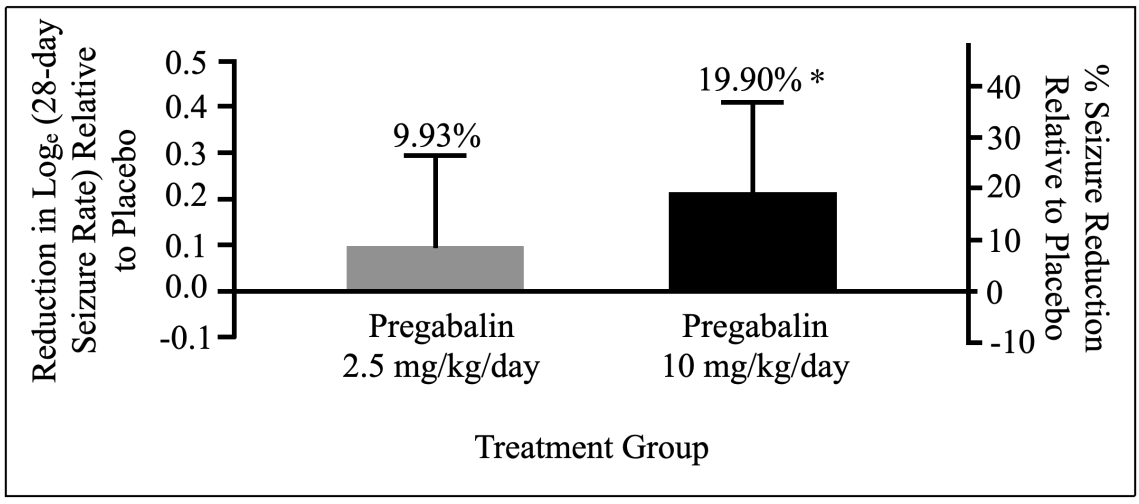


Figure 1. Least squares mean (95% confidence interval) and percentage treatment differences (pregabalin minus placebo) in log- transformed 28-day seizure rate during the double-blind treatment phase (1).
*P = .0185 with pregabalin 10 mg/kg/day; the difference was numeric and not statistically significant 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 2.) (1).

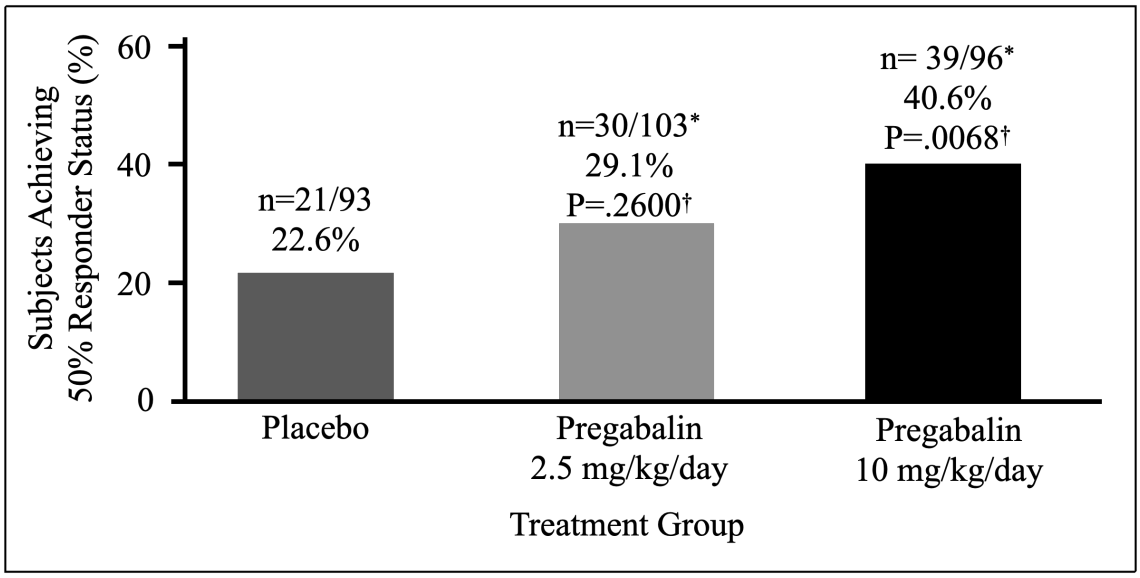


Figure 2. Percentage of subjects achieving 50% responder status (reduction in seizures) during the double-blind treatment phase by treatment group (1).
*One subject in each pregabalin group was not evaluated at the end of the double-blind treatment phase because they did not return seizure diary data.
†P value versus placebo.

The most commonly reported treatment-emergent adverse events (TEAEs) 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%]) (1).

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 (1).

IV.1.2 Pregabalin in pediatric patients younger than 4 years

In the trial focusing on patients younger than 4 years overall 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.

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 3). 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 3.) (2).

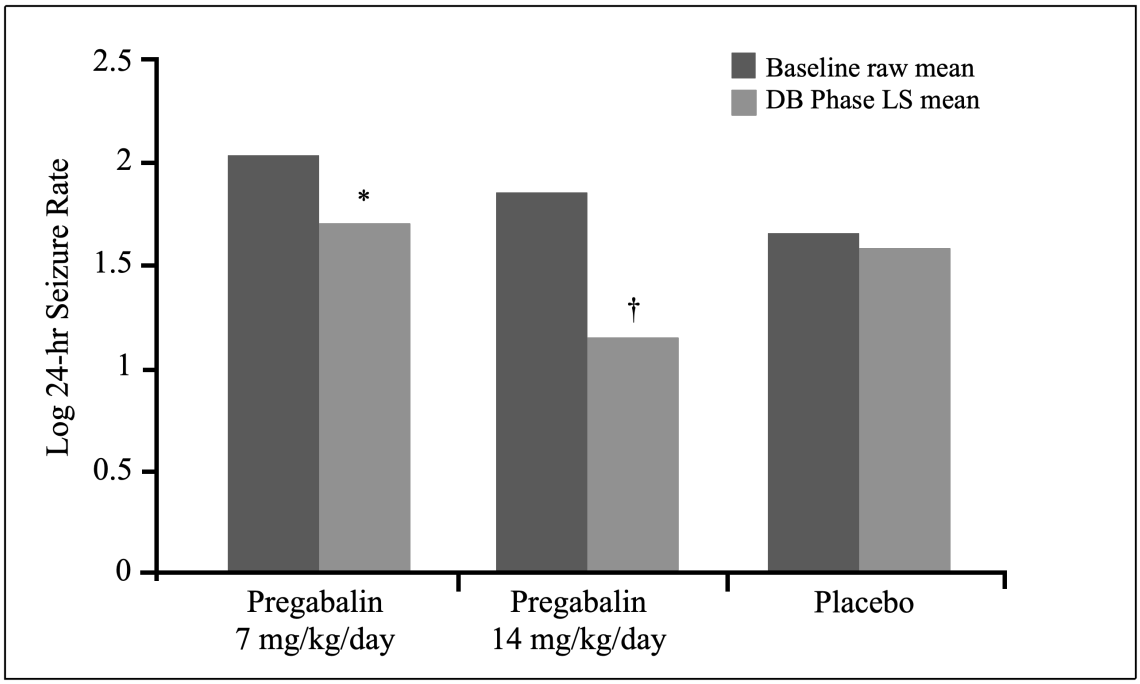


Figure 3. Least squares (LS) mean $\log_e$(24-day seizure rate + 1) for focal onset seizures for each treatment group during double-blind (DB) treatment phase. (2). **P* = .4606 relative to placebo, †*P* = .0223 relative to placebo

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 (2).

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. 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 (2).

IV.2 Lacosamide

Altogether 103 patients were enrolled and completed the EP0060 open-label trial (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. Patients had a mean age of 8.6 years, and 57 (55.3%) were female 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 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%]). (3).

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 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 4.). No patients in the ≥1 month to <8 years age cohort received more than two infusions (3).

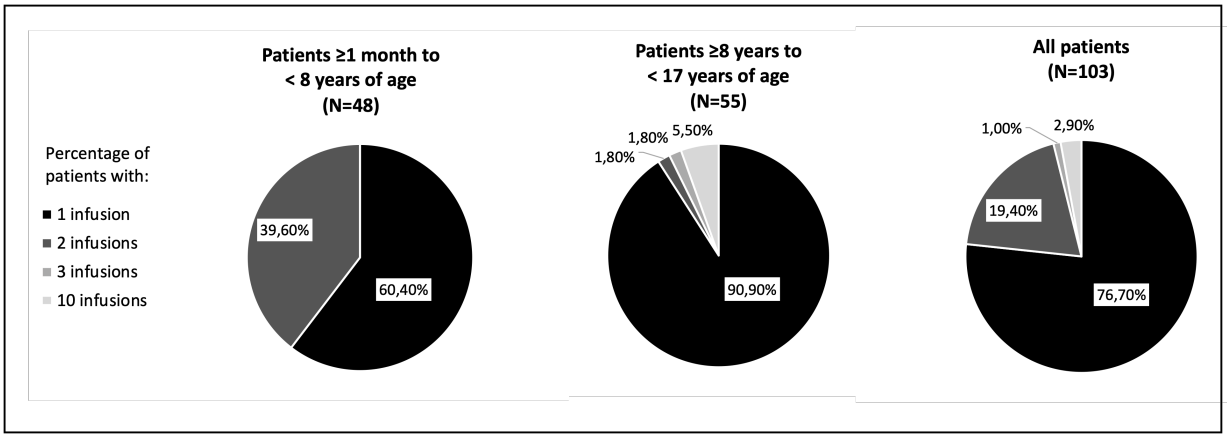


Figure 4. Number of infusions by cohort and overall (SS-IV) (3). Abbreviation SS-IV, intravenous Safety Set

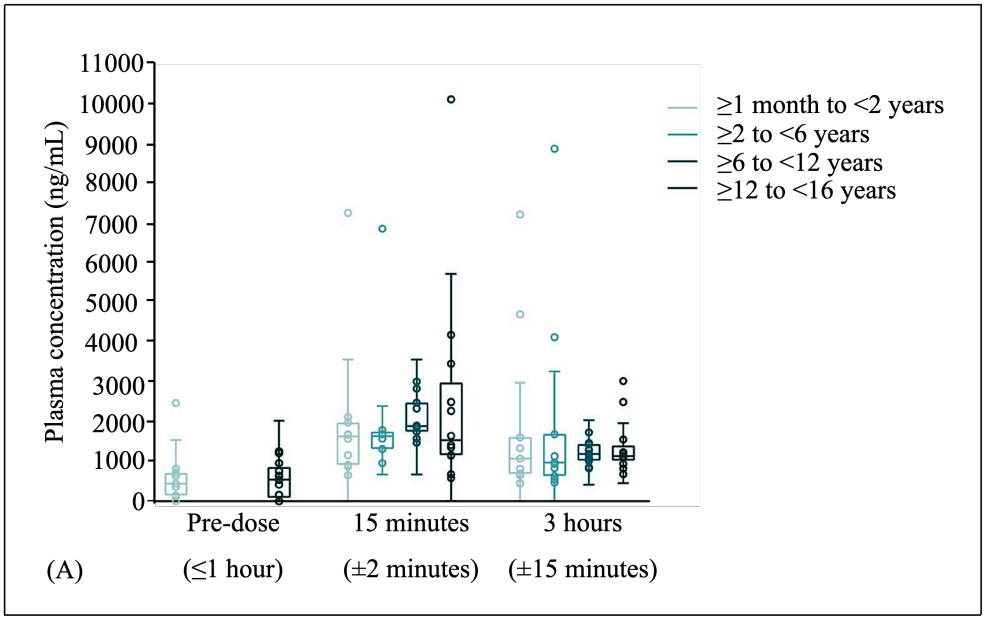
A total of seven TEAEs were reported in five (4.9%) patients following treatment with IV lacosamide. No serious TEAEs, severe TEAEs, or discontinuation due to TEAEs were reported. No TEAEs were considered drug-related by the investigator, and no deaths were reported during the trial (3).

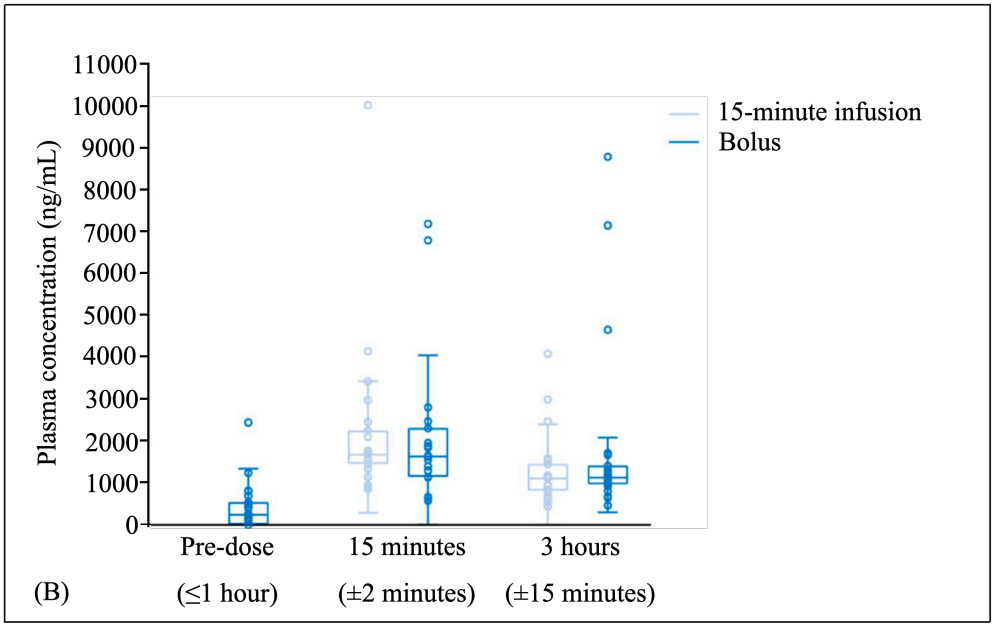
Mean values for the majority of haematology and clinical chemistry parameters remained within the normal ranges for the duration of the trial. No consistent or clinically relevant changes from baseline were observed in vital sign parameters. There were no treatment-emergent clinically significant ECG 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 (3).

IV.3 Brivaracetam

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 initiating oral brivaracetam (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. PK outcomes were consistent with the expected results and expected ranges for this population (Figure 5.) (4).





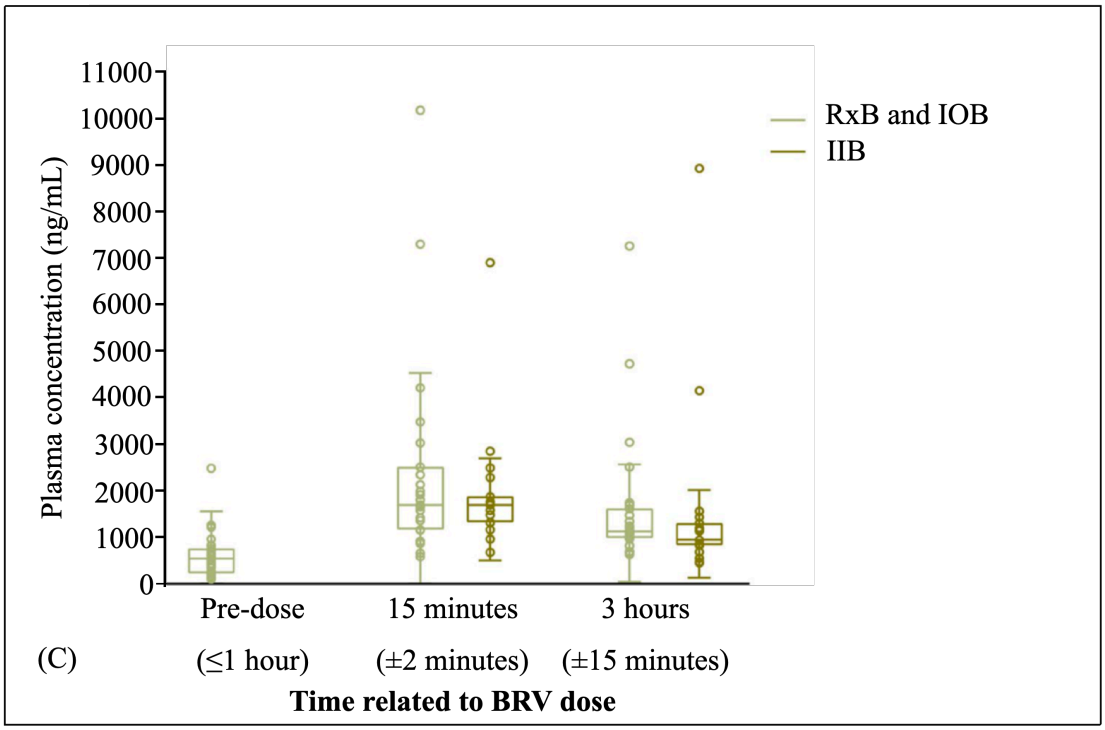


Figure 5. Brivaracetam plasma concentrations at Visit 3 by
(A) age cohort,
(B) administration, and
(C) patient group (IV PK period) (4).
Values below the limit of quantification were replaced by the value of the limit of quantification in all calculations. Data are only displayed if at least two-thirds 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; 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 5) (4).

Overall, 14 patients (28.0%) experienced 18 TEAEs during the trial, including one patient (2.0%) with a severe TEAE (somnolence). 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. There was no obvious difference in the incidences of TEAEs between the 15-min infusion and bolus groups (4).

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. There were no clinically significant changes observed in vital signs or electrocardiogram parameters. No deaths occurred in the trial (4).

V. Conclusions

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 (1, 2, 3, 4).

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 (1).

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 (2).

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 (3).

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 (4).

VI. Bibliography of the candidate's publications

VI.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**, 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

4. **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

VI.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